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ALL ABSTRACTS - ALPHABETICAL ORDER

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Fractal Geometry in the Assessment of Oral Epithelial Dysplasia Grading System

Background: Oral epithelial dysplasia is linked to the possibility of progression to oral squamous cell carcinoma. The severity of atypic features and the height in the epithelium to which they extend have been used in grading dysplasia into mild, moderate and severe. Precise grading is a source of disagreement as the assessment carries a degree of subjectivity [1,2]. There is therefore a need for developing new morphological definitions for grading dysplasia based on research into the pathogenesis of premalignancy [3]. The aim of this study is developing objective aids in the diagnosis and classification of epithelial dysplasia based on image analysis, and using mathematical descriptors of morphology, both at the tissue and cellular levels.

Materials and Methods: Eighty images of haematoxylin and eosin stained dysplasia images (mild (25), moderate (27), severe (28)) were analyzed to extract the epithelial connective tissue interface (ECTI) profiles using different thresholding methods. Box counting, local and local connected fractal geometry techniques were then applied to assess the complexity of the ECTI profiles. The spatial distribution of a set of dysplasia cell nuclei were also assessed in different dysplasia grades. Statistical analyses to compare the different grades of dysplasia were performed.

Results: Preliminary results showed that the global complexity of ECTI profiles as described by the box fractal dimension (DBOX) was statistically different between mild (DBOX= 1.09) and both moderate (DBOX=1.13) and severe dysplasia (DBOX=1.14) ($p< 0.05$, one-way ANOVA), while moderate and severe dysplasia did not show any significant difference. The local connected fractal dimension (LCFD) was not statistically different between mild (LCFD=1.34), moderate (LCFD=1.34) or severe dysplasia (LCFD=1.34) ($p> 0.05$, one- way ANOVA).

Conclusion: The initial results of this study agree with our previous findings [4,5] and provides further evidence that the traditional classification of dysplastic changes into three grades might not represent accurately the morphological characteristic of the premalignant change This emphasizes the problems of using methods that have elements of subjectivity. A quantitative classification system is therefore a

much preferred options. The use of quantifiable methods such as different measures of fractal geometry might be of use in establishing new, reproducible systems.

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Multiscale modeling of biological systems: from physical tools to applications in cancer modeling II; Saturday, July 2, 11:00

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Phase Field Crysyal Model for Liquid Crystals

On the basis of static and dynamical density functional theory, a phase-field-crystal model is derived which involves both the translational density and the orientational degree of ordering as well as a local director field. The equilibrium free-energy functional involves local powers of the order parameters up to fourth order, gradients of the order parameters up to fourth order, and different couplings between the order parameters [**1**]. The stable phases of the equilibrium free-energy functional are calculated for various coupling parameters. Phase diagrams were obtained by numerical minimization of the free-energy functional. Among the stable liquid-crystalline states are the isotropic, nematic, columnar, smectic A, and plastic crystalline phases [**2**]. The plastic crystals can have triangular, square, and honeycomb lattices and exhibit orientational patterns with a complex topology involving a sublattice with topological defects. As far as the dynamics is concerned, the translational density is a conserved order parameter while the orientational ordering is non-conserved. The derived phase-field-crystal model can serve for use in efficient numerical investigations of various nonequilibrium situations in liquid crystals.

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Vector-borne diseases; Tuesday, June 28, 14:30

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Man bites mosquito: human movement and the urban epidemiology of vector-borne disease

Some vector-borne diseases, such as dengue, thrive in urban environments. Eradication and control are significant public health challenges. The mosquito populations of metropolitan areas may be heterogeneously distributed in patches of high and low density. These mosquito population patches may remain stable over time, but people travel frequently and extensively, often in highly structured patterns. Here we investigate the role of this type of human movement in the epidemiology of vector-borne pathogens. We use a metapopulation model in which mobile humans connect static mosquito subpopulations. We focus on the impact of the size distribution of the mosquito subpopulations and the variability in people's travel patterns. We assess how these factors determine the contribution of each population subgroup to the basic reproductive number, the maintenance of the endemic equilibrium and long-term disease persistence. We conclude that hubs and reservoirs of infection can be places people visit frequently, even if only briefly. A few patches with large mosquito populations can make a city vulnerable to disease outbreaks. Variability in travel people's travel patterns can reduce this vulnerability, but may also enhance the rescue effect and so increase the persistence of endemic disease. Successful public health intervention may require identifying areas with large mosquito populations and a form of contact tracing that maps the recent movements of infected people to pinpoint the mosquito subpopulation from which they acquired the infection, and those to which they may have transmitted it.

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Immune cross-reaction and the phase structure of subharmonic oscillations in seasonal SIR models

SIR type epidemiological models forced by seasonal variation in transmission may exhibit subharmonic oscillations in which the epidemic period is an integer multiple of the forcing period. In models with two pathogen strains the occurrence and structure of these long period epidemic patterns is influenced by the immunological cross-reaction between the strains. Here we consider the impact of immunological cross-protection and cross-enhancement in an annually forced model for an acute infectious disease. We focus on the phase relationship between the epidemics of each strain. We find that most subharmonic solutions have an in phase structure. Out of phase structures only occur when the intensity of cross-protection is within a narrow interval. The underlying causes of this relationship are bound up in the way the phase structure amplifies or moderates the impact of the immune cross-reaction. Time series data for the prevalence of dengue virus and RSV show multi-annual epidemics of different subtypes with an out of phase pattern. Our model analysis suggests that these patterns are unusual, and likely to be sensitive to any changes in the immune cross-reaction between subtypes resulting from intervention or evolution.

Analysis of mathematical models for cancer growth and treatment, Part V; Wednesday, June 29, 11:00

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Cancer Modeling: Frameworks, Approaches, and Insights

As biomedicine becomes increasingly quantitative in scope and content and various challenges are encountered in the prevention, detection, treatment, and management of the cancers, mathematical models correspondingly assume importance in synthesizing and comprehending some of the dynamics underlying the behavior of cell aggregates and systems. Within this framework, diverse approaches are adopted for obtaining some models that describe the development and propagation of malignancy in the disease state. Various techniques are employed in analyzing the models and biomedical insights that they engender are discussed and placed in relevant context. Predictions offered by the models are then considered and conclusions are drawn.

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Modelling dengue fever epidemiology: complex dynamics and its implication for data analysis.

It is estimated that every year, there are $70 - 500$ million dengue infections, 36 million cases of dengue fever (DF) and 2.1 million cases of dengue hemorragic fever (DHF), with more than 20.000 deaths per year [**1, 2**]. In many countries in Asia and South America DF and DHF has become a substantial public health concern leading to serious social-economic costs. Mathematical models describing the transmission of dengue viruses has focussed on ADE effect and temporary cross immunity trying to explain the irregular behavior of dengue epidemics by analyzing the available data. However, no systematic investigation of the possible dynamical structures has been performed so far. Our study focuses on a seasonally forced (non-autonomous) two-strain model with temporary cross immunity and possible secondary infection, motivated by dengue fever epidemiology. We extend the previous studied non-seasonal (autonomous) model[**3, 4, 5**]. by adding seasonal forcing and low import rate of infected individuals, which is realistic in the dynamics of dengue fever epidemics. A comparative study between three different scenarios (non-seasonal, low seasonal and high seasonal with a low import of infected individuals) is processed and the results are shown and discussed. The extended models show complex dynamics and qualitatively a very good result when comparing empirical DHF and simulation. We discuss the role of the seasonal force and import of infected individuals in such systems, the biological relevance and the implications of the new results in the analysis of the available dengue data [**6**].

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Fractals and Complexity II; Wednesday, June 29, 17:00

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Fractal Dimension of Anal Intraepithelial Neoplasia (AIN)

AIN is a precancerous condition that is interrelated to infections by human papillomaviruses (HPV) and HIV. The histological classification of AIN is getting more and more important, due to increasing HPV infection rates throughout human population. Distinct grades of neoplasia are known, whereas high grades indicate a high risk for a tumor progression. Nevertheless, the grading diagnosis of histological slides is not always clear because of varying subjective conditions. In addition to subjective diagnoses, quantitative classification methods would be attractive but sophisticated solutions have not quantitatively been developed so far. Therefore, this study intends to evaluate digital images of AIN tissues by incorporating nonlinear morphological analysis. AIN tissues were H&E stained and digitally photographed with a standard microscope. Three distinct grades were diagnosed by a well trained pathologist in order to get a reference. The fractal dimensions of the images grey value landscapes using Fourier transformation were calculated and compared to the subjective diagnoses. Distinct grades of AIN led to distinct and well separated values of the fractal dimension. Higher grades of AIN yielded higher values of the fractal dimension. The conclusion is that fractal geometry is well suited for the diagnosis of AIN. The fractal dimension reflects the roughness of the images grey value distribution and is in accordance with the grading. Therefore, the fractal dimension is a quantitative value that may routinely support subjective diagnoses.

Keywords: intraepithelial neoplasia, image processing, fractal dimension, Fourier transformation

Information, human behaviour and disease; Saturday, July 2, 11:00

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Risk perception and 2009 H1N1 pandemic influenza spread in Italy

In Italy, the 2009 H1N1 pandemic influenza spread in a peculiar way: after an initial period characterized by a slow exponential increase in the weekly H1N1 incidence, a sudden and sharp increase of the growth rate was observed. Were behavioral changes spontaneously performed by the population responsible for such a notable pattern? In order to answer this question, a mathematical model of influenza transmission is proposed and validated. The performed investigation, based on model fit to epidemiological data and on the analysis of antiviral drugs purchase, reveals that an initial overestimation of the risk of infection during the early stage of the epidemic, possibly induced by the high concern for the emergence of a new influenza pandemic, results in a pattern of spread compliant with the observed one. This study suggests that individual choices may have driven the H1N1 dynamics in Italy during its initial phases and that they can drastically affect the spread of future epidemics, by altering timing, dynamics and overall number of cases. In conclusion, to correctly inform public health decisions, spontaneous behavioral changes cannot be neglected in epidemic modeling.

Bioinformatics and System Biology; Wednesday, June 29, 14:30

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Automatic generation of mathematical models of molecular-genetic systems

Mathematical models of molecular-genetic systems are based on the information about the structural and functional organization of gene networks and their dynamic properties that disseminated over hundreds and thousands of scientific papers. The problem arises of data comparison and analysis of non-uniformed experimental data, analysis of cause-and-effect relations between molecular structure, dynamics and phenotypic features of molecular-genetic system, and software development for automatic generation of mathematical models, storage of creating models in the database and their numerical analysis. In the context of solving some of the above mentioned problems we have developed an integrated computer system and models database that do not only render automatically the process of mathematical models reconstruction based on the structural and functional organization of gene networks but also implements original approaches and algorithms to modeling and studying molecular-genetic systems. The examples of using of the system are demonstrated on a modeling of some gene regulatory networks.

Population Genetics; Friday, July 1, 14:30

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Local adaptation under diversifying selection: A two-locus migration- selection model

A population-genetic model of local adaption in discrete space and time is studied. We model a population inhabiting two discrete demes with gene flow between them. Genetic drift is ignored as we assume that the population size is large. We consider two linked loci under selection and assume that the environment favors alternative alleles in the two demes. An important interpretation of the model is in terms of a quantitative trait that is under directional selection acting in opposite direction in the two demes. The trait is assumed to be determined additively, i.e., without epistasis, by two loci that may exhibit dominance. Thus, essentially, disruptive selection acts on the trait. This scenario allows us to answer interesting questions on local adaptation and the maintenance of genetic variation. We derive explicit results for the existence and amount of polymorphism in several limiting cases such as weak migration, weak selection, tight linkage, and free recombination. In particular, we present informative approximations of well-known measures of linkage disequilibrium and investigate the consequences of linkage and dominance on local adaption and genetic variation.

References.

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Poster Session; Friday, July 1, 20:00

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A Mathematical Model of Cleavage

In the present paper, we propose a mathematical model of cleavage. Cleavage is a process during the early stages of development in which the fertile egg undergoes repeated division keeping the cluster size almost constant. During the cleavage process individual cells repeat cell division in an orderly manner to form a blastula, however, the mechanism which achieves such a coordination is still not very clear. In the present research, we took sea urchin as an example and focused on the diffusion of chemical substances from the animal and vegetal pole. By considering chemotactic motion of the centrosomes, we constructed a mathematical model that describes the processes in the early stages of cleavage.

For example, in a sea urchin, the 1st cleavage and the 2nd cleavage happen along a field including an animal pole and a vegetal pole (meridional cleavage). This detects the concentration gradient of a certain chemical substance from the animal pole to a vegetal pole, and is considered to use for the determination of a cleavage plane. The 3rd following cleavage is a field which intersects perpendicularly with the 1st and the 2nd cleavage plane. However, if it inserts with glass and pressure is put and changed from two poles, it is known that the 3rd cleavage will turn into a meridional cleavage. It has suggested that the determination of a cleavage plane is not necessarily decided only by distribution of a chemical substance, and receives influence in a dynamic factor, a geometric factor, etc. from this. Cell division may think that it is prescribed by the aster. Normal division takes place, when one pair of asters exist in one cell, and cleavage does not happen without an aster. When four asters exist in a cell, being divided in four is reported. The centrosome located at the center of an aster determines the position of an aster. In order to form one pair of asters, it is required to divide a centrosome in two and to arrange it in advance of it, in a suitable position. As mentioned above, it turns out that the decisive role is played when the position of the centrosome which has opted for arrangement of the aster determines the geometry of cell division. Well then, how does this centrosphere move? The microtubule has connected with the centrosome and the aster is constituted. By work of a duplication region microtubule, an aster is repelled with another aster. Furthermore, the spindle could maintain a fixed distance within a cell, in order for an aster microtubule to receive restitution also

from a film. However, only in such assumption, the directivity of division of an egg does not become settled. Then, we assumed that the factor of the diffusion which exists in an animal pole and a vegetal pole exerted taxis on a centrosphere. We did the numerical computation of the directivity and the position of a spindle from the form and the diffusion field of the egg. As a result, it found out that the convexity of a concentration gradient can determine the directivity of cell division. We introduce the details about this research.

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Mathematical modeling and simulations of angiogenesis II; Wednesday, June 29, 11:00

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A flow-coupled phase-field model of tumour-induced angiogenesis

We present a first attempt to formulate a biophysically motivated model of structural vascular adaptation and angiogenesis. In several models of angiogenesis so far, the model of vascular structural adaptation being used is the one proposed by Pries, Secomb and co-workers. This model was proposed for modelling blood flow in rat mesentery and, therefore, is unlikely to be an accurate model for tumour vasculature. We discuss a model of vascular adaptation based on a biophysical (including elasticity, surface tension, etc) description of the response of capillaries to increased demands of blood flow.

Cancer; Tuesday, June 28, 14:30

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Regulation of Tumour Intracellular pH: A Mathematical Model Examining the interplay between hydrogen ions and lactate

Non-invasive measurements of pH have shown that both tumour and normal cells have intracellular pH (pHi) that lies on the alkaline side of neutrality (7.1-7.2). However, extracellular pH (pHe) is reported to be more acidic in some tumours compared to normal tissues. Many cellular processes and therapeutic agents are known to be highly pH dependent which makes the study of intracellular pH regulation of paramount importance. We thus develop a mathematical model that examines the role of various membrane-based ion transporters in tumour pH regulation, in particular, with a focus on the interplay between lactate and H+ ions and whether the lactate/H+ symporter activity is sufficient to give rise to the observed reversed pH gradient. Using linear stability analysis and numerical methods, we are able to gain a clear understanding of the relationship between lactate and H+ ions. We extend this analysis using perturbation techniques to specifically examine a rapid change in the H+ ions concentrations relative to lactate. We finally perform a parameter sensitivity analysis to explore the solution robustness to parameter variations. An important result from our study is that a reversed pH gradient is possible but for unrealistic parameter estimates-pointing to the possible involvement of other mechanisms in this phenomenon such as acidic vesicles, lysosomes, golgi and endosomes.

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Within-host parasite cooperation and the evolution of virulence

Infections by multiple genotypes are common in nature and are known to select for higher levels of virulence in some pathogens. It has been argued that for parasites whose virulence is determined by the production of public goods, such co-infections can select for lower levels of virulence. However, this prediction is rooted in a perspective that neglects epidemiological feedbacks. Here, we analyse the case of parasites producing a public good, for example siderophore-producing bacteria, using a nested model that ties together within-host and epidemiological processes. Making the epidemiology explicit with an SI model reveals that the current prediction that co-infection should select for less virulent strains for public-goods producing parasites is only valid if both parasite transmission and virulence are a linear function of parasite density. If there is a trade-off relationship such that virulence increases more rapidly than transmission, or if virulence also depends on the total amount of public goods produced, then co-infections should select for more virulent strains. This suggests that theoretical or empirical studies that seek to determine optimal virulence within a single host may not be representative of the selection pressures faced by parasites at the population level. At the same time, it underlines the importance of including epidemiological processes when studying the evolution of infectious diseases.

Mechanical Models of Movement and Growth of Cells and Tissues II;
Wednesday, June 29, 17:00

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Mechanical feedback drives cell polarization, adhesion and migration

Besides frequently studied regulatory pathways for spatial assembly of molecular motor molecules and cell-cell/matrix adhesion proteins, cf. [1], mainly responsible for the functioning of cell migration and tissue formation are primary biophysical "actors" such as mass flow, traction force, tension and pressure. Their dynamics determine the processes of cell deformation and translocation as well as cell-cell cohesion.

As basis for a most simple mechanical model of single cell motility we use a two-phase "reactive, viscous and contractive fluid" continuum model, written as a hyperbolic-elliptic PDE system of Navier-Stokes type. This model is able to reproduce the observed chaotic dynamics of actin/myosin cluster formation [2]. Then we combine it with a suitable system of diffusion-transport-reaction equations for free and bound myosin dimers and integrin adhesion sites [3].

Numerical simulations of two- and one-dimensional model variants reveal spontaneous and induced front-rear polarization and, subsequently, directional persistence of cell migration. Thereby we demonstrate, how these experimentally observed phenomena of cell motility can be traced back to an interaction of different biophysical and biochemical mechanisms such as cell edge protrusion, adhesion site maturation and force-induced integrin-bond disrupture.

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Heart rate dynamics: models and measures of complexity (part II);
Wednesday, June 29, 17:00

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Time series models for healthy people and patients with LVSD

The aim of the talk is to discuss time series models which are found as characteristic for two groups interesting for cardiology. ARIMA models with GARCH for residuals of ARIMA or squared residuals of ARIMA were fitted to RR intervals of 24h ECG Holter monitoring in group of 50 normal subjects without past history of cardiovascular diseases (average age of 53 10yrs). Specific subclass od ARIMA models were fitted to RR intervals of 24h ECG Holter monitoring in group of 48 patients (average age of 57 10yrs) with LVSD.

Heart rate dynamics: models and measures of complexity (part I);
Wednesday, June 29, 14:30

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An overview of permutation entropy

Permutation entropy was introduced in 2002 by Bandt and Pompe as a complexity measure for time series. Roughly speaking, permutation entropy replaces the probabilities of length-L symbol blocks in the definition of Shannons entropy by the probabilities of length-L ordinal patterns, each pattern being a digest of the ups and downs of L consecutive elements of a time series. Since then permutation entropy itself, along with different tools based on ordinal patterns, have found a number of interesting applications. To mention a few: Estimation of metric and topological entropy, complexity analysis of time series, detection of determinism in noisy time series, recovery of control parameters in symbolic sequences of unimodal maps, and characterization of synchronization. In all these applications, computational efficiency and robustness against observational noise are a crucial advantage.

The first part of the talk will be a review of the basics of permutation entropy. In the second part, the focus will be on applications to the analysis of biomedical series. In particular, we expect to report on work in progress in this field.

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Evolutionary Ecology; Wednesday, June 29, 11:00

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Modelling the outcome of climate change driven invasion: effects of apparent competition on the resident and invasive forest herbivore population dynamics.

Invasive species can have profound effects on the resident community via indirect interactions. Particularly, forest insect herbivores are known to be able to affect the invaded ecosystems by trophic interactions. Of the indirect mechanisms, apparent competition is a highly plausible but less frequently studied structuring phenomenon in terrestrial herbivore communities. Nevertheless, surprisingly few studies have been made of apparent competition in the context of invasive insect species. The tendency of long periodic cycles in herbivore population dynamics can make the observations of the indirect effects difficult using experimental setups. Furthermore, dynamic monophagy in established communities may prevent the observations of the effects of apparent competition on the community. However, the ongoing invasions of non-native species into new environments create a stage to observe apparent competition before adaptation obscures the interactions. Modelling invasions based on real invader-resident communities can therefore be of particular help when determining the undetectable and long term effects of invasive species.

The winter moth, a cyclic foliage feeding geometrid moth, has expanded its outbreak range during recent years due to warming winter temperatures. The mountain birches in the new invaded areas (the dominant green leafed tree in these areas) have previously been defoliated on a 9 to 10 year basis by the resident autumnal moth. The autumnal moth itself is able to cause drastic foliage loss in the mountain birch forests occasionally resulting in vast tree deaths. The new invader, the winter moth, has already been observed to be capable of total forest defoliation of similar magnitude. The two species share, in addition to the host tree, generalist predators and parasitoids in these Fennoscandian areas. Asymmetric preference at both parasitism and predation rates has been recently observed. In order to fully see the consequences of asymmetric effects of natural enemies on the 9 to 11-year population cycles, a modelling approach was called for. We were especially interested in, are these asymmetries able to cause asynchronous population cycles as seen in the area of sympatric occurrence. In addition, the long term effects of the invasion on the resident community are of particular interest, since recent evidence shows that winter moths are interacting in several ways with the local community and further range expansion of this forest pest does not seem to be restricted by neither abiotic nor biotic interactions.

We used empirical data from the recent invasion of the cyclic winter moths in northern Fennoscandia as a starting point and modelled the outcome of observed short term asymmetric effects via generalist predators and parasitoids on the long term population dynamics of the invasive winter and resident autumnal moths. Adaptive dynamics theory was used and invasion of the winter moth into the resident community was modelled. Based on the results, apparent competition and asymmetries in the effects of generalist predators are able to produce the observed asynchronous cycles. However, instead of evolutionary branching resulting in evolutionary stable coexistence of the two species, the system experiences cycles of evolutionary branching and extinction. Furthermore, independent of the modelled dynamics, the invasive species was observed have the potential to inflict drastic changes in the mountain birch community.

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Mathematical modeling of the spatio-temporal dynamics of aphid-paraistoid-plant-virus interactions

Aphids cause considerable damage to agricultural crops, mainly due to their ability to transmit a variety of plant viruses. Understanding the underlying processes that contribute to plant disease dynamics and how to contain the spread of disease requires a combination of biological and theoretical study. The theoretical undertaking requires not only an analysis of the temporal dynamics of the system, which has been the focus of previous work, but also an analysis of the spatial dynamics. Environmental stochasticity operates both spatially and temporally and is likely to influence aphid population processes. As a result, disease transmission by aphids might be influenced by factors acting in addition to density-dependent processes.

To construct a realistic model of an aphid-natural enemy-plant-virus system, we are developing a spatial individual-based model of the aphid *Macrosiphum euphorbiae* on potato plants. Focus is on the dynamics of the summer asexual aphid populations since aphid outbreaks occur when plant material becomes abundant. Individuals move randomly and/or via chemotaxis on a 2-dimensional domain representing one or more plants. We take into account both parasitoid wasp (e.g. *Aphidius ervi*) and predator (e.g. syrphid larvae, coccinellids) natural enemies. Environmental stochasticity is incorporated into the model by changing variables such as patch quality, temperature and light intensity. Parameter estimates for the model are obtained from experimental quantification of population processes in aphids that harbour particular secondary bacteria or that are free of secondary symbionts. A number of aphid clones have been established in culture and their secondary bacteria status confirmed using diagnostic PCR. The individual-based model is used to assess how secondary endosymbionts affect aphid population dynamics, vector capacity and trophic interactions. Previous work on host-parasitoid models (Preedy et al. 2007; Pearce et al. 2006; Schofield et al. 2005) suggests that a broad-range of dynamics including spatio-temporal heterogeneity and chaos can emerge from these systems and similar results are observed in our model.

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Population Dynamics; Wednesday, June 29, 17:00

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Interspecific competition models derived from competition between individuals

Population dynamics, including the dynamics of interacting populations, result from behavior of individuals comprising populations and interactions between them. It is important to reveal relationship between population dynamics and local interactions between individuals, and an effective way to do so is deriving population models from first principles. In a previous study, I derived various discrete-time population models for a single species from first principles, and provided a unified view to understand how various population models interrelate with each other. Extending the study above, this study aims at deriving discrete-time interspecific competition models, which describe dynamics of competing two populations, by considering competition for resource between individuals and spatial distribution of individuals. Competition type of each species is assumed to be scramble, contest or an intermediate of these two types. Interspecific competition models are derived for various combinations of the competition types of the two species and several types of spatial distribution of individuals. Furthermore, a general interspecific competition model that includes various competition models as special cases is derived for each distribution of individuals. Finally, I discuss coexistence of two species, based on competition models derived for contest vs. scramble case, and show that the ease of coexistence depends greatly on the type of spatial distribution of individuals.

The emergence of resistance in cancer using mathematical modelling;
Saturday, July 2, 08:30

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Regulating drug resistance: Evolution and the double-bind

Treatment of cancer cell populations with chemotherapeutic drugs is nearly always associated with the onset of resistance, where minor populations of cells escape from therapy and continue to proliferate and lead to cancer recurrence and subsequent treatment failure. Resistance is also a common issue in the ecology field, where insects become resistant to chemical pesticides after repeated treatments. However, unlike the oncology field, the ecologists have used other strategies to control insect populations. Specifically, by using biological agents such as predators, parasites, pathogens, and parasitoids control has been achieved without any resulting resistance. One possible mechanism for the success of such biological agents is an evolutionary double-bind, where in order to adapt to a given treatment an insect pays the high cost of becoming significantly less fit in comparison to the unadapted population. Here we present an Evolutionary Game Theory (EGT) model to investigate such a double-bind approach in the treatment of cancer. Specifically, we use EGT to better understand the use of combination chemotherapeutic strategies when mono-therapies ultimately always lead to drug resistance.

Mathematical models of evolutionary dynamics of infectious agents;
Tuesday, June 28, 17:00

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The final size of an epidemic with two competing strains

The competition between two pathogen strains during the course of an epidemic represents a fundamental step in the early evolution of emerging diseases as well as the antigenic drift process. The outcome however, depends not only on the epidemic properties of the two strains but also on the timing and size of the introduction, characteristics that are poorly captured by deterministic mean-field epidemic models. I will present a framework that allows us to describe those aspects of the competition that can be determined from the mean-field models giving the range of possible outcomes that could be observed in an epidemic with two cross-reacting strains.

Population Dynamics; Wednesday, June 29, 08:30

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Mathematical model of Wood Frog Population

The aim of this work is to embed into a mathematical model the Wood Frog, *Rana sylvatica*, population data collected by Berven, [3], over more than 25 years. The life cycle of the frogs includes aquatic and terrestrial phases, and the competition in each phase is for different resources. Hence, we deal with separate populations, each one providing the new recruits for the other one, see, e.g., [1]. In the case of the Wood Frogs, there are three main stages of development where the individuals compete for different resources. The toads live in the water, and following their metamorphosis they become juvenile frogs, not yet large enough to reproduce. The third stage is of mature egg laying frogs. The populations in these three stages of development have different dynamics. Hence, they are modelled with different mathematical tools, which makes assembling the model an interesting mathematical problem. Due to the seasons in Michigan, the eggs are laid over a short time period and the juveniles emerge from the water more or less the same time, so, we model these two events by impulses, [4]. The success of the metamorphosis depends mainly on the size of the toads. Hence, the size distribution of toads at the time of metamorphosis determines both the number of juveniles and their initial size. Similarly, the transfer from juvenile to adults depends mainly on the size of the frogs. It does not occur at a fixed time, and the juveniles who do not grow sufficiently to mate need to wait for a year before laying eggs. The growth of the toads and the juveniles in size is not uniform across the population and depends on external factors, as well. It is modelled using PDEs for the density size distribution at time t. The death and fertility rates of mature frogs are not related to their age. So their population is assumed to be homogeneous and is modelled by an ODE. Thus, the derived model comprises a system of ordinary and partial impulsive differential equations. The mathematical analysis of such a model can be complicated, see, e.g., [1]. Our analysis and numerical simulations focus on the global properties of the model as a dynamical system, as in [2]. The results show that the model may have a unique solution that converges to a stable periodic cycle.

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Bridging Time Scales in Biological Sciences; Saturday, July 2, 14:30

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Hierarchical approaches for the investigation of biomolecular recognition

One of the major bottlenecks for the computational description of biological processes on the molecular and atomistic level is the limitation in the time scale and system size which can be treated by the existing theoretical methods. Much research has been devoted to this problem and many advanced biophysical methods have been developed for this task. Most of them are, however, very time consuming and not applicable to applications for which very complex systems must be investigated and if many different situations must be investigated simultaneously, like in computational drug or protein design. To be able to deal with such applications, we develop hierarchical models, which combine very efficient, discrete methods from computational biology with more demanding continuous biophysical approaches. In the presentation an overview over the methodology will be presented together with examples for their practical applications.

Mathematical Models in Eco-epidemiology II; Wednesday, June 29, 11:00

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Travelling wave solutions for integro-differential equations from population dynamics

Our talk concerns some classes of integro-differential equations from population dynamics, where the integral term describes the nonlocal consumption of resources. Both monostable case and bistable case are investigated. Fredholm property of the corresponding linear operators can help to prove the existence of travelling wave solutions. For some models, we can prove the existence of traveling waves only when the support of the integral is sufficiently small. In this case, the integro-differential operator is close to the differential one. One uses a perturbation method which combines the Fredholm property of the linearized operators and the implicit function theorem. For large support, numerical simulations show the propagation of periodic travelling waves. For some other models, Leray-Schauder method can be applied. This implies the construction of a topological degree for the corresponding operators and the establishment of a priori estimates for the solution. Some biological interpretations follow from this study.

Regulatory Networks; Tuesday, June 28, 17:00

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Identifying the core of biochemical networks: complexity reduction preserving dynamical behavior

Biochemical systems are often very complex. The complexity stems from both the number of components and the intricate interactions that may occur. When a mathematical model is used to describe such a system, its complexity may lead to a very long computing time, non-identification of parameters, and most importantly may hinder us in understanding the underlying mechanism of the biochemical system. Therefore, effective methods are required to capture the key components and interactions of the system.

We present a novel and efficient reduction method to identify the core of a biochemical system. This new method is based on the exploration of the so-called admissible region, that is the set of parameters for which the mathematical model yields the required output. For illustrational purpose, the reduction is first applied to a very small artificial network, consists of just three nodes and three parameters. Our method reveals that there are many parameter sets that give rise to similar dynamical behavior, which indicates, despite its simplicity, the system is not identifiable. Next, the reduction is applied to an epidermal growth factor receptor (EGFR) network model. It turns out only about 62% of the network components are required to yield the correct response to epidermal growth factor (EGF), whereas the rest could be considered redundant. Furthermore, although parameter sensitivity is expected to give an indication to the redundancy of a parameter, we found that a highly sensitive parameter is not always necessarily important, whereas a slightly sensitive parameter is not always removable. This implies that parameter sensitivity on its own is not a reliable tool for model reduction.

Poster Session; Friday, July 1, 20:00

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A mathematical model for assessing the spraying as a vector control strategy for Chagas disease in Colombia

Chagas disease or American trypanosomiasis is a neglected disease in Latin America, which means that attacks people already affected by poverty and inequality. Over time its manifestations lead to arrhythmias and heart failure, and in some cases can cause death. In Colombia this parasitic disease, that affects 1.2 million people (with a population of 3 million more at risk of contracting it), is transmitted by the insect Rhodnius prolixus in a cycle in which wild animals, domestic animals and humans, act as reservoir. While research aimed at combating the disease in the country has shown progress in different fields, one of the most important questions to be answered is how efficacious and efficient are the control interventions. Little is known about them and nowadays there is no quantitative tool that allows for prediction, so that can be used for control and prevention. The purpose of this work is to propose a mathematical model for describing the population dynamics of the vector and identifying different scenarios that might contribute to the spread of the disease. In particular we want to explore the effects of insecticide house spraying. Our approach consists of a system of nonlinear differential equations that describes the rate of change of the susceptible and infected classes of three populations: domiciliated vectors, domestic animals and man. We present an analytical approach to get the basic reproductive number, the steady states and the equilibria as well as an implementation of the model for computer simulations. In addition, we show alternatives to reduce the domiciliated vector population. We expect that these preliminary results can be useful in the reduction of uncertainty of control strategies at local level, and thereby improve decision making about preventive management of the disease.

Game theoretical modelling and optimization in evolution and ecology I;
Tuesday, June 28, 11:00

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In which currency are paid payoffs in evolutionary games?

In the standard approach to evolutionary games and replicator dynamics, differences in fitness can be interpreted as an excess from mean malthusian growth rate in the population. In the underlying reasoning, related to the analysis of "costs" and "benefits", there is a silent assumption that fitness can be described in some kind of "units". However, in most cases these units of measure are not explicitly specified. Then the question arises: are these theories testable? How can we measure "benefit" or "cost"? It would be useful to describe and justify strategic "costs" versus "benefits" reasoning in the terminology of demography, because basic events that shape outcomes of natural selection are births and deaths. In our talk, we will present the consequences of such an explicit analysis of births and deaths in an evolutionary game theoretic framework.

We will investigate different types of mortality pressures, their combinations and the possibility of trade offs between mortality and fertility. We will show that within this new approach it is possible to model how strictly ecological factors, which seemed neutral in classical theory, can affect outcomes of the game. For example we will show that density dependence, affecting the mortality of newborns, can seriously change the outcome of the game.

We will illustrate this in the case of an example game, the Hawk-Dove Game. Reformulated in terms of our new approach, this game shows new details and produces new biological predictions. The solutions of the new model are less abstract; instead of the condition that "cost" should exceed "benefit" we obtain results in terms of the fractions of dead (that can be interpreted as probability of death) individuals and per capita number of newborns, which can be easily estimated from data. We show that in the classical approach to tradeoff analysis, "cost" caused by increased mortality, can in some cases depend on the value of expected benefit interpreted as an increase in fertility.

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Bioinformatics and System Biology; Wednesday, June 29, 17:00

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Transaction costs and structure formation: an economic approach to biological systems

We harness insights from economics and information theory and apply them to biological systems. Using information theory as a conceptual bridge between biology and economics, biological and economic systems can be analyzed and compared, thereby paving the way towards new models in bioeconomics. Driven by the interplay of replication, variation and selection, systems in biology and economics evolve towards ever more refined information architecture, thus lowering transaction costs in general and information costs in particular. Hence, transaction costs drive structure formation. To illustrate this principle, we present a wide range of examples from biology and economics, and explain the following concepts: First, the role of entropy in biological and economic systems and three applications: the Kelly criterion, which relates the Shannon information entropy to the limits of biological and economic growth; structure formation as local entropy reduction; and the maximum entropy principle. Second, the role of higher-order information and Schelling points in biological and economic systems: the occurrence of Schelling points, or focal points, can transform information of first and second order into information of higher order as well as common knowledge and hence fundamentally change the information architecture of a system. Third, bounded rationality: due to the limitations of computational capacity, biological and economic systems face fundamental tradeoffs when processing information. Fourth, strategic evolution and the adaptive market hypothesis. And fifth, the importance of non-equilibrium: escaping local maxima in biology and economics. Utilizing these concepts and comparing the information architecture of biological systems and economic systems allows to determine the potential of applying economic theory to biology, as well as the limits of such applications.

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Comparative model analyis of the Calvin-Benson cycle

Carbon fixation, especially the Calvin-Benson cycle (CBC), is the initial pathway for energy storage in carbohydrate products in C_3-plants. Understanding the interplay between regulation and efficiency of CBC and its end-products (*e.g.*, sucrose, starch and amino acids) requires the development of mathematical models which can explain the observed dynamics of metabolic transformations. Here, we address this question by comparing and ranking the existing models of the CBC to determine the set of best-performing models.

The importance of the CBC and the related pathways for the increase of plant biomass has already resulted in 15 models with various level of detail. The existing models can be categorized biologically based on: (1) chosen boundaries, *i.e.*, models of CBC including or excluding end-product synthesis, (2) details of reaction modeling, *i.e.*, leaf, cell, or compartment-level, and (3) hierarchy of kinetics **[4]**, translating the model structure into mathematical equations amenable to extensive analysis of spatiotemporal properties. Our focus is placed on mass action, Michaelis-Menten-like, equilibrium approximations, and special functions in conjunction with the regulation terms.

The ranking of the SBML-implemented compendium of models is carried out with respect to the following criteria: (1) stability analysis **[3]**, (2) sensitivity analysis, (3) ability to capture key features extracted from the data **[1]**, and (4) analysis of yield. The obtained scores are then combined through a comprehensive model ranking scheme, based on which the set of best-performing models is selected with regard to metabolomics data and detection of candidates for genetic engineering.

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Epidemics; Tuesday, June 28, 14:30

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The ratio of expectations distribution as an alternative to quasi-stationarity in stochastic biological models

Many stochastic systems, including biological applications, use Markov chains in which there is a set of absorbing states. It is then needed to consider analogues of the stationary distribution of an irreducible chain. In this context, quasi-stationary distributions play a fundamental role to describe the long-term behavior of the system. The rationale for using quasi-stationary distribution is well established in the abundant existing literature. The aim of this study is to reformulate the ratio of means approach which provides a simple alternative. We have a two-fold objective

i) to view the quasi-stationarity and ratio of expectations as two different approaches for understanding he dynamics of the system before absorption, and

ii) to investigate the possibility of using the ratio of expectations distribution as an approximation to the quasi-stationary distribution.

Both distributions are compared for some selected scenarios, which are mainly inspired in stochastic epidemic models. Previously, the rate of convergence to the quasi-stationary regime is taking into account in order to make meaningful the comparison.

Mathematical models of evolutionary dynamics of infectious agents;
Tuesday, June 28, 17:00

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Severe First and Mild Later: Temporal Strategies in Pathogen Evolution

Because pathogens replicate within hosts and transmit between them, selection takes place on multiple levels. There has been ongoing interest for more than two decades in trying to understand the conditions favoring the evolution of acute, highly transmissible infections, focusing on trade-offs such as the transmissibility-virulence trade-off and the invasion-persistence trade-off. Studies have shown that these types of trade-offs lead to intermediate pathogen attack rates. These earlier studies typically consider the evolution of a single trait under a defined trade-off. However, for some pathogens, the course of infection within the host is likely to be more complex, determined by more than a single dimension, opening the door for more complicated strategies related to disease severity. The protozoa Plasmodium falciparum (Pf), which causes the most severe type of malaria in humans, is one example of such a pathogen. During the course of an infection, Pf has the ability to express up to 60 different variants of surface proteins (PfEMP1) encoded by a family of var genes, which are recognized by the host immune system and which also act as virulence factors.

In this talk we examine the role of temporal variation of life history traits during the course of an infection, and we ask whether the addition of a temporal dimension can assist in reducing the burden arising from multiple selective pressures. We allow the life history traits of different stages to evolve independently, and as a case study, we assume there is a trade-off between transmission and duration. To capture multiple selective pressures acting on the parasite, we consider invasion persistence trade-offs in terms of critical community size of hosts. We demonstrate that a composite strategy that is ordered in time and consists of a more transmissible stage at first, followed by a less transmissible one later, confers a higher fitness than any single, constant, strategy. These results are relevant to ordered expression in P. falciparum of severe vs. mild var genes, as well as for acute infections that are followed by milder symptoms in some bacterial pathogens.

Poster Session; Friday, July 1, 20:00

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Mathematical model of the mammalian circadian center as a many-body system of the limit cycle oscillators

In the present study, we propose a mathematical model of the mammalian circadian center, or the suprachiasmatic nucleus (SCN), which is described as a many-body system composed of limit cycle oscillators. Each oscillation unit in the SCN was described as a limit cycle oscillator based on a negative autoregulation of per genes by its protein product PER previously reported (Goldbeter 1995, Leloup & Goldbeter 1998, Kurosawa et al. 2002, Gonze et al. 2006). We adopted another assumption that oscillators interacted with each other only through a humoral factor, and ignored other possible neural interaction or network. Then, their nonlinear equations were reduced to the Stuart Landau equation forms (Kuramoto, 1996). Our present model was also constructed on the recent finding that most of oscillating neurons in the SCN shows damping under the isolated environment (Webb et al. 2009). Therefore, we assumed that most of oscillating neurons in the SCN were damping oscillators but have potential to generate limit cycle oscillators by appropriate external forces. In addition, we supposed a phase-dependent gate in the oscillators in the VLSCN which shut out the photic input to the SCN during the day, which had been recognized in the VLSCN of mammalians. We examined whether the model reproduced the asymmetrical resynchronization process associated with the abrupt shift of light: dark cycle (LD cycle; L:D=12h:12h). An abrupt shift of the LD cycle yielded internal desynchrony between VLSCN and DMSCN transiently which caused a jet lag syndrome (Nagano et al. 2003). The asymmetry appeared in the way of resynchronization; it took five days to restore synchronization after 10-hour delay and took more than 10 days after six-hour advance. The present model reproduced the asymmetrical expended time spent in resynchronization process after the rapid shift of the LD cycle. The model also reproduced the intrinsic phase wave shown in the SCN. The phase wave is propagated from the medial regions to the lateral regions in the SCN. By placing a small region containing short period oscillators (short period region: SPR: $\tau < 24h$) and remaining large region containing long period oscillators (long period region: LPR: $\tau > 24h$), the phase wave appeared, being initiated at SPR and propagated to LPR. Moreover, the phase response curve (PRC) generated from the present model by using the pulse-like input considerably corresponded to empirical PRCs obtained from locomotor activities of rats and mice.

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Migration processes of interacting cancerous cells: beyond the mean field approximation

One of the main aspects of studying diffuse tumors is understanding how they diffuse inside the hosting tissues and how fast they spread. To shed light on these issues, we use an approach based on a microscopical description of the cells' dynamics to reproduce the evolution at the meso-macroscopical scale. An example of a tumor is the glioblastoma which grows in the brain and is very invasive. The glioma cells of the glioblastoma interact with other cancerous cells exchanging small molecules and ions through very short links named gap junction connections [1]. In [2], the authors proposed a model in the framework of automaton for the migration of cancerous cells that takes into consideration gap junction type interactions. In [3], the hydrodynamic limit of the cells' diffusion equation in the mean field-approximation is found, and some differences with the numerical simulations are shown. Using the approach proposed in [3], we study and analyze the effects of the migration process of cancerous cells on the two-points correlation function. The cells move on a single occupancy hexagonal sites lattice with periodical border conditions and interact with the nearest neighbors. The interaction affects the motion of cells by imposing the condition of preserving at least one gap junction connection among the closest neighbors with a given probability. We show the continuous limit of the correlation function and the comparison between the theory and numerical simulations for different values of the cancerous cells' density and interaction parameter. The interaction introduces a short length correlation among cells that dynamically evolves toward stable values depending on the system variables. Numerical simulations show the stable condition differs from the uniform condition due to spatial inhomogeneity and clusters formation also in absence of sources and sinks.

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Glycosylation Networks in Tomato, Top-down and Bottom-up Inference Combined

Tomato (*Solanum Lycopersicum*) is a common element in human diet. In 2009, more than 140000 million tons of tomatoes were produced worldwide. Tomato fruit contains relatively large amounts of flavonoids. Flavonoids have recently gained growing interest due to their anticipated positive health effects as antioxidants. As is the case for many plant metabolites, flavonoids mainly occur in glycosylated form. Although it is widely accepted that glycosylation is of great importance to maintain metabolic homeostasis, the pathway leading to the diverse glycosides, and the specificity of the involved enzymes is not known. In this study, we combine experiments and mathematical modeling to infer the network governing flavonol glycosylation, and study its functioning in vivo.

Tomato seedlings are grown under different conditions, and flavonoid glycoside concentrations are measured for a number of consecutive days. To infer the flavonoid glycosylation network from the resulting time-series, we combine two different approaches. First, we make use of a top-down approach that has as starting point a priori obtained general biological knowledge of molecular reactions and metabolic pathways in plants. This knowledge leads to a number of candidate structures for the network. In a fitting procedure, we estimate the reaction rates in the model, formulated in terms of ordinary differential equations, by applying an iterative minimization method in order to match the model with the observations. The best fitting network is then selected.

In the bottom-up approach one directly infers the network structure from the data via a statistical approach. We explore a method that involves only simple matrix manipulations and standard statistics. In both frameworks we inherently exploit the time-series structure of the data. Because the data are noisy, it turned out difficult to identify the flavonoid network using either the top-down or the bottom-up approach separately. However, by combining both approaches we were able to obtain a reliable estimate of the network model for flavonoid glycosylation in spite of the presence of considerable noise.

Poster Session; Friday, July 1, 20:00

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On The Stability of the Steady-State Solutions of Cell Equations in a Tumor Growth Model

The stability of the steady-state solutions of endothelial, pericyte and macrophage cells equations in a mathematical model originally presented in Levine, H.A., et al., A mathematical model for the roles of pericytes and macrophages in the initiation of angiogenesis. I. The role of protease inhibitors in preventing angiogenesis, Math.Biosci., 168(1) 2000, 77-115, is studied. Trajectories near the critical points are drawn and the biological importance of the results are provided.

Epidemics; Thursday, June 30, 11:30

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Case detection rate: what can be estimated without prevalence surveys?

Case detection rate (CDR) defined as the proportion of incident cases of a disease that are detected (i.e. diagnosed and notified) is of great importance both for monitoring the epidemiological situation and for forecasting and operational research. Moreover, case detection rates are used as target indicators in political documents (for example, target 70% CDR for smear-positive tuberculosis had been set by the Millennium Development Goals [1]).

It is often stated that CDR is hard to estimate because it is calculated as the ratio of the routinely notified incidence to an estimate of full (unobserved) incidence, with the latter being very unreliable. In the field of tuberculosis, the usual recommendation is performing regular prevalence surveys to calculate incidence either directly or indirectly. But representative prevalence surveys are rather costly and often logistically complicated. The workarounds for the problem include using expert estimates of CDR [2] and analysis of long-term trends and interactions with HIV [3].

In the talk, presented will be a model that regards case detection and disease progression as competing processes, thus deriving a relationship between the intensity of case detection and the severity (or age) of disease at the moment of detection [4]. In many settings some kind of disease severity measure is available from the routine notification data, and so it is possible to estimate the CDR. For tuberculosis, such a measure may use data on smear microscopy, bacteriological tests, chest X-ray, and the physician's diagnosis.

This approach may be extended to incorporate individual socio-economical properties and their effect on individual case detection intensity [5]. The analysis of the data shows that the cases substantially differ in their availability for detection, with "social involvement" and sex being the most significant factors.

This result erects the question how much the heterogeneity of the population affects the models based on homogeneity assumptions – in this case, on evenly effective detection system. In fact, the model estimates CDR for the social strata readily available for case detection. This estimate alone may be a useful point indicator of practical efficiency of the case detection system. But with some support form prevalence studies (especially targeting the "ill-detectable" strata) it is possible to estimate CDR and incidence accurately for the whole population.

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Models in Spatial Ecology; Tuesday, June 28, 17:00

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The spatial dynamics of the diphenic planthopper

We study the spatial dynamics of a wing diphenic insect species (when two phenotypes can arise from the same genotype) where the size of wings can vary largely, from almost inexistent (brachypterous) to fully developed (macropterous).

Macropterous individuals are born only when the total density is higher than a certain value. This induces a density-dependent diffusion of the species.

We construct a stage structured (nymphs and adults) model, with adults further sub-divided in macropterous and brachypterous. Space is introduced explicitly by means of diffusion equations, with the diffusion constant of the macropterous subpopulation being much higher than the others.

We focus of the dynamics originating from an initially small and concentrated population, which is shown to expand, with macropterous individuals as predecessors of the other stages. The invasion front displays a particular form, originating from the stage-structure of the model.

Modeling physiological systems: model validation and experimental design issues; Wednesday, June 29, 11:00

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Mathematical modeling of glucose insulin system during hemodialysis using different dialysate glucose concentrations.

This talk we will presents sensitivity identifiably analysis of a mathematical model of glucose insulin system during hemodialysis based on minimal model. This model incorporates sufficient structure and complexity to allow for examining the metabolic action and regulation of glucose and insulin systems. The complexity of the model allows for the representation of a variety of modes and sites for action but at the same time the number of parameters renders the validation with accessible data limitation problematic. Subset selection techniques are employed to examine which parameters are mostly likely identifiable for a variety of potential sources of data on the state of the system.

Recent developments in the study of Lotka-Volterra and Kolmogorov systems; Saturday, July 2, 14:30

Stephen Baigent
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The curvature of carrying simplices for competitive Lotka-Volterra systems

The N dimensional totally competitive Lotka-Volterra equations have a Lipschitz invariant manifold that attracts all points in the first quadrant except the origin. For N=2 it is known that this manifold is either convex or concave, and for N=3 numerical evidence suggests that the curvature of the manifold cannot change sign. I shall discuss a new method for proving the N=2 case and also outline some recent progress towards understanding the N=3 case, including special cases where the manifold can be shown to be convex, saddle-like or a developable surface.

Poster Session; Friday, July 1, 20:00

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Computational analysis of the cell growth regulatory network of fission yeast cells

The rod shaped fission yeast cells grow only at their tip, unidirectional growth in G1 is followed by length extension also from the other end in G2. Microtubules are responsible for the proper localization of the growth zones at the tips and localized actin polymerization is needed for growth induction. Similar actin polymerization process in the middle of the cell is needed for cytokinesis. Several members of the molecular network that connect microtubule and actin dynamics to cell growth and cell division are identified and some of their interactions are also known, but these data do not give a complete picture of the system. After identifying the conserved regulatory molecules and their interactions in other organisms we perform network analysis on the predicted interaction network of fission yeast growth regulatory system to identify the key core components and the links that connect cell growth and cell cycle regulation. We are analyzing the networks also from bottom-up by creating computational models for the interactions of the core regulators of cell division and cell polarity.

Connecting microscale and macroscale models of cellular migration;
Tuesday, June 28, 17:00

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Corrected mean-field models for spatially-dependent advection-diffusion-reaction phenomena

In the exclusion-process literature, mean-field models are often derived by assuming that the occupancy status of lattice sites is independent. Although this assumption is questionable, it is the foundation of many mean-field models. In this work we develop methods to relax the independence assumption for a range of discrete exclusion process-based mechanisms motivated by applications from the cell biology literature. Previous investigations that focussed on relaxing the independence assumption have been limited to studying initially-uniform populations and ignored any spatial variations. These previous corrected mean-field models could not be applied to many important problems in cell biology such as invasion waves of cells that are characterised by moving fronts. Here we propose methods that relax the independence assumption leading to corrected mean-field descriptions of a range of exclusion process-based models that incorporate (i) unbiased motility, (ii) biased motility, and (iii) unbiased motility with agent birth and death processes. The corrected mean-field models derived here are applicable to spatially-variable processes including invasion wave-type problems. We show that there can be large deviations between simulation data and traditional mean-field models based on invoking the independence assumption. Furthermore, we show that the corrected mean-field models give an improved match to the simulation data in all cases considered.

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Breaking the symmetry: understanding Centrosomin incorporation in Drosophila centrosomes in order to study asymmetric division of neural stem cells.

A size asymmetry between the centrosomes in certain Drosophila stem cells is important for proper asymmetric cell division. How this centrosome size asymmetry is controlled is a key question in stem cell biology. It has recently been shown that differential rates of Centrosomin (Cnn) incorporation into centrosomes may lead to centrosome size asymmetry in Drosophila neural stem cells. Cnn forms a gradient in pericentriolar matrix (PCM) and live imaging combined with fluorescence recovery after photobleaching (FRAP) analysis has revealed that Cnn molecules first incorporate into the centre of the PCM and then spreads outwards throughout the rest of the PCM. In this work we propose a mathematical model composed of a coupled system of nonlinear reaction-diffusion type equations to explain the observed Cnn behaviour. We hypothesise that Cnn binds to its receptors near the centre of the PCM and is converted into a 'heavy' form which diffuses slowly as compared to cytoplasmic Cnn. Diffusion of heavy Cnn then creates a gradient in the PCM. Steady state analysis shows that heavy Cnn forms an exponentially decreasing gradient at steady state, which matches well with the experimentally observed Cnn gradient. Numerical simulations of the model also predict the FRAP kinetics of Cnn. Once we understand the mechanism of Cnn incorporation, we may be able to predict how this mechanism could be exploited to create centrosome size asymmetry in Drosophila neural stem cells.

Recent developments in the study of Lotka-Volterra and Kolmogorov systems; Saturday, July 2, 14:30

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Average conditions for permanence in N-species nonautonomous competitive systems of PDEs

In this talk we consider a nonautonomous systems of PDEs

$$\begin{cases} \dfrac{\partial u_i}{\partial t} = \Delta u_i + f_i(t, x, u_1, \ldots, u_N)u_i, & t > 0,\ x \in \Omega,\ i = 1, \ldots, N \\ \mathcal{B}u_i = 0, & t > 0,\ x \in \partial\Omega,\ i = 1, \ldots, N, \end{cases}$$

where Ω is a bounded domain with sufficiently smooth boundary $\partial\Omega$, Δ is the Laplace operator on Ω, and $\mathcal{B}$ is the boundary operator of the Neumann or Dirichlet type. Applying the Ahmad and Lazer's definitions of lower and upper averages of a function we give average conditions for the permanence of the system. In the Neumann case we also give a sufficient condition for the system to be globally attractive.

Poster Session; Friday, July 1, 20:00

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A Combined Experimental and Mathematical Approach for Molecular-based Personalization of Irinotecan Circadian Delivery

Irinotecan is an anticancer drug which is currently in use for chemotherapy against colorectal cancer. Its pharmacokinetics (PK- what the cells do to the drug, e.g. metabolization, transport), and pharmacodynamics (PD- what the drug does to the cells, e.g. DNA damage) are largely influenced by 24-hour-period rhythms of certain proteins including the drug target Topoisomerase I, the activation enzymes (Carboxylesterases), the deactivation enzymes (UGT1A1,UGT1A9) and the ABC transporters which are responsible for the efflux of the drug. Indeed circadian rhythms have been described for most of those proteins both in humans and in mice. A chronomodulated scheme of administration for Irinotecan is already used in clinic but recent findings highlight the need of personalized chronotherapeutics delivery pattern according to the patient gender and genetic background ([1]). Within the European project TEMPO, Irinotecan chronotoxicity has been studied in mice and three classes have been determined with regards to Irinotecan best circadian hour of administration (i.e. the hour which induces the minimal toxicity). Our modeling approach aims at identifying molecular biomarkers which could discriminate between the classes and at designing optimal chronomodulated infusion scheme for each of them. A whole body physiologically-based PK-PD model has been built starting from a previous mathematical model designed thanks to a cell culture study ([2]) . Parameters have been estimated for each mouse class by fitting available data on tissular PK for two different circadian hours of administration and on circadian rhythms of relevant proteins. Validation of the mathematical model by comparing its output with independent experimental data is in progress. Then the parameter set will be compared in order to find differences between the classes and optimization algorithms will be applied to the model to design theoretically optimal chronomodulated scheme of administration. This study in mice may give a hint for determining molecular biomarkers which should be measured in patients in order to tailored chronomodulated infusion schemes.

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Structure and Dynamics of Biochemical Reaction Networks II; Tuesday, June 28, 17:00

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Monotone dynamics in chemical reaction networks

Proving that the allowed dynamics of certain classes of chemical reaction networks (CRNs) is necessarily simple regardless of the kinetics is both of interest in itself, and potentially provides insight into how more complex dynamics can arise. Here, recent theory on monotone dynamical systems is applied to demonstrate local and global stability of equilibria for a class of CRNs. The stability results arise from the interaction of two structures which occur frequently in CRNs: preservation of a partial order and the existence of constants of motion. The class shown to have strong stability properties is defined via the network structure, with only weak assumptions on the reaction kinetics. The key conditions on the network are (i) that the stoichiometric matrix can be factorised in a certain way, and (ii) that an associated digraph is strongly connected.

Plants, growth and transport processes II; Tuesday, June 28, 14:30

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Modelling hormone-regulated plant root growth

Researchers at the Centre for Plant Integrative Biology are using systems approaches to investigate plant root growth and development. In this talk, we present a multiscale model that describes how the hormone GA regulates growth in the root elongation zone. The model includes: (i) hormone diffusion and dilution, (ii) a genetic regulatory network that details how the hormone affects the DELLA proteins, (iii) a description of how the DELLA proteins influence the cell-wall remodelling enzymes, and finally (iv) a submodel linking cell-wall remodeling to growth. Using detailed morphological measurements, our model shows that cell growth causes significant hormone dilution which can led to spatial variations in the key growth-regulating proteins. By modelling this feedback loop, we provide understanding of the phenotypes observed in wild-type and mutant plants.

Poster Session; Friday, July 1, 20:00

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Cell migration inspired design of crawling robots

Animal tissue cells (as fibroblasts and keratinocytes) are utilising a unique principle of locomotion: the adhesive cell migration for crawling on a fixed substratum. It is a higly complex process involving the cytoskeleton and multiple regulation mechanisms [1]. The moving cell is polarised as a result of asymmetric cytoskeleton modifications by assembling and disassembling microfilaments [2]. Transmembrane glycoproteines such as integrins adhere to the substratum and are dynamically coupled to actin filaments inside the cell, which are cross-linked to myosin dimers. By exertion of contractile stress this actomyosin complex is able to transfer a traction force onto the substratum, enhancing cell polarisation: at the front, 'soft' centripetal forces pull the cell body forwards, whereas in the rear, 'stiff' centripetal forces mechanically disrupts the cell from the substratum [3].
This project is using the basic physical principles causing the propulsion during cell migration as a bio-inspired approach for designing a new form of crawling robot locomotion. The aim is not to copy the cell migration mechanism itself but rather its basic physical outline. This outline consists of an autonomously induced *gradient of stiffness* of the adhering cell cortex, increasing from front to rear, persisting during migration due to the successive assembly and strengthening of microfilaments at the adhesion sites. These physical properties are implemented into a computational model with corresponding simulations of an autonomous self-crawling and self-deforming robot. The two-dimensional model consists of double elastic chains, linked by radial elastic segments, which adapt their stiffness and elasticity to their adhesion or non-adhesion state over time: building up a gradient of stiffness during adhesion and decreasing it after disruption.
Simulation runs demonstrate that this model is able to move autonomously and that it is capable to move upwards inclinations and walls without losing stability. The model is designed simple enough for construction in reality. This leads to possibly new forms of crawling locomotion in robotics, advantageous in situations, where legged and wheeled propulsion is not usable or working.

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Deterministic Chaos vs. Stochastic Oscillation in an Eco-epidemic Model

Eco-epidemiological models of prey-predator interaction in presence of disease affecting either or both the species have received significant attention from various researchers. Some recent investigation reveals chaotic dynamics for certain range of parameter values. Unusual disease related death or higher growth rate of susceptible species or sudden outbreak of the disease or high rate of infection are possible explanation behind the chaotic dynamics. Most of these modeling approaches neglected the demographic stochasticity as well as environmental stochasticity. Main objective of the presentation is to construct the stochastic eco-epidemic model based upon the existing deterministic model and study the dynamics for a wide range of parameter values. The dynamics of the stochastic model is investigated for two types of parameter values, first set correspond to stationary or periodic scenario and second set correspond to chaotic oscillation for the deterministic model. It is interesting to note that the evolution of either species is not chaotic within stochastic setup rather they exhibit non-equilibrium fluctuation around some average values for both types of parameter values. Chance of extinction and expected time to extinction is also studied with the help of exhaustive numerical simulations.

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Delay equations for the cell cycle of tumoral cells

Cancer is nowadays one of the most complex severe diseases in the world. To better understand it, mathematical biologists have been working for the last decades on the theoretical aspects of the disease.
In this work, we model a combined treatment of immuno- and chemotherapy and its effects on a solid tumor.

Many authors (e.g. Arino, Dyson *et al.*) suggested structured population models in the context of cancer biology. Here, we start with a tumoral cell population structured by age and introduce the effects of drugs and immunotherapy on the tumoral mass. For a better description of the effects of phase-specific drugs, we define three sub-populations for interphase, mitotic and quiescent cells. Effectors from the immune system work against every kind of tumor cells, whereas chemotherapy is assumed to be mitosis-specific only.
Following a similar approach to that of Bocharov and Hadeler (2000), we derive a system of delay differential equations equivalent to the original age-structured model. Although our results apparently resemble those of Villasana (2003) and Liu (2007), the model here is not deduced from the mass action kinetics principles. But our approach allows us to take care of all delayed and undelayed variables and to locate them at the right place in the equations, thus providing a better description of the biological phenomenon.
We investigate the delay model both from the analytical and the numerical point of view and focus on the stability of the cancer-free equilibrium. Inspired by the work of other authors (e.g. d'Onofrio, 2010), we simulate different kinds of immunotherapy and estimate their effects on the tumor growth. Our aim is to find conditions for the eradication of the tumor or for its reduction to a life-compatible size.

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Mathematical Modeling of Mosquito-Borne Diseases; Tuesday, June 28, 11:00

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A genetic model for the spread of insecticide resistance in a heterogeneous environment

Protection measures against insect borne diseases predominantly depend upon the usage of insecticides. Different strategies of delivery can use single insecticides or use them in combination. The effects of combined control interventions on the evolution of insecticide resistance in a mosquito population has not been assessed and the model presented here is designed to be a starting point.

We incorporate the use of insecticides outside the household and the advent of new generation long-lasting insecticidal nets that allegedly have increased efficacy against pyrethroid-resistant malaria vectors. Here we describe a model that allows mosquitoes to encounter insecticides in several environments and explicity investigate the use of synergists on bednets.

The model includes two parameters that quantify the effects of using a synergist in combination with a insecticide: the reduce survival due the synergist and the proportions of mosquitoes (males and females) that encounter both chemicals. These parameters had a small correlation with male and female mean fitness suggesting that their impact in the spreading of resistance is small. A sensitivity analysis pinpointed the baseline fitness of susceptible homozygotes and the proportion of mosquitoes that enter the household as the most influential parameters and the ones that play the major role in the spread of insecticide resistance.

Evolutionary Ecology; Wednesday, June 29, 14:30

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Multivariate comparative analysis

The need for taking into account phylogenetic dependencies between trait measurements in comparative analysis is something which has become obvious. One approach to capture this dependency is to assume that the trait(s) evolve as a time dependent branching stochastic differential equation along the phylogenentic tree. The development of this branch of comparative analysis started with [1] and was continued in [2],[3],[4],[5]. However all these proposed methods lacked a fully multivariate implementation of the proposed models. We have developed a generalization of these models into the fully multivariate setting and implemented an estimation package in `R` to analyze comparative data under these models. The multivariate setting gives us much more flexibility and allows to e.g. model codevelopment of allometry, indications of a trade-off and gain understanding of trait coevolution. In the talk we will discuss the multivariate model, possible hypothesis (allometry, trade-off) one can study with it and go through an example study of how sexual selection acts on the development of male canine and body sizes in Primates.

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Population Genetics; Wednesday, June 29, 17:00

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On dynamics of quadratic stochastic processes and their applications in biology

A *quadratic stochastic operator* $\mathbf{Q} : \mathfrak{X} \to \mathfrak{X}$ is defined by a cubic (finite or infinite) array of nonnegative real numbers $[q_{ij,k}]_{i,j,k\geq 1}$ which satisfy

(1) $0 \leq q_{ij,k} = q_{ji,k} \leq 1$ for all $i, j, k \geq 1$,
(2) $\sum_{k=1} q_{ij,k} = 1$ for any pair (i, j),

where $\mathfrak{X}$ is ℓ^1 or ℓ^1_{d} equipped with a standard norm. The family of all quadratic stochastic operators is denoted by $\mathfrak{Q}$. Any quadratic stochastic operator (process) $\mathbf{Q}$ may be viewed as a bilinear mapping $\mathbf{Q} : \mathfrak{X} \times \mathfrak{X} \to \mathfrak{X}$ if we set $\mathbf{Q}(\underline{x}, \underline{y})(k) = \sum_{i=1,j=1} x_i y_j q_{ij,k}$. Clearly $\mathbf{Q}$ is monotone (i.e. $\mathbf{Q}(\underline{x}, \underline{y}) \geq \mathbf{Q}(\underline{u}, \underline{w})$ whenever $\underline{x} \geq \underline{u} \geq 0$ and $\underline{y} \geq \underline{w} \geq 0$) and is bounded as $\sup_{\|\underline{x}\|_1, \|\underline{y}\|_1 \leq 1} \|\mathbf{Q}(\underline{x}, \underline{y})\|_1 = 1$. It follows that $\mathbf{Q}$ may also be viewed as a mapping $\mathbf{Q} : \mathcal{D} \times \mathcal{D} \to \mathcal{D}$, where $\mathcal{D}$ stands for the simplex of probability vectors. In population genetics a special attention is paid to a nonlinear mapping $\mathcal{D} \ni \underline{p} \to \mathbb{Q}(\underline{p}) = \mathbf{Q}(\underline{p}, \underline{p})$. Here $\mathbb{Q} : \mathcal{D} \to \mathcal{D}$. Roughly speaking $\mathbb{Q}(\underline{p})$ represents a distribution of genes in the next generation if parent's gens have a distribution $\underline{p}$. In this simplified model the iterates $\mathbb{Q}^k(\underline{p})$, where $k = 0, 1, \ldots$, describe the evolution of a genom. Given an initial distribution $\underline{p} \in \mathcal{D}$ one may ask about asymptotic behaviour of the trajectory (i.e. the sequence $(\mathbb{Q}^n(\underline{p}))_{n\geq 0}$). Because of nonlinearity, the trajectories enjoy several unexpected features (as it was conjectured by S. Ulam). In this talk we discuss some generic properties in the set $\mathfrak{Q}$. We also present conditions for asymptotic stability of $\mathbf{Q} \in \mathfrak{Q}$.

The emergence of resistance in cancer using mathematical modelling;
Saturday, July 2, 08:30

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Tumour heterogeneity and its role in the emergence of resistance

Cancers are known to be heterogeneous which is the source of their strength explaining both progression and resistance. Nonetheless, the nature of this heterogeneity is still poorly understood, especially regarding its impact on the evolution of resistance to treatment. In this talk we will briefly discuss the evolutionary mechanisms that lead to this heterogeneity as well as it is impact in the emergence of resistance. Special attention will be given to the role of interactions between tumur cells and between the tumour and stroma and the stability of these interactions as a potential therapeutic target.

Poster Session; Friday, July 1, 20:00

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The role of genetic and environmental insults in glioblastoma carcinogenesis

Glioblastoma, the most common primary brain tumor, is uniformly fatal, with a majority of patients dying within 2 years of diagnosis. Emerging data suggests a small subpopulation of cells in glioblastoma have stem cell-like properties and are key to tumourigenesis. Concerted efforts to understand the underlying biology regulating these cells are currently underway, with an overarching goal of identifying novel tumor-specific pathways that may be effectively targeted as a strategy for anti-cancer therapy.

An important advancement towards our understanding of glioblastoma stem-like cells has been identifying the similarities these cells share with normal neural stem cells; most notable being the role the physical microenvironment plays in regulating their phenotype. Although the majority of the theoretical work has focused on elements extrinsic to the tumour microenvironment, the microenvironment that has yet to be explored in relation to glioblastoma stem-like cell biology. Further, current laboratory-based models are limited in providing meaningful insight into how the complex adaptive systems defining the tumor microenvironment may interact to contribute towards glioblastoma tumorigenesis. Our goal is to apply an integrative approach, coupling mathematical modelling with laboratory-based investigations, to better understand the interplay between glioblastoma stem-like cells and the microenvironment driving tumour initiation and the role hypoxia may play in modulating the tumor stem-cell niche.

Mathematical Models in Eco-epidemiology II; Wednesday, June 29, 11:00

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Complex dynamics in an eco-epidemiological model

In this talk, we incorporate a disease on a predator in a Holling type II predator-prey model. We establish that the disease can have a stabilising effect on the system, bringing predator-prey oscillations to coexistent equilibrium. However, results become complex when disease dynamics are much faster than the predator-prey dynamics, i.e. for high transmission and disease-induced death rates. Numerical solutions indicate the existence of saddle-node and subcritical Hopf bifurcations, as well as turning points and branching in periodic solutions. This means that there are regions of bistability, in which the disease can have both a stabilising and destabilising effect. This holds for both density-dependent and frequency-dependent transmission.

Modeling physiological systems: model validation and experimental design issues; Wednesday, June 29, 11:00

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Methods of Sensitivity Identifiability Analysis in Modeling Human Physiological Systems

In this talk we discuss techniques to quantify the parameter estimation problem in models that characterize human physiological systems. In general, the issue is to balance model complexity and parameter number with available data, data that is often restricted by such constraints as accessibility to measurement sites, the degree of error in measurements, cost of collecting data, and in the clinical setting, the need to screen patients with tests that are minimally invasive.

As a template example we will present a mathematical model of the cardiovascular control system of mid-level complexity that reflects the various pathways for short-term blood pressure control in response to various cardiovascular stresses. The model includes 10 vascular compartments and baroreflex feedback control that can alter resistance, heart rate and heart contractility, and unstressed volume to counteract a perturbation in blood pressure, returning the pressure to its more or less steady state of operation. The unstressed blood volume of a vascular element is the natural filling volume that can be accommodated before stretching of the vascular wall begins. Additional volume generates transmural pressures that stretch the vascular wall (stressed volume). Unstressed volume does not contribute to the dynamic pressure which determines blood flow. It is therefore a reservoir (particularly venous unstressed volume) that can be transferred (mobilized) by control mechanisms (through constriction of vessels) to stressed volume when blood volume is reduced. The model presented is sufficiently complex to characterize responses to a variety of system stresses including reduction in blood volume.

Orthostatic stress is caused by blood pooling in the lower limbs when standing upright, a consequence of gravity. This pooling removes a percentage of blood from the dynamic circulation. In changing from the prone to standing position, the control system must compensate for what is in effect a reduction in blood volume. A number of experimental protocols such as head up tilt (HUT) and lower body negative pressure (LBNP) are used to examine system response to orthostatic stress. To illustrate the difficulties that arise in assessing control response via diagnostic testing, we note that the HUT and LBNP protocols each have specific effects on overall physiology which can obscure the examination and characterization of system response. For example, unstressed blood volume is mobilized in different ways during LBNP, HUT, and orthostasis [**2**].

Several aspects and problems of model validation will be discussed. Various tools derived from sensitivity analysis will be applied, including both classical and generalized sensitivities and subset selection [**1, 3**]. Applied jointly, these tools can

provide insight into how specific experimental protocols such as HUT and LBNP impact model response and the potential for parameter estimation.

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Cell and Tissue Biophysics; Saturday, July 2, 11:00

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A queueing theory model for the dynamics of microtubules and microfilaments

Dynamic features of microtubules and microfilaments are essential to cell division, cell motility, and other cellular processes. ATP-bound monomeric actin and GTP-bound tubulin polymerize to actin filaments and microtubules, respectively. After assembly into polymers, nucleotide hydrolysis occurs, which can lead to a change in the on- and off-rates at the polymer ends. A simple stochastic model of such a polymer from nucleation until complete depolymerization is presented. The model assumes that there is a sharp boundary between the "newer" part of the polymer containing only ATP-bound actin—the ATP cap (GTP cap in the case of tubulin), and the "older" part, where all nucleotides have undergone hydrolysis. The ATP cap and GTP cap are modeled as a single-server queue with reneging, where the server rate (rate of nucleotide hydrolysis) plus the reneging rate (off-rate at plus end of filament) exceeds the arrival rate (on-rate at plus end of filament). Coupled to this queue is another single server queue that describes the length of the entire filament and whose arrival and reneging rate switch between two regimes depending on whether the ATP cap has disappeared (first server empty) or not. The model exhibits dynamic instability and treadmilling for proper choice of hydrolysis rate and on/off-rates at polymer ends. Analytic expressions for the distribution of the life time and length of polymers together with Monte Carlo simulations are presented and their fit to experimental data discussed.

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A mathematical model of brain tumor and normal tissue responses to radiation therapy

The present work introduces a mathematical model that simulates the progression of malignant brain tumors as well as the effect of radiotherapy on cancerous and normal tissue. The spatio-temporal dynamics of a tumor cell density is described on the basis of a reaction-diffusion equation. In addition to passive diffusion and proliferation [1–3] this equation incorporates the effect of irradiation [2,3]. To account for the anisotropy of tumor diffusion within white matter, tensor information deduced from a probabilistic white matter atlas is incorporated into the model. The model also assumes logistic growth of the tumor cell population resulting in a lower net proliferation in regions of high cell density. The spatio-temporal effect of radiation is described by the linear-quadratic model.

In current mathematical models used to predict tumor growth and the biological effect of different treatment schedules, the mathematical description of radiation response in general is limited to cancerous cells. An optimization of treatment outcome, which includes a maximization of tumor control while minimizing normal tissue toxicity, however necessitates not only a quantification of the biological effect on cancerous tissue but also on healthy tissue. The present model therefore extends the standard approaches [2,3] by also modeling the effect of radiotherapy on normal tissue. A second differential equation describes the spatio-temporal progression of the necrotic density, incorporating the effects of irradiation on cancerous and normal tissue and a degradation due to phagocytosis. Furthermore, the tumor radiosensitivity is varied according to the local density of cancerous cells. This allows for indirectly considering the oxygenation and its influence on the radiosensitivity, as the growing tumor increases the lack of oxygen, which directly corresponds to the extent of radioresistance.

The numerical results show that the progression of primary brain tumors can plausibly be determined. The model is also used to quantitatively study the efficacy of irradiation under a variety of treatment schedules and dose distributions. The results illustrate the potential of the proposed model in finding a trade-off between tumor control and normal tissue toxicity. Incorporation into clinical planning systems could ultimately facilitate the administration of more appropriate, patient-specific treatment schedules and offers the promise of highly individualized radiation treatment for cancer patients. Avenues for future research include further clinical evaluations, incorporation of cell cycle dynamics and extension to other types of external beam radiation therapy.

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Multi-cell, Multi-scale Models of Vertebrate Somitogenesis

Somitogenesis is an early developmental process that establishes the first signs of segmentation in all vertebrates, patterning the precursors of the vertebrae, ribs, and skeletal muscles of the back and limbs. This process requires coordination between biological mechanisms at several scales, ranging from genetic regulatory networks to structural changes at the tissue level. Understanding how these mechanisms interact across scales and how events are coordinated in space and time is necessary for a complete comprehension of somitogenesis, including its evolutionary flexibility and how we can best apply observations at single scales and in different species to understand, prevent and one day treat somitogenesis defects in humans. So far, mechanisms of somitogenesis have been studied independently, leading to a scattered set of single-scale models. To test the consistency, integrability and combined explanatory power of current prevailing hypotheses, we built a multi-cell composite clock-and-wavefront model that includes submodels of the intracellular segmentation clock, intercellular coupling via Delta/Notch signaling, an FGF8 determination front, delayed differentiation, clock-wavefront readout and differential cell-cell adhesion-driven cell sorting. We identify inconsistencies between existing submodels and gaps in the current understanding of somitogenesis mechanisms and propose novel submodels and extensions of existing submodels where necessary. 2D simulations of our models with reasonable initial conditions robustly generate spatially and temporally regular somites, realistic dynamic morphologies and spontaneous emergence of traveling stripes of Lfng. Our model is flexible enough to generate interspecies-like variation in somite size in response to changes in PSM growth rate and segmentation clock period, and in the number and width of Lfng stripes in response to changes in PSM growth rate, segmentation clock period and Wnt3a levels. To our knowledge, our work presents the first embryogenesis model to successfully combine such a broad range of scales and mechanisms, representing an important step in predictive developmental modeling. The model is modular in nature, which will allow technically straightforward model extensions and comparisons between sets of hypothesized mechanisms and interactions.

Analysis of mathematical models for cancer growth and treatment, Part III; Tuesday, June 28, 17:00

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Optimal schedules for therapies in metastatic cancers.

An actual important challenge in oncology is to determine the best temporal administration protocols for either a given drug or the combination of various treatments, in order to reduce the cancer disease or at least stabilize it. In this talk, we present a model for the evolution of the density of the metastatic population structured by size and "angiogenic capacity" (= vasculature) modified by the action of both an anti-angiogenic treatment which affects the vasculature of the tumors and a cytotoxic treatment attacking the cancerous cells. The model is a non-autonomous transport equation in dimension 2 with a nonlocal boundary condition

$$(1)\begin{cases} \partial_t \rho + \mathrm{div}(G\rho) = 0 &]0,\infty[\times\Omega \\ -G\cdot\overrightarrow{\nu}\,\rho(t,\sigma) = N(\sigma)\int_\Omega \beta(x,\theta)\rho(t,x,\theta)dxd\theta + f(t,\sigma) &]0,\infty[\times\partial\Omega \\ \rho(0,\cdot) = \rho^0(\cdot) & \Omega \end{cases} .$$

First, we will show the well-posedness of this problem : existence and uniqueness of solutions. The existence is proved by convergence of a numerical scheme consisting in straightening the characteristics and discretize them. We also present the numerical analysis of this scheme. We use then the model to investigate *in silico* the effect of various schedules of anticancerous drugs both on the primary tumor and the metastases, for example in the problem of the combination of a cytotoxic drug (chemotherapy) and an anti-angiogenic one. These considerations lead us to define and investigate an optimal control problem for determining the best schedule of the drug integrating both the metastases and primary tumor dynamics.

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Population Dynamics; Tuesday, June 28, 17:00

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Individual's memory as a parameter to differentiate population distribution patterns

Recent studies including satellite analysis have shown that movement of Mongolian gazelles can be classified as nomadic. One explanation emerges from the fact that their habitat is a dynamic environment. It was proposed recently the dependence on spatial heterogeneity and temporal predictability of resources for migration, nomadism and residence movement. One can define residence as distributions in which an individual over its lifetime occupies a relatively small area compared to the population range; migration as a regular, long-distance pattern of movement, and is typically observed in systems with regular, seasonal fluctuations in environmental conditions; and nomadism occurs when animals are neither resident nor migratory, and instead move across the landscape in routes that do not repeat across years. Here, we propose, at the individual level, that a dependence on memory is also an important parameter characterizing the population distribution pattern. The movement decisions are based on known areas due to the animal's memory. Migratory animals may have a long memory, perhaps they know all way between different locations in their journey. In another way, nomadic animals remember some last visited areas, where they stayed for a while. Therefore, the comparison between the memories together with the landscape predictability can clarify the individual behavior behind the population distribution pattern. Based on this approach, we propose some tools for analyzing animals movement.

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Double impact of sterilizing pathogens: added value of increased life expectancy on pest control effectiveness

Sterilizing pathogens are commonly assumed not to affect longevity of infected individuals, and if they do then negatively. Examples abound, however, of species in which the absence of reproduction actually increases life expectancy. This happens because by decreasing the energy outlay on reproduction individuals with lowered reproduction can live longer. Alternatively, fertile individuals are more susceptible to predators or parasitoids if the latter can capitalize on mating signals of the former. Here we develop and analyze an SI epidemiological model to explore whether and to what extent does such a life expectancy prolongation due to sterilizing pathogens affect host dynamics. In particular, we are interested in an added value of increased life expectancy on the possibility of successful pest control, that is, the effect of increased lifespan and hence increased potential of the infected individuals to spread the disease on pest control effectiveness. We show that although the parameter range in which we observe an effect of increased lifespan of infectives is not large, the effect itself can be significant. In particular, the increase in pest control effectiveness can be very dramatic when disease transmission efficiency is close to birth rate, mortality rate of susceptibles is relatively high (i.e., the species is relatively short-lived), and sterilization efficiency is relatively high. Our results thus characterize pathogens that are promising candidates for an effective pest control and that might possibly be engineered if not occurring naturally.

Population Dynamics; Saturday, July 2, 14:30

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Spatial explicit dispersal modeling for the conservation of jaguars in Colombia

Mathematical models that go beyond traditional conservation paradigms that allow for the identification of corridors and potential areas for species dispersion have proven to be an important and useful tool in the proposal of new conservation and management plans (Adriaensen et al., 2003; Beier et al., 2009; Ray et al., 2002; Rabinowitz & Zeller, 2009). Particularly in the conservation of jaguars, Rabinowitz & Zeller (2009) gave a first push by analyzing the species at a metapopulation level and measuring connectivity as they produced a complex path of interconnected populations. This model was based on a least-cost methodology that in spite of its virtuosity gave only a steady state analysis of the connectivity and distribution of the jaguars that does not necessarily reflects the current situation. Their results identified Colombia as a key element for connectivity between north and south populations, but for some parts of the country it did not accurately capture the most suitable areas for dispersion. We previously proposed an spatially explicit dispersal model based on the least-cost matrix obtained from the least-cost analysis, to provide temporal information about the sustainability of the areas for jaguar dispersion, and increase accuracy by scaling the area of study to Colombia. The model proved to be a better tool for dynamical studies, however some of the simulations showed a deviation from total population prediction respect to field data. We speculated that this discrepancy is mainly due to our way to compute diffusion coefficients, carrying capacities and boundary conditions. Here we present a modification of the model that includes a new methodology for estimating those parameters that includes the notion of jaguar conservation units (JCU), as defined by the current conservation program. Here we present preliminary results from this modified model and compare it with previous simulations. We found that accurately defining the carrying capacity and including boundary conditions that mimic better the ecology of the specie gives an overall improvement in terms of our ability to predict current population densities and temporal aspects of the population dynamics.

Delay Differential Equations and Applications II; Saturday, July 2, 08:30

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Distributed delays stabilize negative feedback loops

We study the stability of the linear differential equation with distributed delays

$$\dot{x} = -ax - b\int_0^\infty x(t-\tau)d\eta(\tau) \tag{1}$$

where the coefficients a and b are constant, and $\eta(\tau)$ is the distribution of delays. In biological applications, discrete delays in the feedback loop are often used to account for the finite time required to perform essential steps before $x(t)$ is affected. Linear stability properties of scalar delayed equations are fairly well characterized. However, lumping intermediate steps into a delayed term can produce broad and atypical delay distributions, and it is still not clear how that affects the stability compared to a discrete delay [**1**].

When η is a single discrete delay (a Dirac mass), the asymptotic stability of the zero solution of Eq. (1) is fully determined by a theoren originally due to Hayes [**2**].

The aim of this paper is to study the effect of delay distributions on the stability of the trivial solution of Eq. (1). It has been conjectured that among distributions with a given mean E, the discrete delay is the least stable one [**3, 4**]. This conjecture has been proved for $a = 0$ using Lyapunov-Razumikhin functions [**5**], and for distributions that are symmetric about their means [$f(E-\tau) = f(E+\tau)$] [**6, 3, 4, 7**]. Here, we show that the conjecture is true.

The general strategy for proving the stability of distributed delays is the following. We use a geometric argument to bound the roots of characteric equation by the roots of the characteristic equation for a single discrete delay. More precisely, if the leading roots associated to the discrete delay are a pair of imaginary roots, then all the roots associated to the distribution of delays have negative real parts. We first state a criterion for stability. We then show that a distribution of n discrete delays is more stable than a certain distribution $*$ with two delays. We construct this most "unstable" distribution and determine that only one of the delays is positive, so that its stability can be determined using Hayes Theorem. We then generalize for any distribution of delays, and obtaine the most complete picture of the stability of Eq. (1) when the only information about the distribution of delays is the mean.

Theorem 1. *The trivial solution of Eq. (1) is asymptotically stable if* $a > -b$ *and* $a \geq |b|$*, or if* $b > |a|$ *and the mean* E *of* η *satisfies*

$$E < \frac{\arccos(-a/b)}{\sqrt{b^2 - a^2}}.$$

The zero solution of Eq. (1) may be asymptotically stable (depending on the particular distribution) if $b > |a|$ *and*

$$E \geq \frac{\arccos(-a/b)}{\sqrt{b^2 - a^2}}.$$

The zero solution of Eq. (1) is unstable if $a \leq -b$.

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Modeling of immune responses and calcium signaling I; Tuesday, June 28, 17:00

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IRF3 and NF-κB: Transcription factors acting in a coordinated way under double stranded RNA stimulation

Dynamics of innate immunity system under viral attack is still not understood in detail. However, new insights are emerging based both on novel experiments and on system modeling approach. We report a model of coordinated response of IRF3 and NF-κB transcription factors pathways in A549 lung cancer cells, under double stranded RNA (dsRNA) stimulation, itself a model for viral RNA. Viral infection leads to multiplication of viral RNA which is sensed by the innate immune system at a later stage. dsRNA, instead, rapidly activates the IRF3 and NF-κB pathways, leading to responses which are stronger and better localized in time.

dsRNA is sensed both by RIG-like family of helicases (RIG-I) and toll-like receptor 3 (TLR3). Activation of RIG-I leads, via multistep pathway, to the nuclear translocation of IRF3. In turn activation of TLR3 leads to phosphorylation and degradation of primary NF-κB inhibitor IκBα, freeing NF-κB which also translocates to the nucleus. IRF3 and NF-κB are independently and cooperatively responsible of the activation of a number of genes involved in innate immune and inflammatory responses, in particular both IRF3 and NF-κB are needed for the activation of the interferon β. In addtion NF-κB also activates a number of inhibitors, among them IκBα and A20, inhibiting both pathways or selectively one pathway.

Three kind of experiments were performed:

- Time series (0, 0.5, 1, 2, 4 and 6 hours) of key mRNAs induced by NFkB and IRF3 transcription factors.
- Time series of key phosphorylated proteins at same time points as above.
- Knock-down experiments using small interfering RNA (siRNA) on NF-κB, IRF3, RIG-I, and IKKγ with and without dsRNA stimulation.

The emerging deterministic mathematical model considers 87 species and 147 reaction. It seems to be the first aggregate model of dynamics of NF-κB and IRF3, and shows agreement with experimental data. In addition we carried out stochastic simulations of hypothetical single-cell experiments, which display bimodality of responses not visible in cell-population experiments.

Evolutionary Ecology; Wednesday, June 29, 08:30

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Host resistance and coevolution in spatially structured populations

Most natural, agricultural and human populations are structured, with a proportion of interactions occurring locally or within social groups rather than at random. This within-population spatial and social structure is important to the evolution of parasites (e.g. [**1**]) but little attention has been paid to how spatial structure affects the evolution of host resistance, and as a consequence the coevolutionary outcome. We examined the evolution of resistance across a range of mixing patterns using an approximate mathematical model (pair approximation) and stochastic simulations. We found that as reproduction becomes increasingly local, hosts are always selected to increase resistance. More localised transmission also selects for higher resistance, but only if reproduction is also predominantly local. If the hosts disperse, lower resistance evolves as transmission becomes more local. These effects can be understood as a combination of genetic (kin) and ecological structuring on individual fitness. When hosts and parasites coevolve, local interactions select for hosts with high defence and parasites with low transmissibility and virulence. Crucially, this means that more population mixing may lead to the evolution of both fast-transmitting highly virulent parasites and reduced resistance in the host [**2**].

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Poster Session; Friday, July 1, 20:00

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Are metastases from metastases clinically relevant? A novel computer model helps understanding the metastatic progression

The process of metastasis formation remains enigmatic. Different models exist for predicting the metastatic spread of malignant tumors. However, it is difficult to evaluate these different models for their clinical relevance. Therefore a novel computer model was developed which permits comparison of the different models quantitatively with clinical data and which additionally predicts the outcome of treatment interventions. The computer model is based on a discrete events simulation approach. The growth of the primary tumor and the metastases is described via analytical functions, while a rate function models the intravasation events of the primary tumor and its metastases. Events describe the behavior of the emitted malignant cells until the formation of new metastases. With the help of the computer model it was evaluated whether metastases are able to metastasise and if late disseminated tumour cells are still capable to form metastases. The simulation results were compared with clinical data from an untreated patient with hepatocellular carcinoma and multiple metastases in the liver. Additionally, the resection of the primary tumour was simulated. The results of the computer simulations reveal that the number of metastases varies significantly between scenarios where metastases metastasise and scenarios where they not. In contrast, the total tumour mass is nearly unaffected by this mode of metastasis formation. Furthermore, the results provide evidence that late disseminated tumour cells are still capable of forming metastases. The simulation results show that in this particular case of hepatocellular carcinoma, carcinoma metastases exhibit the same growth pattern as the primary tumour. Simulations also allow estimating how the resection of the primary tumour delays or even prevents the patients death. The simulation results indicate that for this particular case of a hepatocellular carcinoma late metastases, i.e. metastases from metastases, are irrelevant in terms of total tumour mass. Hence metastases seeded from metastases are clinically irrelevant in our model system. Only the first metastases seeded from the primary tumour contribute significantly to the tumour burden and thus cause the patients death.

Neurosciences; Thursday, June 30, 11:30

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Mathematical and numerical modeling of presynaptic phase of fast transport

Neurotransmitters in the terminal bouton of a presynaptic neuron are stored in vesicles, which diffuse in the cytoplasm and, after a stimulation signal is received, fuse with the membrane and release its contents into the synaptic cleft. It is commonly assumed that vesicles belong to three pools whose content is gradually exploited during the stimulation.
The physiological assumptions that lead to the proposed model are the following:

1. Terminal bouton occupies a fixed domain, a fixed part of the domain boundary are the vesicle release sites.
2. The unknown of the model is the concentration of vesicles in the cytoplasm. The unit in which this value is expressed can either be the mass or the quantity of the vesicles or the fraction of cytoplasm volume they occupy.
3. Vesicles diffuse inside the terminal bouton and they are synthesized in some subdomain of the bouton.
4. The efficiency of the vesicle synthesis is proportional to the difference between the equilibrium concentration (above which the synthesis does not take place) and current concentration.
5. Vesicles do not leave the domain unless the action potential arrives. The arrival of the action potential triggers the possibility of the vesicles release through some fixed period of time. The number of vesicles that can be released in a unit time through the unit area is proportional to the vesicle concentration in the vicinity of the release site.
6. Neither re-uptake nor recycling of released vesicles is considered.
7. The availability of vesicles for release depends only on their location. The docking sites are modeled implicitly as the areas in the vicinity of the release sites specified on the bouton boundary.

The following variables and parameters which express various physiological quantities are introduced:

(i) $\Omega \subset \mathbb{R}^N,\ N \in \{2,3\}$ - the domain of the terminal bouton,
(ii) $\Omega_1 \subset \Omega$ - the domain of neurotransmitter production,
(iii) $\partial\Omega_d \subset \partial\Omega$ - neurotransmitter release sites on the cell membrane,
(iv) $f : \Omega \to \mathbb{R}$ - neurotransmitter source density defined, for example, by $f(x) = 0$ outside Ω_1 and $f(x) = f_z$ on Ω_1,
(v) $\bar{\rho}$ - the balance concentration of neurotransmitter in the bouton,

(vi) α - the coefficient denoting the rate of neurotransmitter exocytosis, α is the number of vesicles (or molecules) which are released through the unit area of the membrane in unit time by the unit difference of the concentration in the cell and outside the cell (1 action potential activates 300 vesicles and 1 vesicle contains $10^3 - 10^4$ molecules of neurotransmitter),

(vii) $a_{ij} : \Omega \to \mathbb{R}$ - the diffusion tensor for the vesicles with a neurotransmitter,

(viii) τ - the time period through which the neurotransmitter is released from the docked vesicles to the cleft (0.2 - 0.5 ms),

(ix) t_0 - the arrival moment of the potential (it is possible that there are many such moments during the simulation).

The unknown in the model is the function $\rho : \Omega \times [0, T] \to \mathbb{R}$ denoting the concentration of the vesicles with neurotransmitter.
The function is the solution of the equation

$$\frac{\partial \rho(x,t)}{\partial t} = \sum_{i,j=1}^{N} \frac{\partial}{\partial x_i} \left(a_{ij}(x) \frac{\partial \rho(x,t)}{\partial x_j} \right) + f(x)(\bar{\rho} - \rho(x,t))^+. \tag{1}$$

The equation is accompanied by boundary and initial conditions implied directly by physiology of vesicle release as well as their initial distribution (see [1,2]):

$$\sum_{i,j=1}^{N} a_{ij} \frac{\partial \rho(x,t)}{\partial x_j} n_i = 0 \quad \text{for} \quad (x,t) \in (\partial\Omega - \partial\Omega_d) \times [0,T], \tag{2}$$

$$\sum_{i,j=1}^{N} a_{ij} \frac{\partial \rho(x,t)}{\partial x_j} n_i = 0 \quad \text{for} \quad (x,t) \in \partial\Omega_d \times ([0,t_0) \cup (t_0+\tau, T]), \tag{3}$$

$$\sum_{i,j=1}^{N} a_{ij} \frac{\partial \rho(x,t)}{\partial x_j} n_i = \alpha \rho(x,t) \quad \text{for} \quad (x,t) \in \partial\Omega_d \times [t_0, t_0+\tau], \tag{4}$$

$$\rho(x,0) = \rho_0(x) \quad \text{on} \quad \Omega, \tag{5}$$

where $(n_i)_{i=1}^N$ is the unit normal vector directed outside Ω.
The model is analyzed and simulations of the vesicular kinetics using Finite Element Method are done.

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Poster Session; Friday, July 1, 20:00

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Intra-host dissemination dynamics of *Borrelia sp.* during Lyme disease

Chronic inflammatory diseases, caused by bacteria, viruses and eukaryotic parasites pose a threat to public health. A strong inflammatory reaction causing tissue damage often plays an important role in the pathogenesis of these infections. Lyme disease, caused by an infection by spirochetes of the *Borrelia burgdorferi* sensu lato group (*B. afzelii, B. garinii, B. burgdorferi* s.s.), is a common tick-borne disease in North America, Europe and parts of Asia. The early infection stage consists of mild and mainly localized symptoms. In later stages, the spirochetes can migrate to different tissues, including the central nervous system, heart and joints, where it causes strong inflammatory reactions and tissue damage, leading to severe clinical symptoms. The infection of these tissues can also become chronic.

This project aims at modelling the dissemination of the bacteria from the infected skin site to other tissues inside a mouse. The model is based on experimental data on the bacterial concentrations in different tissues from qPCR studies of artificially infected mice of a strain displaying clinical disease symptoms similar to those in humans and also develops a systemic infection. The dynamics of this dissemination are described by a simple deterministic model on the level of bacterial populations in three different compartments, including the interactions of macrophages and spirochetes as an important component of the innate immune response and inflammatory reaction caused by *B. burgdorferi*. Central questions that may be answered by this model include the infectious bacterial concentration and elucidation of the transition from the acute to the chronic infection.

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Modeling of prokaryotic genome evolution using coding signal as selection pressure

Protein coding genes in prokaryotic chromosomes are subjected to two different asymmetric mutational pressures associated with various replication mechanisms of DNA strands (leading and lagging). To simulate evolution of prokaryotic protein coding sequences under this asymmetric mutational pressure, we elaborated a simulation model based on the Borrelia burgdorferi genome. As the mutational pressure we applied nucleotide substitution matrices empirically found for the leading and lagging DNA strands of the genome. The selection pressure was based on the modified algorithm for protein coding gene finding, trained on annotated B. burgdorferi protein coding genes. We simulated the evolution of genes from differently replicating strand under the constant, opposite and changing mutational conditions, mimicking sequence inversions.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits I; Wednesday, June 29, 14:30

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The effect of nonlocal cellular interactions on pattern formation

Cells interact with their local environment, and these interactions affect the the proliferation, differentiation and movement of cells. While modelling these interactions is obviously important, doing so in a continuous model has proved difficult.

In this talk I will present a continuous partial differential equation model of a two population system, using integral terms to describe the effect of local environment on interacting cells. I will use this model to explore particular cellular interactions, and present the spatial patterning that can be obtained from such a system.

Semigroups of Operators in Mathematical Biology II; Saturday, July 2, 11:00

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From a PDE model to an ODE model of dynamics of synaptic depression

We provide a link between two recent models of dynamics of synaptic depression. To this end, we correct the erroneous boundary condition and specify the missing transmission conditions in the PDE model of Bielecki and Kalita, and show that as the diffusion coefficients tend to infinity and the relative permeability coefficients of the membranes involved tend to zero, the solutions to the PDE model tend to those of the original ODE model of Aristizabal and Glavinovič. Hence, from the mathematical point of view the ODE model is obtained as a singular perturbation of the PDE model with singularities both in the operator and in the boundary and transmission conditions. The result is therefore conveniently put in the context of degenerate convergence of semigroups of operators, where a sequence of strongly continuous semigroups approaches a semigroup that is strongly continuous only on a subspace of the original Banach space. Biologically, our approach allows a new, natural interpretation of the ODE model's parameters.

Poster Session; Friday, July 1, 20:00

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On shape and force – from single to interactive cell motion

One of the fundamental organization forms of tissue in multi-cellular organisms is the epi- or endothelium, in which the cells assemble into a single-layered structure supported by a strong basal membrane. If an injury damages this barrier, the cells perform a so-called epithelial-mesenchymal transition: they break their mutual connections and start to migrate. Here we study the mechanics of cell motion in these effectively two-dimensional environments, where both cooperation and individualism contribute to the biological function.

The motility mechanics of individual cells can be understood in terms of two-phase flow models [1]. Extending our earlier 1D work [2], we project the underlying hyperbolic-elliptic PDE system of Stokes type onto the unit circle. At the lamella tip we incorporate enhanced actin polymerization by prescribing suitable pressure BCs. This enables us to obtain both shape dynamics and the migration trajectory of a quasi 2D model cell simultaneously. The corresponding simulations exhibit a correlation between migration speed and cell shape, as observed in experiments.

For cooperative motility, we argue that the cells' motion is governed by essentially the same microscopic stochastic process: cadherin cell-cell adhesion molecules merely add an attractive interaction. In this way, cytoskeletal contraction stresses propagate across adjacent cells and determine the shape of the border in between. The geometry of this stress-induced competition for space can be formalized by means of Voronoi tessellations. In order overcome the conventional polygonal cell approximation, we propose a consistent generalization to partition space into individual cells with piecewise spherical or elliptic border [3]. Combined with aforementioned stochastic motility processes, the model tissue displays characteristic morphogenetic rearrangement patterns.

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Crowd Dynamics: Modeling, Analysis and Simulation (Part 2); Wednesday, June 29, 14:30

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Social networks and models for collective motion

The theory of collective motion and the study of social networks have, each individually, received much attention. Currently, most models of collective motion do not consider social network structure. The implications for considering collective motion and social networks together are likely to be important. Social networks could determine how populations move in, split up into and form separate groups (social networks affecting collective motion). Conversely, collective movement could change the structure of social networks by creating social ties that did not exist previously and maintaining existing ties (collective motion affecting social networks). Thus, there is a need to combine the two areas of research and examine the relationship between network structure and collective motion. I will briefly review different modelling approaches that combine social network structures and collective motion (e.g. in pedestrian crowds or evacuation wcenarios) and present examples of my own work suggesting how social networks could impact on positioning and leader-follower relationships within groups and navigation at the group level.

Regulatory Networks; Friday, July 1, 14:30

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Protein activation by calcium oscillations and Jensen's Inequality

Oscillating concentrations of cellular Ca^{2+}-ions are of great importance for the signalling in the cell. It is widely believed that the information of extracellular stimuli is encoded into an oscillating Ca^{2+} pattern, which subsequently is decoded by the activation of Ca^{2+}-sensitive proteins. Besides this advantage of an oscillating Ca^{2+} signal, we here show that oscillations additionally lead to a better activation of the target proteins compared to a constant signal. In two asymptotic cases we can analytically prove this for arbitrary oscillation shapes and a very general decoding model, which comprises most previous models of Ca^{2+}-sensitive proteins. For this we use Jensen's inequality that relates the value of a convex function of an average to the average of the convex function. Moreover, numerical simulations indicate that oscillations lead to a better activation not only in the two asymptotic cases. The results underline the importance of the cooperativity of the binding of Ca^{2+} and of zero-order ultrasensitivity, which are two properties that are often observed in experiments on the activation of Ca^{2+}-sensitive target proteins. We compare our theoretical predictions with data from experimental studies investigating the activation of NFAT and Ras by oscillatory and constant signals.

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Crowd Dynamics: Modeling, Analysis and Simulation (Part 2); Wednesday, June 29, 14:30

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Derivation of macroscopic equations for individual cell-based models.

Typically, in individual cell-based models cells interact by means of some pair potential and are assumed to evolve according to some stochastic or deterministic dynamics. Because these models try to describe interaction between individuals they are often called microscopic models. They can describe quite complicated phenomena. The rule which governs the cells dynamics can be usually easily implemented and the numerical simulation might give some solutions, in particular in the case of cellular automata models. On the other hand, if we try to give a precise mathematical description it is usually complicated and the mathematical analysis of such models is very difficult if possible. Often it is also very difficult to identify the most relevant parameters or group of parameters and its influence on the dynamics.

Our talk will be focused on a very particular type of models that are analogous to many of the model studied in the literature. We will assume that the centres of the cells evolve according to ordinary differential equation

$$\frac{d}{dt}X_N(k,t) = -\sum_{\substack{i=1\\ i\neq k}}^{N} \nabla V_N(X_N(k,t) - X_N(i,t))\,,$$

where N is a number of cells and functions $X_N(k,t)$ describe the position of the k-th cell. We assume that dominant effect in the dynamics is cell friction and for that reason only one derivative appears on the left-hand side. We will derive a equation that can describe a macroscopic behaviour of the system. In the case of "long-range" potentials, this is when one cell/particle interacts with many others the evolution of the cell/particle density is described by a type of porous-medium equation. On the other hand, if interaction are "short", this is a support of potential V is of the order of typical distance between cells/particles the structure of the equilibrium state of the microscopic system appears in the macroscopic equation. In 1-D this leads to a version of porous-medium equation discrete in space. However for higher dimensions a directional densities have to be considered.

References.

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Delay can stabilise: population and love affairs dynamics.

It is well known that time delay may lead to destabilisation of a steady state and oscillations may arise due to the Hopf bifurcation. We show that for the system of two equations with one delay the unstable steady state can be stabilised by time delay. Namely, if for delay equal to 0 the steady state is an unstable node or unstable spring, then the steady state may gain stability for larger time delays. We give a condition which guarantees this kind of behaviour and we illustrate it with some linear and non-linear sociological models of romantic relationship.

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Two theorems on singularly perturbed semigroups with applications to some genetic models

In our talk we present two theorems on convergence of semigroups related to singularly perturbed abstract Cauchy problems, and apply them to some examples of recent models in applied mathematics. The semigroups considered are related to piecewise deterministic Markov processes jumping between several copies of a rectangle in M-dimensional Euclidean space and moving along deterministic integral curves of some ODEs between jumps. Our theorems describe limit behavior of the processes in the cases of fast jumps and fast motions in the direction of chosen variables. These results are motivated by Kepler-Elston's model of gene regulation and Lipniacki's model of gene expression. We will also shortly discuss applications to other models, including those of mathematical economics.

Poster Session; Friday, July 1, 20:00

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Modeling Viral Spread on Tissue or Cell Culture Level

Spreading of viral infections in tissues as well as in artificial cell cultures relies on various microscopical effects between individual cells. Besides the well known diffusion of free virions, which is primitive but important, experimentalist have recently discovered a vast variety of more or less elementary active and directed transport mechanisms (cf. [1], [2]). Amongst these *viral surfing* (cf. [3]) between cells is particularly interesting, since it may bridge significant distances. In these experiments transport of a few individual virions from a single infected towards a single uninfected cell (within a culture of only few cells) has been observed via different techniques such as live cell imaging and electron microscopy. To our knowledge the role of these transport processes on a larger scale has not yet been subject to any systematic studies — neither experimental nor theoretical.

To mathematically describe these phenomena a microscopic model including different contributions of transport and replication of viruses is set up and discussed. This is considered as a preparatory step towards an effective description of the overall viral transport on a meso-scale level. The future goal is to use homogenization techniques to gain more understanding for the role of these different microscopic processes for the quantitative and qualitative effects on spreading of viral infections in living tissues or cell cultures.

References.

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Population Dynamics; Tuesday, June 28, 14:30

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Multi-level modeling of the stochastic spatio-temporal dynamics of phototrophic biofilms

Phototrophic biofilms are complex microbial communities encased in an extracellular polymeric matrix and fueled by a significantly present photosynthesizing fraction (e.g. cyanobacteria) existing in symbiosis with heterotrophic bacteria [1]. In the present work we present our ongoing work on the development of several integrated, quantitative approaches to modeling the spatio-temporal dynamics of the biofilm life cycle. In particular an SDE model predicting the deterministic development of biofilm biomass as well as the frequency and size of abrupt biomass detachments, the so-called sloughing events, is discussed [2]. We furthermore analyze a kinetic flux-balance based PDE model for the spatio-temporal distributions of 16 particulate and solute biofilm components [3], which has originally been developed for the modeling framework AQUASIM [4]. Here, we report on our efforts to reduce the complexity of this model in terms of variables and parameters, in order to obtain a minimal model for the spatio-temporal dynamics of phototrophic biofilms, and achieve integration with generic PDE-modeling approaches to biofilms [5]. Our final aim is to connect both models in a coherent fashion, and furthermore adjust them with evidence from experimental data of biofilm physiology and morphology, obtained within a European project on phototrophic biofilms (http://www.photobiofilms.org).

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Mathematical models of evolutionary dynamics of infectious agents;
Tuesday, June 28, 17:00

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Within-host viral evolution in a heterogeneous environment: insights into the HIV co-receptor switch

From the point of view of a pathogen, a host is a structured and a heterogeneous environment. In the case of HIV, for instance, the existence of spatial structure is supported by the fact that the virus is found in different tissues while environmental heterogeneity originates from the pathogen being able to exploit different types of immune cells. We present a simple mathematical model that incorporates two types of target cells and some spatial structuring and discuss the conditions under which viral diversification occurs within a host. Applying the model to the case of HIV, we show that it captures three main properties of the so called 'co-receptor switch' that is observed in many HIV infections: the initial dominance of virus strains that infect CCR5+ cells, the late switch in some (but, importantly, not all) HIV infections and the associated drop in the number of uninfected T-cells. This suggests that the co-receptor switch could result from gradual adaptation of the virus population to target cell heterogeneity. More generally, we argue that evolutionary ecology can help us better understand the course of some infections. The talk is based on joint work with Samuel Alizon [**1**].

References.

[1] A. Alizon, B. Boldin: *Within-host viral evolution in a heterogeneous environment: insights into the HIV co-receptor switch.* Journal of Evolutionary Biology, **23**, No. 12, (2010), pp. 2625-2635.

Poster Session; Friday, July 1, 20:00

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Implementation of PK-PD Models for viral kinetics in patients with HCV

PK-PD models are used to describe the mechanisms of antiviral activity of drugs and combinations of drugs in patients with chronic viral diseases like HCV. They play an important role in drug development and optimizing antiviral therapy. In order to describe the viral kinetics we implemented a full PK-PD model using the ordinary differential equation system shown bellow. Target cells, T, are infected by HCV, V, with rate β. Infected cells are lost at rate δ per cell and free virions are cleared at rate c. Further details are given by the model equations basing on the general PK-PD model for Hepatitis C viral kinetics as proposed in Shudo et al.[**1**]

$$\dot{V_I}(t) = (1-\varepsilon)(1-\varrho)pI(t) - cV(t)$$
$$\dot{V_N}(t) = (1-\varepsilon)\varrho pI(t) - cV_n(t)$$
$$\dot{I}(t) = \beta T(t)V(t) + p_I I(t)(1 - \tfrac{T(t)+I(t)}{T(0)+I(0)}) - \delta I(t)$$
$$\dot{T}(t) = \gamma(1 - \tfrac{T(t)+I(t)}{T(0)+I(0)})$$

- T and I are the numbers of target cells and infected cells, resp.
- V represents infectious virons
- V_N represents non infectious virons
- $V = V_I + V_N$ is the viral load
- p is describing the viral production rate in the untreated chronic patient
- p_I is the proliferation rate, as in Dahari et al.[**2**]
- γ is the regeneration rate as in Herrmann et al.[**3**]
- $\varepsilon(t)$ is the effectiveness of IFN
- ϱ is describing the antiviral effect of Ribavirin to split the newly produced virus in infectable virus (V_I and V_N resp.) as in Dixit et al.[**4**]

For the PD model, we set $\varepsilon(t)$ to $\varepsilon(t) = \frac{C(t)^h}{IC_{50}^h + C(t)^h}$, where $C(t)$ is the drug concentration in serum, IC_{50} is the drug level which blocks the viral production by 50% and the parameter h is the Hill coefficient ($h \geq 1$). The drug effectiveness, $\varepsilon(t)$ gradually increases and then decreases during the first week of therapy, as $C(t)$ does the same for each patient. For fitting the equation of $C(t)$ to each patient's PK data, we estimate all the parameters of the equation. Afterwards PK parameters are used to fit individual patient's Log HCV RNA kinetic data by maximum likelihood in order to estimate c, δ, V_0, IC_{50} and h. We used an optimization algorithm basing on the Nelder and Mead method and an ODE solver for stiff equations. We also

present an example of such an implementation in MatLab as well as with R to fit viral kinetic and pharmacokinetic data with the described full PK-PD model.

References.

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Recent advances in infectious disease modelling II; Saturday, July 2, 14:30

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Timeliness of intervention in epidemic outbreaks

During an epidemic outbreak the question about which intervention measures should be applied is tightly linked to how timely these measures can be applied. As a general rule, the earlier an intervention is applied the better is its result, however, due to logistics, policies, money, people and reality in general, delays on the application of interventions are inevitable. Therefore, the question comes down to decide, e.g., whether is it still worth applying a determined intervention (i.e., is it already too late for it to do something?), or whether a quicker intervention on a smaller group would have a better (or worse) effect than a slower intervention on a larger group. To answer this question we employ models to analyse the outcome of epidemics depending on when and to whom are the interventions applied. We show two examples where the models can support decision making. The first case shows the effect of vaccination during a measles outbreak in a school depending on when after the start of the outbreak vaccination is implemented. The second case investigates the effect of employing a quicker but less sensitive test than the gold standard to diagnose H1N1, followed by the isolation of positively diagnosed individuals.

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Factors determining length distribution of telomeric structures in absence of telomerase

Absence of telomerase in cellular structures requires an alternative telomerase-independent pathway for telomeric sequence length regulation. Telomeric circles possibly play an important role in a universal mechanism for stabilization of the ends of linear DNA that possibly dates back to pre-telomerase ages. It was observed that their length distribution varies significantly in various types of organelles and organisms. How to explain these different outcomes of experiments? In this work we try to identify and estimate key factors influencing the length distribution of telomeric circles, loops and strand invasions using numerical simulations for a model we have constructed for C. parapsilosis.

Evolutionary Ecology; Friday, July 1, 14:30

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Cellular automaton eco-systems the simple way to simulate macroevolution

Keywords: Macroevolution; Coevolution; Individual-based models; Predator-Prey; Cellular automata; Artificial life; Phylogenetic Trees; Food Networks;

In this short talk I will present a simple lattice, cellular automaton like model of a multi-species ecosystem suitable for the study of emergent properties of macroevolution. In this model the number of species is not fixednew species continuously emerge by mutation from existing species, then survive or extinct depending on the energetic balance between local ecological interactions. The Monte-Carlo numerical simulations show that this model is able to qualitatively reproduce phenomena that have been empirically observed, like the dependence between size of the isolated area and the number of species inhabiting there or between primary production and complexity of food network. The model allows also studying formation and transformation of food-networks, influence of general factors (like intensity of primary productions) and possible causes of mass extinctions, and more generally, the role of ecological rules and pure chance in macroevolution. Some results were published jet (see below), some new will be presented.
HOMEPAGE: www.iss.uw.edu.pl/borkowski/

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Poster Session; Friday, July 1, 20:00

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Synchronization in coupled nonlinear dynamical systems

The study of coupling in dynamical systems has received an increasing interest since the 1990s. Recent studies of synchronization have included various measures for the detection of the different types of synchronization. Nevertheless, a comparison of different measures between coupled dynamical systems in controlled settings is still missing. For this aim the notion of synchronization will be used in a loose sense as the synonym of correlation, the similarity of the signals or the similarity of their dynamics. We present some of the nonlinear dynamics methods of synchronization: the mutual correlation dimension, the cross-approximate entropy, the mutual information function, the nonlinear interdependencies S, H, N and apply these measures to three coupled model systems. As the reference method, the linear cross-correlation function was used. We use the coupled Lorenz, Rössler and Lorenz-Rössler systems. Signals appearing here were used to illustrate the problems of reconstruction of attractors in the phase space, validation of methods for different parameters with the coupling strength. Mutual correlation dimension is the amount of information exchanged between systems. It allows to specify the relationship between systems dynamics. Cross approximate entropy is a method of measuring the complexity or irregularity of the signal. More regular signal has less value of approximate entropy. Mutual information is a measure of statistical independence of signals, if the value of zero means that two signals are independent. Low value (close to zero) measures S, H, N indicates the independence between the systems, while a high value indicates the synchronization. Correlation function is the dependence of the correlation of two signals. The results obtained by means of different algorithms failed to answer the question of which method is the best. It turns out that the results depend on the system and the type of coupling.

Poster Session; Friday, July 1, 20:00

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The cost and benefit of enzyme expression

The resources a microorganism has at it's disposal are limited. Among other things, this implies that expressing enzymes is costly. Consider for instance the specific growth rate, which is the rate of biomass synthesis per unit biomass. Expressing a certain enzyme increases the total biomass and thus, unless it contributes in some way to the biomass synthesis rate, will decreases the growth rate. Indeed, it has been observed that expressing "dummy" proteins has a negative effect on the growth rate [1,2].

In order to quantify the cost and benefit of enzyme expression, we generalized a definition previously proposed by Dekel and Alon [1]. The benefit function is closely related to the flux control coefficient, the cost is the directly related to the fraction of the resources dedicated to the enzyme. The flux is optimized if for each enzyme its control coefficient equals its contribution to the total resource usages. This is generalization of, and consistent with, earlier observations by Klipp and He [3].

The relation between the benefit function and the flux control coefficients allows us to intuitively understand the effects of kinetic parameters such as catalytic constants and Michaelis-Menten constants on the (optimal) flux, at least for small pathways. For instance, an enzyme with a high catalytic constant typically has a flux control coefficient that rapidly decreases with it's concentration, and we expect this enzyme to have a low expression in the optimal state.

We are currently applying the cost-benefit analysis to self-replicator models [4].

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Evolutionary Ecology; Thursday, June 30, 11:30

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Evolutionary behaviour in single-species discrete-time models: the importance of trade-offs, the underlying population dynamics and density dependence

We study a class of discrete-time single-species models typified by the logistic, Hassell and Ricker forms. These have been used to assess the population behaviour of ecological systems as, despite their relative simplicity, they can produce a wide variety of dynamics from stable equilibria and cycles to chaos. Here, we investigate the evolutionary behaviour of these models which has received much less attention. We use adaptive dynamics (supported by simulations) and assume there are two evolving parameters linked by a trade-off. We show that, for equilibrium underlying population dynamics, the evolutionary behaviour is restricted to an evolutionary attractor or an evolutionary repellor depending on the shape of the trade-off; branching cannot be exhibited. We further show that, in contrast to recent studies, this restriction in evolutionary behaviour is maintained in the standard Hassell model, and models which have a similar separable form, when the underlying population dynamics are cyclic. To gain a broader range of evolutionary behaviour requires considering models in which density-dependence operates differently on reproduction and survival. Such models can additionally for some trade-off shapes exhibit evolutionary branching or Garden of Eden evolutionary behaviour when the underlying population dynamics are non-equilibrium. Fundamental to such outcomes are discontinuous changes in the boundary for convergence stability (with respect to a measure of trade-off shape) across transitions (induced by parameter variation) between different types of underlying population dynamics. Trade-off shape and the nature of the underlying population dynamics can both have a marked effect on the evolutionary behaviour of ecological systems

Evolutionary Ecology; Wednesday, June 29, 08:30

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Stability and limit behavior of a distributed replicator system

The replicator equation is known to provide a general modeling framework for several distinct areas in mathematical biology. In particular, it arises as a selection equation in population genetics, as a dynamic description of the evolutionary game theory, and as a model for putative chemical reactions describing prebiotic evolution. In its simplest form, when the fitness of the species is a linear function of the relative abundances of other species, the replicator equation takes the form

$$\dot{v}_i = v_i \left[(\mathbf{A}\mathbf{v})_i - f^{loc}(t) \right], \quad i = 1, \dots, n, \tag{1}$$

where $\mathbf{v} = \mathbf{v}(t) = (v_1, \dots, v_n)$, $\mathbf{A}$ is an $n \times n$ matrix with elements a_{ij} describing the contribution of the j-th species to the fitness of the i-th species, $(\mathbf{A}\mathbf{v})_i = \sum_{j=1}^{n} a_{ij} v_j$, and the mean fitness $f^{loc}(t) = \langle \mathbf{A}\mathbf{v}, \mathbf{v} \rangle = \sum_{i=1}^{n} (\mathbf{A}\mathbf{v})_i v_i$ is chosen such that $\mathbf{v} \in S_n = \{\mathbf{v} \colon \sum_{i=1}^{n} v_i = 1\}$.

There are several different approaches to add space to (1). We suggest that the global regulation represents a natural and convenient approach to consider the replicator equation with an explicit spatial structure. To be exact, as a counterpart of the local model (1) we consider the model

$$\frac{\partial u_i}{\partial t} = u_i \left[(\mathbf{A}\mathbf{u})_i - f^{sp}(t) \right] + d_i \Delta u_i, \quad i = 1, \dots, n, \tag{2}$$

where now $\mathbf{u} = \mathbf{u}(\mathbf{x}, t)$, $\mathbf{x} \in \Omega \subset \mathbb{R}^k$, $k = 1, 2, 3$, $d_i > 0$ are diffusion coefficients, and the mean integral fitness is given, assuming Niemann's boundary conditions, by $f^{sp}(t) = \int_\Omega \langle \mathbf{A}\mathbf{u}, \mathbf{u} \rangle \, d\mathbf{x}$. This approach allows analytical investigation of (2): the tool which was mainly missing in the analysis of replicator equations with explicit space. In particular, it is possible to find the conditions for asymptotically stable rest points of (1) to be asymptotically stable homogeneous equilibria of (2). In our work, we show that for some values of the diffusion coefficients spatially heterogeneous solutions appear. Using a definition for the stability in the mean integral sense we prove that these heterogeneous solutions can be attracting; in particular this is the case for Eigen's hypercycle. Defining in some natural way evolutionary stable states for the distributed system (2), we provide the conditions for this distributed state to be an asymptotically stable stationary solution to (2).

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Profit optimization issues in livestock production in a randomly variable environment

We use quite general stochastic differential equation models to describe the dynamical behaviour of the individual growth of animals raised in a randomly varying environment. These models are conceptually more adequate to describe the effects of random environmental variations on growth than the classical regression techniques (which are appropriate to describe measurement errors). We describe parameter estimation and prediction methods, illustrating with data on cow growth of the Mertolengo breed raised in Alentejo (Portugal) under natural conditions and show that they outperform the traditional regression models in predictive power. Mixed models, with random variation among animals of average asymptotic size, are also considered.

An application of these models to profit optimization in livestock production is shown.

Assuming the animal is to be sold when it reaches some prescribed age and that there are fixed and variable costs (per unit time) in raising the animal and the selling price is proportional to the animal's weight, we determine the optimal age at which an animal should be sold in order to maximize profit.

The first passage time distribution through a prescribed size is studied and used to determine the optimal size at which the animal should be sold. We can then determine which policy (selling at a fixed age or selling at a fixed size) is preferable in terms of expected profit.

Some issues related to optimization for the simultaneous raising of several animals will also be discussed.

Recent advances in infectious disease modelling II; Saturday, July 2, 14:30

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The nationwide incidence of hepatitis C in Egypt: Toward realistic estimates

Recently, the nationwide incidence of hepatitis C in Egypt has attracted much attention both in the scientific literature and mass media. Alarming new estimates exceeding 500 000 new cases per year (6.9/1000 per person-year) have been made based on data originating from the Egyptian Demographic and Health Survey performed in 2008. However, a more complete analysis of the hepatitis C epidemiology in Egypt, based on additional national-level as well as cohort-level data, reveals a very different story. First, it unveils a complex epidemic dynamics that violates the simplistic methodological assumptions made for the incidence estimates; it thus becomes obvious that incidence has been overestimated. Second, a comparison with direct incidence measurements in rural cohorts suggests that the overestimation is by at least a factor of three. Accurate estimate of the hepatitis C incidence in Egypt remains a task for the future.

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Information, human behaviour and disease; Saturday, July 2, 11:00

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Health newscasts for increasing influenza vaccination coverage: How much is too much?

Both pandemic and seasonal influenza are receiving more attention from mass-media than ever before. Frequent topics are epidemic severity, vaccination, etc., changing the way in which we perceive the utility of disease prevention. Voluntary influenza vaccination has been recently modeled using inductive reasoning games. Thus, it has been found that severe epidemics cannot be prevented by voluntary vaccination unless vaccination incentives are offered. However, a key assumption has been that individuals make vaccination decisions based on whether there was an epidemic each influenza season; no other epidemiological information is available to them. In this work, we relax this assumption and investigate the consequences of making more informed vaccination decisions while no incentives are offered. We obtain two major results. First, providing additional epidemiological information to the public may stabilize the vaccination coverage and suppress severe influenza epidemics. Second, when severe epidemics are prevented, if even more epidemiological information is released to the public, then the vaccination coverage decreases. We discuss three scenarios where individuals know (i) the prevalence, (ii) the vaccination coverage and (iii) both the prevalence and the vaccination coverage every influenza season, in addition to whether there was an epidemic.

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Poster Session; Friday, July 1, 20:00

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Wave–pinning Mathematical Model of Plant Root Hair Initiation

A simple mathematical model is developed of a key cellular–level process in plant morphogenesis, namely the biochemical process wich triggers outgrowth of a hair within a root hair cell of *Arabidopsis*. It involves the dynamics of the small *G–proteins* known as *ROPs* which bind to a specific location on the cell membrane, triggering cell wall softening and subsequent hair growth. A non–homogeneous reaction–diffusion model is taking into account where a catalytic effect of the hormone auxin is described which is experimentally known to play an important role in the location of the hair on the cell. Local analysis, numerical bifurcation analysis and numerical simulation in 1D are used to the better understanding the dynamics of location point of the root hair formation.

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Population Dynamics; Wednesday, June 29, 11:00

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Interspecific kleptoparasitism

Although interspecific kleptoparasitism is widespread, theoretical models have focussed on the intraspecific case. We develop a game-theoretic model of interspecific kleptoparasitism, ultimately based on Ruxton and Moody [1], considering optimal host and parasite strategies. We explore the possibility that, on an ecological time scale, the system does not settle to a steady state but to oscillatory behaviour in strategy space.

References.

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Epidemic models: Networks and stochasticity II; Thursday, June 30, 11:30

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Dynamic networks in dynamic populations

We study a randomly growing population (where new individuals are born and old die) in which edges between individuals appear and disappear randomly over time. A specific feature of the model is that individuals are born with a "social index" which affects how frequently they create new neighbours. For this model we study asymptotic properties valid after a long time: the degree distribution, degree correlation and a threshold condition determining whether a giant connected component exists or not. (Joint work with Mathias Lindholm and Tatyana Turova)

Epidemics; Tuesday, June 28, 11:00

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Tuberculosis - the family disease?

Tuberculosis (TB) cases have been long been noted to cluster within households. In 1820, when the famous English poet John Keats died of TB, he was the third in his family to do so: two years earlier, his brother died of TB, and eight years before that, their mother had also died of TB. Years later in 1841, a third brother developed and died of TB.

It is unclear whether clustering of cases represents household transmission or shared household risk factors. TB is a chronic disease and the long timescales between infection and disease mean that the transmission processes can be difficult to untangle. In this presentation, I examine cross-sectional TB data from households in Lima, Peru, to estimate the importance of household transmission, the average time between cases, and the immunity afforded by a previous TB infection. Using probabilistic and SIR-type models with household structure, we investigate how the distribution of cases changes during the course of an epidemic. The framework lends itself for investigating the role of multiple reinfections and immunity in transmission. In this population, we estimate that protective immunity conferred up to 35% reduction in the risk of disease. Like the Keats family, we find that household cases can occur decades apart, although the average time between cases within households is 3.8 years.

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Game theoretical modelling and optimization in evolution and ecology II;
Tuesday, June 28, 14:30

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Evolution in structured populations: modelling the interactions of individuals and groups

Recently models of evolution have begun to incorporate structured populations, including spatial structure, through the modelling of evolutionary processes on graphs (evolutionary graph theory). One limitation of this otherwise quite general framework is that interactions are restricted to pairwise ones, through the edges connecting pairs of individuals. Yet many animal interactions can involve many players, and theoretical models also describe such multi-player interactions. We shall discuss a more general modelling framework of interactions of structured populations with the focus on competition between territorial animals, where each animal or animal group has a "home range" which overlaps with a number of others, and interactions between various group sizes are possible. Depending upon the behaviour concerned we can embed the results of different evolutionary games within our structure, as occurs for pairwise games such as the prisoner's dilemma or the Hawk-Dove game on graphs. We discuss some examples together with some important differences between this approach and evolutionary graph theory.

Poster Session; Friday, July 1, 20:00

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A model for cyst lumen expansion and size regulation via fluid secretion

Many internal epithelial organs derive from cysts, which are tissues comprised of bent epithelial cell layers enclosing a lumen. Ion accumulation in the lumen drives water influx and consequently water accumulation and cyst expansion. Lumen-size recognition is important for the regulation of organ size. When lumen size and cyst size are not controlled, diseases can result; for instance, renal failure of the kidney. We develop a mechanistic mathematical model of lumen expansion in order to investigate the mechanisms for saturation of cyst growth. We include fluid accumulation in the lumen, osmotic and elastic pressure, ion transport and stretch-induced cell division. We find that the lumen volume increases in two phases: first, due to fluid accumulation stretching the cells, then in the second phase, the volume increase follows the increase in cell number until proliferation ceases as stretch forces relax. The model is quantitatively fitted to published data of in vitro cyst growth and predicts steady state lumen size as a function of the model parameters.

Multi-scale mathematics of the liver: From intracellular signaling to intercellular interaction; Wednesday, June 29, 08:30

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Modelling Endocytosis - from the Molecules to the Liver Cell

Endocytosis is a conserved cellular process in eukaryotes by which nutrients are assimilated by the cell. Internalized material is transported by endosomes and sorted by means of endosome transitions. Endosome transitions result from dynamic interactions among Rab GTPases. We focus on Rab5-Rab7 and Rab5-Rab4/11 interactions underlying respectively early-to-late and early-to-recycling endosome transitions that select among the degradative, recycling and transcytotic routes in liver cells. As a model of endosome transitions, we consider the spatial concentration profiles of competing GTPases and the shift of the resulting concentration front in a one-dimensional system across the endosomal membrane. Locally, interacting GTPases can be modelled as a bistable system of either the cut-out switch or the toggle switch type [1]. For the toggle switch, all stable steady state solutions depend monotonically on parameters whereas the cut-out switch yields an increasing solution which then switches off. We extend those two models by diffusive spatial coupling. Heterogeneous initial conditions of the reaction-diffusion system lead to spatially alternating GTPase concentration domains and interjacent concentration fronts. In general, the front is invading that domain which has the smaller concentration difference from the unstable saddle solution. Hence, an intermediate parameter value exists at which the front remains stationary. The toggle switch kinetics yields this expected behaviour whereas the cut-out switch system shows novel behaviour. Corresponding to the toggle switch properties, we propose that this mechanism underlies the observed coexistence of Rab5-Rab4/11 domains during the early-to-recycling endosome transition. On the other hand, the behaviour of the spatially extended cut-out switch system reinforces the role of the cut-out switch for early-to-late endosome transitions. Moreover, we link this molecular understanding to the cell level by means of an agent-based model representing the population of and biophysical interactions between early endosomes within one cell. Simulation results identify critical regulatory steps that control efficient cargo flux which is essential for liver cells.

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Keywords: endocytosis, Rab GTPAses, reaction-diffusion system, traveling-wave solutions, cut-out switch, toggle switch

Heart rate dynamics: models and measures of complexity (part II);
Wednesday, June 29, 17:00

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Oscillations and synchronization in human circulatory system

Human cardiovascular system exhibits interesting dynamics, which is expressed in beat-by-beat changes of such variables as heart rate (interbeat interval) and blood pressure. As the system is complex, the origin of this dynamics is complex as well. Part of the dynamics is of neural or electrophysiological nature, depending on the functional state of the heart muscle, which is an example of an active medium, subject to neural control. Another part of the dynamics is related with the vascular response to the hemodynamic heart action. This response depends on vascular resistance and on elastic properties of the vascular wall. The resulting blood pressure and chemical properties (pH) are constantly monitored by specific receptors that initiate neural reflexes, which applies neural control to specific variables. There are many independent mechanisms that may be activated in order to respond to certain fluctuations. Moreover, the characteristic times of different control loops may differ by order of magnitude.

Another source of complex oscillations, crucially important for homeostasis is the respiratory system. All the systems are interrelated in a complex way and give rise to the complex cardiovascular dynamics. One of interesting phenomena that arises in such a system is the cardiorespiratory synchronization and the related phenomenon of the interdependence between short-term dynamics of blood pressure, heart rate and breathing. Both problems will be addressed in the talk.

Analysis of mathematical models for cancer growth and treatment, Part III; Tuesday, June 28, 17:00

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Mathematical model of the mechanism of the activation killer cells after the BCG treatment in bladder cancer

Bladder cancer (BC) is the most frequently occurring urological cancer and the fifth most common cancer among men, accounting for approximately 200,000 new cases worldwide annually. I would like to present a new mathematical model that describes the growth of superficial bladder cancer and the effect thereupon of immunotherapy based on the administration of Bacillus Calmette-Guerin (BCG) combined or not with interleukin-2 (IL-2). Intravesical instillations of BCG performed after surgical removal of tumors represents an established treatment with approximately 50% success rate. So far, attempts to improve this efficiency have not led to essential changes. However, convincing clinical results have been reported on the combination of IL-2 to BCG, even though this is still not applied in current practice. The present model provides insights into the dynamical outcomes arising in the bladder from the interactions of immune cells with tumor cells in the course of BCG therapy associated or not with IL-2. Specifically, from the simulations performed using nine ordinary and non-linear differential equations we obtained indications on the conditions that would result in successful bladder cancer treatment. We show that immune cells effector lymphocytes, natural killer cells and antigen-presenting cells expand and reach a sustainable plateau under BCG treatment, which may account for its beneficial effect, resulting from inflammatory "side-effects" which eliminate residual or eventual newly arising tumor cells, providing thus protection from further cancer development.

Information, human behaviour and infection control; Saturday, July 2, 08:30

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Nonlinear stability of epidemic models including information-related human behaviour

We study the nonlinear stability properties of epidemic models with a feedback mechanism, which describes the influence of information, and of information- related delays, on human behaviour [3,4]. In particular, we give a special example of application of two stability methods: the geometric method for global stability, due to Li and Muldowney [5], and a Lyapunov-based approach, which provides necessary and sufficient conditions for the local nonlinear stability of equilibria [6]. Some of the results presented here are included in the recent papers [1] and [2].

References.

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Emergence of sparsity and motifs in gene regulatory networks

We consider a simple model of gene regulatory dynamics derived from the statistical framework describing the binding of transcription factors to DNA. We show that the networks representing essential interactions in gene regulation have a minimal connectivity compatible with a given function. We discuss statistical properties using Monte Carlo sampling. We show that functional networks have a specific motifs statistics. In the case where the regulatory networks are to exhibit multi-stability, we find a high frequency of gene pairs that are mutually inhibitory and self-activating. In contrast, networks having periodic gene expression patterns (mimicking for instance the cell cycle) have a high frequency of bifan-like motifs involving four genes with at least one activating and one inhibitory interaction.

Population Genetics; Friday, July 1, 14:30

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The effects of linkage and gene flow on local adaptation: A two-locus continent-island model

We study a population-genetic model of evolution in a derived (island) population that experiences altered environmental conditions and maladaptive gene flow from the ancestral (continental) population. It is assumed that locally advantageous mutations have arisen on the island at two linked loci. Gene flow in concert with selection induces substantial linkage disequilibrium. This has a number of consequences for evolution. The central mathematical result is an explicit characterization of all possible equilibrium configurations. From this, we deduce explicit expressions for two measures of linkage disequilibrium. We determine explicitly how the maximum amount of gene flow that admits the preservation of the locally adapted haplotype depends on the strength of recombination and selection. We also study the invasion of beneficial mutants of small effect that are linked to an already present, locally adapted allele. As a consequence of linkage disequilibrium, mutants of much smaller effect can invade successfully than predicted by naive single-locus theory. This raises interesting questions on the evolution of the genetic architecture, in particular, about the emergence of clusters of tightly linked, slightly beneficial mutations and the evolution of recombination and chromosome inversions. Finally, the influence of linkage on the degree of local adaptation and the migration load is explored.

References.

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Homogenization of a model of propagation of a fungal disease in a heterogenous crop field

For production purpose, crop fields usually display a high degree of periodic spatial structure: vineyards are made of vine rows, orchards of regularly spaced trees...

To model this, we introduce a small parameter $\varepsilon > 0$. The crop field, assumed to be large, is described by a domain $\Omega \subset \mathbb{R}^N$, $N = 1, 2$ or 3. Let $Y = [0,1]^N$ the reference cell, and $Y_1 \subset Y$. The set Y_1 describes the part of Y occupied by the crop. The domain Ω is then equal to $\Omega_1^\varepsilon \cup \Omega_2^\varepsilon$ where

$$\Omega_1^\varepsilon = \{x \in \Omega,\ \chi_{Y_1}(x/\varepsilon) = 1\},\ \Omega_2^\varepsilon = \{x \in \Omega,\ \chi_{Y_1}(x/\varepsilon) = 0\}.$$

For example, in a orchard or in a vineyard, each cell Y could contain a single tree or vine stock. For a vineyard, each cell Y could also contain an entire row of vine stocks. This modeling formalism also applies to the case of cultivar mixture fields that could be used for disease control [2].

We study the propagation of a fungal disease over this field. The following model is a simplified version of the one in [1]. The vectors of the propagation of the disease are the spores produced by the fungus lesions. We assume that these spores disperse according to a Fickian diffusion process. Moreover they may disperse at the cell range, hence the diffusion coefficient will be or order ε^2, or at long range. A very simple model for this is given by the following system of partial differential equations that describe the spores production and dispersal, coupled with an ordinary differential equation of SI type that describes the inoculation of the crop by the fungus:

$$\begin{cases} \dfrac{\partial S_S^\varepsilon(t,x)}{\partial t} - \varepsilon^2 \nabla.(d_S(x,x/\varepsilon)\nabla S_S^\varepsilon(t,x)) + S_S^\varepsilon(t,x) = (1 - P(t,x,x/\varepsilon))I^\varepsilon(t,x), \\ \dfrac{\partial S_L^\varepsilon(t,x)}{\partial t} - \Delta S_L^\varepsilon(t,x) + S_L^\varepsilon(t,x) = P(t,x,x/\varepsilon)I^\varepsilon(t,x), \\ \dfrac{\partial I^\varepsilon(t,x)}{\partial t} = \chi_{Y_1}\left(\dfrac{x}{\varepsilon}\right)(S_S^\varepsilon(t,x) + S_L^\varepsilon(t,x))\,(1 - I^\varepsilon(t,x)) \end{cases}$$

for $t > 0$ and $x \in \Omega$ a regular bounded open subset of $\mathbb{R}^N$, supplemented with Neumann boundary conditions

$$\partial_\nu S_S^\varepsilon(t,x) = \partial_\nu S_L^\varepsilon(t,x) = 0, \quad \forall t > 0 \text{ and } x \in \partial\Omega$$

and with some initial data.

The state variables are: S_S^ε the short range spores density, S_L^ε the long range spores density and I^ε the diseased foliar surface density. The ode describing the evolution of I^ε is non trivial only if $x \in Y_1$.

Now we are able to show that as ε tend to 0, up to a subsequence, the solution of this model converges towards the solution of a homogenized problem. This homogenized problem is a coupled system of equations at the macroscopic scale (in Ω) and at the microscopic one (in Y). To prove this result, we use standard results from homogeneization theory, see e.g. [3]. The benefit from this homogeneization process is that the numerical computation of the solution of the homogenized problem is easier than the original one.

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Cellular Systems Biology; Tuesday, June 28, 14:30

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Modelling in vitro crypt formation

In vitro cultures of intestinal tissue have been tried for decades. Only recently Sato and co-workers succeeded in establishing organoid cultures from single cells [1]. In these cultures intestinal cells expressing the stem cell marker Lgr5 form crypt-like structures similar to those found *in vivo*. The mechanisms that underlie the formation of these spatially-organised structures are currently a matter of debate.

We here present a 3D biophysical model of de novo crypt formation *in vitro*. The model builds on an individual cell-based model of crypt dynamics recently published by us [2]. We extended this model by introducing a flexible basal membrane. This membrane can be reorganised by cells showing active matrix metabolism.

In this model, shape changes of the basal membrane result from a feedback loop between its curvature and the Wnt-activity of adherent cells. Thereby, increased Wnt-activity increases the adhesion strength of the cells and thus, forces local shape changes of the basal membrane. We demonstrate the formation of crypt-like structures within this model depending on the elasticity and stiffness of the basal membrane and on the adhesion properties and matrix metabolisms of the different cell types.

We suggest the proposed mechanism to be a principal one in epithelial gland formation.

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Poster Session; Friday, July 1, 20:00

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Transient chaos measurements using finite-time Lyapunov exponents in model of population dynamics

The family of logistic maps is the best known nonlinear model of population dynamics. The typical analysis of this model is concentrated on its asymptotic behaviour. Special attention is payed to properties of trajectories generated by the maps inside periodic windows, where the periodic behaviour occurs [1]-[3]. However such periodic behaviour is preceded by chaotic transient behaviour. The duration of such transient chaos can be prolonged [4],[5] .

We propose a model for estimating the duration of transient chaos based on calculation of finite-time Lyapunov exponents. Lyapunov exponents belong to the most useful tools applied for measuring sensitivity to initial conditions in the case of asymptotic chaos. We used Lyapunov exponents for characterizing sensitivity to initial conditions in the case of transient chaos. Before doing that we modify the notion of finite-time Lyapunov exponent averaging them over a set of initial conditions and we report results of tests providing evidence in favor of correctness of such an approach. We also present a model reproducing correctly variation in time of the finite-time Lyapunov exponents corresponding to transient chaos.The dependence on time is verified by comparing theoretically predicted values with those obtained numerically.

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Modeling Dynamics of Complex Biological Systems; Tuesday, June 28, 17:00

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Critical roles for intracellular binding proteins in creating a robust retinoic acid morphogen gradient

Retinoic acid (RA) is a vitamin A derivative that acts as a graded morphogen to promote posterior cell fates in the vertebrate central nervous system (CNS). CNS development occurs normally over a 20-fold range of RA concentrations, indicating a remarkable degree of gradient robustness.

Cellular retinoic acid binding proteins (Crabps) transport RA intracellularly but their roles in morphogen gradient formation remain unclear. Using a combination of computational and experimental approaches in zebrafish, we show that both positive and negative feedback by Crabps on RA signaling dramatically improves robustness. Crabps improve robustness within an optimal concentration range and transport of Crabp bound RA to Cyp26 degradation enzymes appears to be critical for these robustness gains. These results suggest that Crabps are essential for modulating the RA signaling gradient in the face of varying levels of dietary vitamin A.

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Spatially-resolved mathematical modeling of T cell antigen recognition

T cells play a crucial role in the adaptive immune response. Interactions with specific antigens initiate T cell signaling but also ensure that the majority of self-reactive cells are selectively deleted in the thymus during its maturation. However, the underlying mechanisms remain unclear as to why T cells can reliably distinguish cognate antigens from other peptides that have only slightly weaker affinity to the T cell receptor (TCR). Recent data indicate that the clustering of TCRs at the interface of T cell and antigen-presenting cell could be the key to the exquisite ligand recognition specificity. We develop a spatially-resolved mathematical model based on the reaction-diffusion dynamics of individual TCRs. We use stochastic Monte Carlo simulations to analyze the model and its ability to exhibit TCR clustering. The model aims at rationalizing experiments that have demonstrated a sharp affinity threshold for thymic selection. It will help us to identify the role of TCR clustering and the core elements initializing T cell signaling during antigen recognition and will inform new experimental work.

Undergraduate Biomathematics Education Beyond BIO 2010 (Part II);
Saturday, July 2, 08:30

Hannah Callender
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What My Biology Students Taught Me About Mathematics

Many colleges and universities struggle with finding ways to meet the quantitative needs of their biology and life science majors. At the University of Portland, these students have in the past been enrolled in the traditional calculus sequence, where the majority of applications are geared heavily towards engineering and physics. Our biology and life science majors come out of this course not only feeling as though calculus had no connection to their discipline, but also struggling more than students in other disciplines, possibly from lack of motivation. Here I will share my experiences in the development and implementation of a first semester biocalculus course and what I learned from my students, including their beliefs about mathematics pre- and post-biocalculus as well as similarities and differences in their styles of learning mathematics.

Ecosystems Dynamics; Tuesday, June 28, 11:00

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Estimation of the stratified dispersal rate

The establishment and spread of invading organisms have dramatic consequences for ecosystems. Many organisms expand their range by being transferred passively over short and long distances simultaneously, thus resulting in a stratified dispersal process [**1, 2**] . The stochastic events of long-distance dispersal complicate the estimation of the spread rate of an invading population. Our goal is to measure the accelerating effect of secondary foci created by long-distance dispersal on the invasion spread rate. We developed a spatially explicit host-pathogen model describing independently continuous short- and stochastic long-distance dispersal processes. Comparison of exact solutions of diffusive spread with results of Monte Carlo simulations of stratified dispersal allowed us to estimate the impact of long-distance dispersal events on the spread rate. Due to independent description of the two modes of dispersal, the developed model can be parameterized easily and used in epidemiology. The explicit representation of the two-dimensional habitat allows coupling our model with a landscape optimization method to design landscapes unfavorable to fast epidemics spread.

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Crowd Dynamics: Modeling, Analysis and Simulation (Part 1); Wednesday, June 29, 11:00

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Calibrating walker models: variations of parameters due to traffic regimes

Modelling the wide range of walking behaviours is not a simple task and several type of walker models have been proposed such as CA [**1**], discrete choice [**2**], social force [**3**] and utility based models [**4**]. Albeit different in their mathematical properties, these models share a modelling assumption in dividing the pedestrian behaviours in components such as path following, pedestrian avoidance and obstacle avoidance behaviours. In all these models the path following component describes the free-flow conditions and the other two components describe how pedestrians deviate from their free-flow behaviours due to the presence of other pedestrians. The effects of the components are simply added and their parameters remain constant regardless of external conditions. In this investigation we show that the hypothesis of invariance of the parameters is incorrect leading to significant modelling errors.

To investigate the pedestrian behaviours we perform a series of calibrations of the Nomad model [**4**] with empirical data from experiments representing different types of flows such as bidirectional, crossing and unidirectional flows. Each pedestrian trajectory is used to estimate one set of parameters using the methodology developed in [**5**]. The estimated parameter set is then associated with the average speed of the pedestrian that produced the trajectory. The average speed accounts for the traffic flow intensity that pedestrians had encountered. We show that the values of the path following parameter display two distinct regimes that correspond to free-flow and congestion, and that between the two regimes there is a smooth variation resembling a sigmoid curve. The parameters of the pedestrian avoidance component also display significant variation with walking speeds. The consequences of these findings is that by showing that the behavioural components are affected by traffic regimes, they should incorporate variation of parameters to improve their estimation quality.

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Cancer; Tuesday, June 28, 11:00

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Population behaviour of cancer stem cells

Stem cells are cells with two specific features - the ability to differentiate into all range of specialized cell types and the ability to renew themselves. There are several possible scenarios of cancer stem cells evolution, among which the asymmetric cell divisions providing self-renewing, is the main one. The main theory for today for either normal or cancer stem cells is that they differentiate when they receive some kind of "instructive" signal influencing the pattern and speed of cell divisions in the given conditions. All current experiments reporting the dynamics of cancer stem cell populations in culture allow to conclude that the main feature is the same - the stability of the percentages of these cell populations in the whole population of cancer cells, independently of the starting conditions. In this paper we compare the qualitative behavior of mathematical models of stem cells evolution, without and with an underlying signal. In absence of an underlying field, we propose a mathematical model described by a system of ordinary differential equations, while in presence of an underlying field it is described by a system of delay differential equations, by admitting a delayed signal originated by the existing cells. In particular we show the stability of percentages for the ODE system, and the possibility of oscillations in the cell populations only in presence of an underlying field. The hope is that the results of this paper may stimulate further experiments to either validate or not the existence of the above mentioned "instructive" signals.

Keywords: Cancer stem cells, delay differential equations, qualitative behavior, stability, oscillations.

Analysis of mathematical models for cancer growth and treatment, Part II; Tuesday, June 28, 14:30

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An hybrid analysis of multiscale models for angiogenesis

Angiogenesis, the growth of new blood vessels, is an important natural process occurring in the body, both in health and in disease. It is an example of complex system: the endothelial cells are the building blocks for the vessels and they interact by regulation signals, forming a network of capillaries in order to reach every part of the body.

As examples of real experimental systems we consider tumour driven angiogenesis and the embryonic mouse retinal angiogenesis.

An angiogenic system is extremely complex, due to its intrinsic multiscale structure; a major source of complexity in the mathematical modelling derives from the strong coupling of the kinetic parameters of the relevant stochastic branching-and-growth of the capillary network at the microscale, with a family of interacting underlying fields at a macroscale. This is the reason why in literature we may find a large variety of mathematical models addressing some of the features of the angiogenic process, and still integration of all relevant features of the process is an open problem.

Thus our main goal is not in providing additional models for the angiogenic phenomenon but in addressing the mathematical problem of reduction of the complexity of such systems by taking advantage of their intrinsic multiscale structure. A satisfactory mathematical modelling of angiogenesis and of many other fiber processes requires a geometric theory of stochastic fibre processes. We present here a simplified stochastic geometric model, largely inspired by current literature, both mathematical and biological ones, for a spatially structured angiogenic process, strongly coupled with a family of relevant underlying fields.

The branching mechanism of blood vessels is modelled as a stochastic marked counting process describing the birth of endothelial cells, while the whole network of vessels is modelled as the union of their trajectories; finally, capillary extensions are expressed by a system of a random number of stochastic differential equations, coupled with the PDEs describing the evolution of the underlying fields involved in the process. On one side the kinetic parameters of the construction of the capillary network depend upon the family of underlying fields, on the other side the evolution of the underlying fields relies on the evolving capillary network. Since this one is a stochastic process, the evolution equations of these fields will be a set of random partial differential equations, leading to random kinetic parameters. We are thus facing a problem of double stochasticity. This is a major source of complexity

which may tremendously increase as the number of cells becomes extremely large, as it may happen in many cases of real interest. Under these last circumstances, by taking into account the natural multiple scale nature of the system a mesoscale may be introduced, which is sufficiently small with respect to the macroscale of the underlying fields, and sufficiently large with respect to typical cell size. At the level of this mesoscale, we may then approximate (law of large numbers) the contribution due to the vascularization process by local mean values, in the equations for the underlying fields thus providing a family of underlying deterministic fields. We may then use these approximate mean fields to drive the evolution of the relevant stochastic processes cells at the microscale. In this way only the simple stochasticity of the geometric processes of birth (branching) and growth is kept, and it is possible to generate a nontrivial and realistic geometric pattern of the capillary network. This kind of models are known as hybrid models since we have substituted all stochastic underlying fields by their averaged counterparts; most of the current literature could now be reinterpreted along these lines. It is necessary to stress that anyhow substituting mean geometric densities of tips, or of full vessels to the corresponding stochastic quantities leads to an acceptable coefficient of variation (percentage error) only when a law of large numbers can be applied, i.e. whenever the relevant numbers per unit volume are sufficiently large; otherwise stochasticity cannot be avoided, and in addition to mean values, the mathematical analysis and/or simulations should provide confidence bands for all quantities of interest. This fact is well evidenced by the numerical simulations. If we homogenize the underlying fields ab initio we obtain a trivial capillary network, which confirms that during the early phases of the network formation, the number of endothelial cells is not sufficiently large to let us apply laws of large numbers yet.

Applications of nonnegative Radon measure spaces with metric structure to population dynamic models; Wednesday, June 29, 17:00

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On some kinetic models of swarming

We will present a kinetic theory for swarming systems of interacting, self-propelled discrete particles. Starting from the the particle model, one can construct solutions to a kinetic equation for the single particle probability distribution function using distances between measures. Moreover, I will introduce related macroscopic hydrodynamic equations. General solutions include flocks of constant density and fixed velocity and other non-trivial morphologies such as compactly supported rotating mills. The kinetic theory approach leads us to the identification of macroscopic structures otherwise not recognized as solutions of the hydrodynamic equations, such as double mills of two superimposed flows. I will also present and analyse the asymptotic behavior of solutions of the continuous kinetic version of flocking by Cucker and Smale, which describes the collective behavior of an ensemble of organisms, animals or devices. This kinetic version introduced in Ha and Tadmor is obtained from a particle model. The large-time behavior of the distribution in phase space is subsequently studied by means of particle approximations and a stability property in distances between measures. A continuous analogue of the theorems of Cucker-Smale will be shown to hold for the solutions on the kinetic model. More precisely, the solutions concentrate exponentially fast their velocity to their mean while in space they will converge towards a translational flocking solution.

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Evolutionary insights from semi-discrete plant epidemic models.

The coexistence of closely related plant parasitic species is ubiquitous in agriculture. However, understanding the ecological determinants of evolutionary divergence in parasites still represents an issue, in both evolutionary biology and agricultural sciences. To our knowledge, the only ecological mechanism which has been generically shown to promote phenotypic divergence in plant parasitic species is spatial host heterogeneity. However, spaceis not the only source of ecological heterogeneity. Interestingly, crop plant parasites face abrupt, periodic changes in host density due to planting and harvesting. In this paper, we investigate whether such heterogeneity in time can promote evolutionary divergence as well. We make use of an epidemic model that combines continuous and discrete dynamics, to capture sharp seasonal events. Performing an evolutionary invasion analysis, we show that evolutionary branching of the parasite phenotype can occur, assuming there is a trade-off between intra- and inter-season transmission abilities. Since there are experimental evidence for such a trade-off, this study provides further ecological bases for the coexistence of closely related plant parasite species. Moreover, this study provides original insights regarding the coexistence of mono- and poly-cyclic sibling plant pathogens.

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Grasshopper population interpolation with Generalized linear models

This study was carried up in grassland areas in Durango México. Between latitude (23.916°, 25.983°) and longitude (-104.997°, -104.010°). There were established sampling sites. At each of these sites, twice a month a grasshopper sampling was done from June to November 2003. Three were the most abundant species. The purpose of this study was to create grasshopper population maps with linear regression.

Since the assumption of normality failed for the dependent variables, the distributions Poisson, Gamma and Inverse binomial of the generalized linear models were analyzed. taking as dependent variable the number of grasshopper surveyed of each species and the independent variables were, latitude (°), longitude (°), altitude (m), slope (percentage), temperature (annual average °C), precipitation (annual mm), landcover, type of vegetation, type of soil and vegetation index. According to the deviance criteria the best model was Gamma with logarithmic link function since the deviance 11.211 with 9 d. f. was lower than 16.91 the 95-th percentile of the chi-squared with 9 d.f. The distributions of the residuals were heterogeneous at the three grasshopper species and the lowest correlation coefficient between predicted grasshopper and observed was R^2=0.83. The generalized linear models are alternative models when the normal assumption has not been reached and when the dependent variable is a count data.

Population Dynamics; Thursday, June 30, 11:30

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Discrete and continous models in evolutionary dynamics

We study the large population limit of the Moran and the Wright-Fisher process, under the assumption of weak-selection, and for different scalings. Depending on the particular choice of scalings, we obtain a continuous model that may highlight the genetic-drift (neutral evolution) or natural selection; for one precise scaling, both effects are present. For the scalings that take the genetic-drift into account, the continuous model is given by a singular diffusion equation, together with two conservation laws that are already present at the discrete level. For scalings that take into account only natural selection, we obtain a hyperbolic singular equation that embeds the Replicator Dynamics and satisfies only one conservation law. The derivation is made in two steps: a formal one, where the candidate limit model is obtained, and a rigorous one, where convergence of the probability density is proved. Additional results on the fixation probabilities are also presented.

Systems Biology of Development; Saturday, July 2, 14:30

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The role of Wnt3 in early Hydra head regeneration

Several organisms including planaria, fish, insects and salamanders respond to injury and amputation by regenerating the lost body part. A general open question is: How does the remaining tissue 'measure' the degree of injury and mount a regeneration response of adequate magnitude? This question is studied in the fresh water polyp Hydra. The Hydra body column can be viewed as a hollow bilayered tissue cylinder with head and foot on opposite ends referred to as apical and basal, respectively. The tissue consists of the following cell types: ectodermal and endodermal cells (in the epithelial lineage), interstitial stem cells, progenitors, neurons, nematocytes and gland cells (in the interstitial lineage). Previous experiments of cutting Hydra into two halves showed secretion of Wnt3 molecules by cells undergoing apoptosis near the amputation plane of the basal half [1].

We model this immediate Wnt3 response and the following response of the different cell types by a system of coupled partial differential equations. We assume that Wnt3 is produced by apoptotic cells near the amputation plane, diffuses deeper into the tissue and subsequently undergoes a lytic degradation. We model the cell dynamics considering cell differentiation, self-renewal, apoptosis (triggered by amputation), basal loss of cells due to migration toward the extremities along with increases in cell proliferation and cell migration in response to the concentration and spatial gradient of Wnt3, respectively.

We implemented the model in a simulation program coded in C++. Model-dependent fitting simulations to the experimental data [1] demonstrated that these mechanisms could be responsible for the measured cell dynamics, corroborating an important role of Wnt3 within the injury response that ultimately determines the fate of the regeneration process in Hydra.

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Analysis of mathematical models for cancer growth and treatment, Part III; Tuesday, June 28, 17:00

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The "Go-or-Grow" hypothesis in glioma growth: mathematical modeling and analysis

Gliomas are very aggressive brain tumors, in which tumor cells gain the ability to penetrate the surrounding normal tissue. The invasion mechanisms of this type of tumor are not yet fully understood. Our work is motivated by the migration/proliferation dichotomy ("Go-or-Grow" hypothesis), *i.e.* the antagonistic migratory and proliferating cellular behaviors in a cell population, which may play a central role in these tumors [**3**].

In a first part, we present results obtained by using a lattice-gas cellular automaton and show the influence of the Go-or-Grow mechanism on the dynamics of glioma growth, which we qualitatively compare to *in vitro* data [**5**].

In a second part, we formulate continuum models to investigate the influence of quiescence phases on the dynamics of a population of glioma cells. We propose a "Go-or-Rest" model and describe cell migration as a velocity-jump process including resting phases. We derive the corresponding macroscopic model and show that anomalous diffusion arises from the switch between motile and quiescent phases. In particular, sub- and super-diffusion regimes can be observed and are governed by a parameter describing intrinsic migratory properties of cells [**2**]. We show that our results are in excellent agreement with *in vitro* data of glioma tumor expansion [**1**] when the switch to quiescence is regulated by the cell density. We furthermore show how this density-regulation allows for the the formation of immotile aggregates in the context of the Turing instability. We use a combination of numerical and analytical techniques to characterize the development of spatio-temporal instabilities and traveling wave solutions generated by our model. We demonstrate that the density-dependent Go-or-Grow mechanism can produce complex dynamics similar to those associated with tumor heterogeneity and invasion.

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Multiscale modeling of biological systems: from physical tools to applications in cancer modeling II; Saturday, July 2, 11:00

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Multiscale modeling of biological systems

Modeling phenomena in biology often requires the inclusion of processes occurring at different spatial and temporal scales. There is an urgent and challenging need to describe biological systems utilizing a multiscale landscape and not just a single scale view. To this end, theories from Mathematics and Physics can provide tools for the modeling and analysis of multiscale phenomena. In this talk, we present a theoretical multiscale framework inspired from Physics, the *Dynamic Density Functional Theory*, which we apply to derive a modeling approach for biological systems that is consistent across the scales.

Our starting point is to model the spatio-temporal evolution of a multi-cellular system by means of the stochastic Langevin equations. In this approach, each cell moves as the result of a balance of forces exerted among the surrounding cells and by the cell microenvironment. A random contribution arises from the local exploration of the neighborhood by the cells.

Methods from statistical physics can be used to derive the corresponding generalized Fokker-Planck equation, which gives the spatio-temporal evolution of the probability distribution of finding the cells of the system at specific locations in the domain.

An interesting level of description consists in assuming the scalar density field as the relevant variable for describing the dynamics of the system. We show how to derive the corresponding *functional* Fokker-Planck equation, which gives the spatio-temporal evolution of the probability that the cells adopt a particular density profile. At this level of description, we show how to include cell proliferation and apoptosis as a stochastic birth-death process in our framework.

Finally, we present the derivation of a *deterministic* macroscopic equation that describes the spatio-temporal evolution of the cell density, including cell movement as a result of a balance of forces, and cell proliferation and death. In this equation, the dynamics of the cell density are regulated by a free energy functional that accounts for interactions among cells and with the microenvironment.

This Dynamic Density Functional Theory is applied to simple interacting multicellular systems. We show how microscopic interactions at the cellular level (*e.g.*, cell-cell adhesion and repulsion) generate correlation terms that contribute to the corresponding macroscopic description at the tissue level. We illustrate our approach for well-established mean-field approximations such as Keller-Segel- and Fisher-Kolmogorov-like models.

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A model of plasma membrane flow and cytosis regulation in growing pollen tubes

In plant sexual reproduction, pollen tubes carry the male genetic information from pollen grains to ovules. These single cells traverse the entire female tissue to reach the eggs. Astonishing high expansion rates and total lengths are achieved: rates of 1 mm/h in lily flowers and lengths of 30 cm in maize. This extreme growth rates and total lengths demand perfect coordination of cell wall expansion, cell wall material deposition and membrane recycling.

During growth, pollen tubes have to have a well defined and tightly regulated distribution of cell wall extensibility. Regulation is achieved by influencing the esterification degree of the cell wall material (mostly pectins) through Pectin Methyl Esterases (PME), which activity is in turn regulated by an inhibitor (PMEI). Distinct patterns of PME and PMEI are found in pollen tubes. While PME is widely distributed along the flanks of the pollen tube, PMEI is only present at the apical cell wall. To achieve these distinct distributions, these enzymes are subjected to specific cytosis patterns. The cell wall material, pectin, reaches also the wall by means of exocytosis. It stands to reason that, mechanics of growing pollen tubes can only be understood completely, if the patterns of endocytosis and exocytosis are also considered.

We present a theoretical approach to understand these patterns. A model of cytosis regulation is developed and simulations presented. We address in particular the question on the minimal assumptions needed to describe the patterns reported recently by Zonia and Munnik, [1]. The movement of plasma membrane in the tip is described by using concepts of flow and conservation of membrane material. After obtaining the central equations, relations describing the rates of endocytosis and exocytosis are proposed. We find that two cytosis receptors (for exocytosis and endocytosis), which have different recycling rates and activation times, suffice to describe a stable growing tube. The simulations show a very good spatial separation between endocytosis and exocytosis, and separation is shown to depend strongly on exocytic vesicle delivery. The model shows also that most vesicles in the clear zone have to be endocytic, in accordance with the literature. Membrane flow is essential to maintain cell polarity, and bi-directional flow is a natural consequence of the proposed mechanism. For the first time, a model addressing plasma membrane flow and cytosis regulation was posed. Therefore, it represents a missing piece in an integrative model of pollen tube growth, in which cell wall mechanics, hydrodynamic fluxes and regulation mechanisms are combined.

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Population Dynamics; Wednesday, June 29, 14:30

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Non-linear impacts of climatic variability on the density dependent regulation of an insect vector of disease

Aedes aegypti is one of the most common urban tropical mosquito species and an important vector of dengue, chikungunya, and yellow fever viruses. It is also an organism with a complex life history where larval stages are aquatic and adults are terrestrial. This ontogenetic niche shift could shape the density dependent regulation of this and other mosquito species because events that occur during the larval stages impact adult densities. Here, we present results from simple density-dependence mathematical models fitted using maximum likelihood methods to weekly time series data from Puerto Rico and Thailand. Density dependent regulation was strong in both populations. Analysis of climatic forcing indicated that populations were more sensitive to climatic variables with low kurtosis (i.e., highly variable around the median) rainfall in Puerto Rico and temperature in Thailand. Changes in environmental variability appear to drive sharp increases in the abundance of mosquitoes. The identification of exogenous factors forcing the sharp increases in disease vector populations using their statistical properties, such as kurtosis, could be useful to assess the impacts of changing climate patterns on the transmission of vector-borne diseases.

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Towards quantitative individual-based and continuum models of tumor multicellular aggregates

Recent development of experimental techniques permits the measurement of an increasing number of parameters necessary to parameterize quantitative models of tumor growth and cancer development.On the one hand, Individual-cell Based Models (IBMs) allow to incorporate a lot of details of cell-level behavior but are limited to the millimeter scale. On the other hand, continuum models are well adapted to larger scales but do not permit such a detailed description. Building a hybrid continuum/discrete model is a promising way to describe the multiscale behavior of tumors from the single cell up to centimeter scale. However, it requires that both approaches lead to the same predictions. Recently, Byrne and Drasdo (J. Math. Biol. 2009) studied continuum models able to capture important aspects of either compact or very diluted tumor aggregates of a previously introduced IBM that has been shown to reproduce the typical growth kinetic of monolayers and multi-cellular spheroids (Drasdo et al., J. Stat. Phys. 2007) . Here we extend this concept towards a continuum model that describes the intermediate range of phenotypes by representing the different aspects of the IBM in more detail. The growth dynamics predicted by these two models are quantitatively compared.

Mathematical modelling of physiological processes in patients on dialysis;
Saturday, July 2, 11:00

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New exact solutions of mathematical models describing peritoneal transport

Mathematical description of fluid and solute transport between blood and dialysis fluid in the peritoneal cavity has not been formulated fully yet, in spite of the well known basic physical laws for such transport. Recent mathematical, theoretical and numerical studies introduced new concepts on peritoneal transport and yielded better results for the transport of fluid and osmotic agent [1]–[4]. However, the problem of a combined description of osmotic ultrafiltration to the peritoneal cavity, absorption of osmotic agent from the peritoneal cavity and leak of macromolecules (proteins, e.g., albumin) from blood to the peritoneal cavity has not been addressed yet. Therefore, we present here a new extended model for these phenomena and investigate its mathematical structure. The model is based on a three-component nonlinear system of two-dimensional partial differential equations with the relevant boundary and initial conditions. In the particular case, this model produces one, which was studied earlier in papers [1]–[3]. The non-constant steady-state solutions of the model obtained are studied. The realistic restrictions on the parameters arising in the model were established with the aim to obtain exact formulae for the non-constant steady-state solutions. As result, the exact formulae for the density of fluid flux from blood to tissue and the volumetric flux across the tissue were constructed, and two linear autonomous ordinary differential equations to find the glucose and albumin concentrations were derived. The analytical results were checked, whether they are applicable for the description of the glucose-albumin transport in peritoneal dialysis.

References.

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Bioengineering; Tuesday, June 28, 14:30

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Protein-DNA interactions: reaching and recognizing the targets

Search and recognition of targets on DNA by DNA-binding proteins is a vital biological process. Some proteins find their target sequences on DNA with the rates that are 100-1000 times faster than predicted by Smoluchowski diffusion in 3D space. It is often claimed that the reduction of dimensionality from 3D in solution to 1D on DNA is the basic key to understand this facilitated diffusion of DNA-sliding proteins. Recent experiments have shown however that protein diffusion along DNA is often much slower than in solution (see data of Ref. [1] for the lac repressor). Thus, the 3D1D space reduction by itself does not ensure a faster target search. That controversy pushed us to revisit the problem [2].

We present two theoretical models that describe some physical and chemical aspects of protein target search and mechanism of DNA-protein electrostatic recognition. First, we consider the protein target search as a sequence of cycles of 3D diffusion in solution and 1D sliding along DNA. Our non-equilibrium model accounts for protein binding/unbinding to DNA [2]. The model contains a new correlation term, missing in previous theories, that comes from the accurate description of protein diffusion process in stochastic DNA-protein potential. We show that the search time is optimal for an intermediate strength of protein-DNA interactions and intermediate protein concentrations. The fast search is achieved by a parallel scanning of DNA by many proteins. Both conclusions are consistent with the outcomes of recent large-scale Monte Carlo simulations of protein diffusion [3].

Then, we focus on DNA-protein electrostatic interactions, known to give a large contribution to protein-DNA binding affinity. Contrary to hydrogen bonding, electrostatic protein-DNA forces are believed to be largely insensitive to DNA sequence. We show however how the complementarity of charge patterns on target DNA sequence and on a model protein can result in electrostatic recognition of a specific track on DNA. This recognition provokes protein pinning near this homologous region on DNA. We obtain analytical expressions for the shape of the capturing well and typical times proteins spend in it before thermal escape. These times are often long enough to allow a reorganization of the protein structure, so-called interaction-induced protein folding, and formation of stronger (hydrogen) bonds with DNA. One can thus suggest a two-step mechanism for DNA-protein recognition [2]: electrostatically mediated protein sliding and pinning followed by chemical recognition interactions.

This mechanism of protein-DNA recognition is reminiscent of charge adjustment predicted by us for sequence-specific DNA-DNA electrostatic interaction [4]. The charge complementarity is also known to dominate the formation of many

protein-protein complexes in solution [5], rendering such charge zipper complexation pretty general.

Theoretical model of protein-DNA charge recognition has been validated by our recent analysis of real DNA-protein complexes [6]. Structure visualization for many DNA-binding proteins indeed reveals a close proximity of positively charged protein residues (Arg, Lys, and Hist) to negative DNA phosphate groups [6]. A detailed computational analysis of Protein Data Bank files of crystallized DNA-protein complexes performed has indicated several important features. We have observed for instance that in particularly for large structural proteins such as nucleosome core particles, the sequence-specific DNA-protein charge zipper effects are strongly pronounced. Namely, the distribution of Lys and Arg on the protein surface in the vicinity of bound DNA fragment is adjusted to provide a better fit to sequence-specific pattern of DNA phosphates. This indicates sequence-specificity of electrostatic interactions for these complexes, the fact largely overlooked in literature before. Analysis of relatively small DNA-protein complexes, that implement standard motifs of DNA recognition, on the contrary, did not reveal any statistical preference in distribution of positively charged protein amino acids with respect to the contacting DNA phosphates [6,7].

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Towards a single-cell-based model of early development in ruminants

Embryonic losses and, after birth, the formation of chronic diseases of metabolic origins such as obesity, diabetes, arterial hypertension, have been observed as critical in early ruminant (sheep, cow) development.

In order to understand the possible mechanisms leading to such failures, the mechanisms controlling two developmental phases, the growth of the blastocyst (a hollow sphere of cells) during late blastula formation as well as early trophoblast development needs to be understood. The trophoblast is the first epithelium that appears at the beginning of embryogenesis in mammals. It forms the wall of the blastocyst and helps for implantation in the uterine wall. During early development of the trophoblast, a temporal window of 15 days from the blastocyst stage, the trophoblast floats in the uterine liquid, and undergoes an extremely fast growth and elongation. This period of early morphogenesis is fundamental for a normal development of the embryo. We established a process chain to quantitatively analyze the two developmental phases by experiments, analysis of images from the embryos of different stages, and mathematical modeling. We analyze confocal images to infer the cellular organization into the tissue sheet, and determine the distribution of cell size and cell shapes prior and during the embryo shape transition. Based on the results of this analysis, we set up a mathematical single-cell-based model. Our model cells are parametrized by measurable biophysical and cell biological quantities. They can migrate, grow and divide, and interact with other cells and extracellular matrix by forces. In the first step we considered a representative section of the developing embryo and studied different mechanisms to explain the deformation. The model permits predictions of several manipulations of cells and embryo that are currently experimentally tested.

Cell and Tissue Biophysics; Friday, July 1, 14:30

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Bleb Statics, Dynamics, Adaptation and Directed Cell Migration

Cellular blebs are spherical cell membrane protrusions powered by cytoplasmic flow. To understand the dynamics of cellular blebs, we develop a quantitative model to study how a bleb develops when a portion of the cell membrane detaches from the underlying cortex. From the model, we calculate the minimum cytoplasmic pressure and minimum unsupported membrane length for a bleb to nucleate and grow. We also show how a bleb may travel around the periphery of the cell. We find that the traveling speed of the bleb is governed by the speed of the pressure pulse induced by local cortical contraction and we construct a phase diagram for bleb existence and motion. Finally, we propose a bleb-based mechanism for directed migration during chemotaxis based on adaptation of the variance of blebbing. This adaptation is shown to be robust and is insensitive to perturbation within a wide range of parameters.

Population Dynamics; Saturday, July 2, 11:00

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A theoretical model linking interspecific variation in density dependence to species abundances

Understanding the factors that govern the commonness and rarity of individual species is a central challenge in community ecology. Empirical studies have often found that abundance is related to traits associated with competitive ability and suitability to the local environment, and more recently also to negative conspecific density dependence. Here, we construct a theoretical framework to show how a species abundance is in general expected to be dependent on its per-capita growth rate when rare and the rate at which its growth rate declines with increasing abundance (strength of stabilization). We argue that per-capita growth rate when rare can be interpreted as competitive ability and that strength of stabilization largely reflects negative conspecific inhibition. We then analyze a simple spatially implicit model in which each species is defined by three parameters that affect its juvenile survival: its generalized competitive effect on others, its generalized response to competition, and an additional negative effect on conspecifics. This model facilitates the stable coexistence of an arbitrarily large number of species and qualitatively reproduces empirical relationships between abundance, competitive ability and negative conspecific density dependence. Our results provide theoretical support for the combined roles of competitive ability and negative density dependence in the determination of species abundances in real ecosystems, and suggest new avenues of research for understanding abundance in models and in real communities.

Mathematical Modeling of Mosquito-Borne Diseases; Tuesday, June 28, 11:00

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Mathematical Modeling to Support Malaria Control and Elimination

We use numerical simulation of an ensemble of mathematical models of malaria in humans and mosquitoes to help develop target product profiles for new interventions and to provide robust quantitative predictions of effectiveness and cost-effectiveness of different strategies in reducing transmission, morbidity and mortality.

The individual-based stochastic simulation models include seasonality of infection; multiple mosquito populations; superinfection, acquired immunity, and variations in parasite densities in humans; and the effects of health systems. We describe the model and show results of simulations of combinations of different interventions including indoor residual spraying (IRS), insecticide-treated nets (ITNs), improved case management, intermittent preventive treatment, and potential vaccine candidates.

Our results suggest that sustained coverage of ITNs and/or IRS reduces malaria prevalence in two to three years but does not lead to further gains. However, in some settings, even with sustained coverage, clinical incidence of malaria increases as the population loses its naturally acquired immunity. In some low to medium transmission settings, our simulations suggest that high coverage of both interventions can lead to interruption of transmission, especially if coupled with an effective transmission blocking vaccine.

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Movement pattern analysis of C.elegans based on Box-Sized-Distribution

It is already known that locomotion by C.elegans delivers characteristic patterns of movements, e.g. forward and backward movement, rest, omega-turn, and coil-type turn. However the previous studies, being interested in the patterns of C.elegans movement, have had limitation to give enough explanation on the immediate connection between movement and pattern. In this study, we introduced a way to deal with C.elegans movement patterns, called Box-Sized-Distribution (BSD), in order to look to the relation between movement and its pattern. BSD is defined by introducing a rectangular box which consists of the width, the longest line formed by any two points on C.elegans, and the height, the longest vertical line determined by width line. We used experimental data sets for 50 individuals, being obtained after each controlled C.elegans was observed by real-time recording system for three hours on the agar plate. As a result, BSD delivers a few interesting facts on the movement patterns of C.elegans : 1) The ratio of width to height of a box can measure the mechanical activity of C.elegans, i.e., speed of movement and turn. 2) BSD makes it possible to explain pattern transition of C.elegans movements. 3) BSD also obeys a Boltzmann statistics based on shape itself.

Ecosystems Dynamics; Tuesday, June 28, 17:00

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Aquatic ecosystem modeling: use of screening sensitivity analysis methods to facilitate the calibration process

In ecological risk assessments, risks imputable to chemicals at the ecosystem level are usually estimated by extrapolation of single-species toxicity test results. But such approaches fail to account for the interactions that inevitably exist among the component species [1]. Alternately, modeling at the whole ecosystem level reveals to be a powerful tool by considering species interactions, and by predicting toxic effects on non-target species populations (indirect effects). The aims of our work are: (i) to develop a new mathematical model which comprehensively describes a whole aquatic ecosystem accounting for species interactions with a clear set of equations including both abiotic and biotic factors; (ii) to incorporate perturbation functions on chosen processes within the model in order to predict potential toxic effects at the ecosystem level and to identify functional groups at risk; (iii) to perform a sensitivity analysis, i.e., to screen parameters having the greatest influence on calculated target endpoints. An extensive literature review allowed us to conceptualize a whole non-contaminated aquatic ecosystem with a compartmental ecological model [2]. Compartments include primary producers (macrophytes and algae from phytoplankton and periphyton), primary consumers (juvenile fish and invertebrate grazers, shredders and collectors) and secondary consumers (invertebrate predators and fish). All compartments are related within a food web as well as to abiotic factors such as light, temperature and nutrients. Another literature review was carried on the most relevant perturbation functions mathematically describing how contaminants impact population dynamics, trophic relationships and ecosystem functionning. These two literature reviews also provided for all parameters point estimates as well as some probability distributions. With 13 state variables (compartments), 23 interactions between species and 63 ecological processes, the number of model parameters was necessarily very high (260), making the calibration process very complex and computationally expensive. To overcome these difficulties, sensitivity analyses (SA) seem particularly relevant [3]. They allow identifying non-influential parameters that can then be fixed at a nominal value without significantly reducing the variance of outputs. Among SA methods, screening ones could be preferred as they are computationally cheap, compared to

global ones. But screening SA methods are only qualitative and do not compute an output variance decomposition based on the input uncertainties. Hence, we first tested and compared two screening SA methods: the Morris [4] method and the method developed by Klepper [4]. In order to check the reliability of their results, we second carried out a comparison with results given by two global quantitative SA methods: the Standardized Regression Coefficients (SRC) method and method FAST. As the last two methods are computationally expensive, we were only able to perform all our comparisons on a reduced version of our model, the "Periphyton-Grazers" submodel, which contained a very small number of parameters (20). The Morris method was finally the best compromise to screen non-influential parameters. Applied to the whole aquatic model, such a method allows one to reduce the complexity of the underlying equations (some parameters are fixed, the others have to be calibrated), and consequently to facilitate the calibration process from experimental data.

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Antibody responses during Hepatitis B viral infection

Infection with hepatitis B virus results in the synthesis of a large excess of subviral particles, which are empty particles with viral proteins on their surface but without viral nucleic acids. The reasons for their overproduction and the contribution they play in HBV pathogenesis is not understood. Here, we investigate whether subviral particles can serve as a decoy by adsorbing neutralizing antibodies and therefore delaying the clearance of infection. We develop a mathematical model of HBV-antibody interaction and determine the quantitative contributions of virus-antibody and subviral particles-antibody formation to the control of infection. We extend the results to account for the presence of multiple Hepatitis B surface proteins, each of which can potentially facilitate infection. Using this extended model we investigate the necessity for the antibody to bind all available surface proteins to offer protection.

Analysis of mathematical models for cancer growth and treatment, Part V; Wednesday, June 29, 11:00

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Numerical optimisation of anticancer therapeutics, especially chronotherapeutics, with toxicity constraints

I will firstly recall previous results on the optimisation of a chronotherapy delivered in the general circulation, with targets on two separate cell populations, healthy and tumour. In this representation, the proliferating cell populations under attack are modelled by simple ordinary differential equations (ODEs). The variables under control are numbers or densities of cells in homogeneous populations, healthy or tumour, the actual drug targets being cell death rates. A Lagrangian is designed from objective (killing cancer cells) and constraint (preserving healthy cells) functions. Its numerical maximization yields suboptimal solutions that can be implemented as continuous drug delivery schedules in programmable pumps that are in use in the clinic. Chronotherapeutics, a method used in the clinical treatment of cancers, takes advantage of circadian clock phase differences that exist between healthy and cancer cells to optimise drug delivery using such pumps. These differences are represented as differences between 24 h-periodic modulations of the drug effects in the cell population models.

Then I will develop more recent aspects of the same optimisation problem, where, instead of ODEs, physiologically structured partial differential equations (PDEs) representing the division cycle in proliferating cell populations are used here, with as variables cell population number or densities, healthy and tumour. The variables under control are however here not cell numbers, but growth rates (first eigenvalues of the linear PDE systems), yielding both the objective function (for tumour cells) and the constraint function (for healthy cells), from which a Lagrangian is also designed. The actual targets of control are in this representation cell cycle phase transition rates, which is much more realistic than cell death rates in the case of cytotoxic drugs, since their effects are not directly exerted by enhancing death rates, but rather by blocking cell cycle checkpoints. These checkpoints are both physiologically (by circadian clocks) and pharmacologically controlled. Differences between healthy and tumour cells are here modelled as different synchronisations between cell cycle phases, since healthy cell populations are assumed to be more synchronised, i.e., with steeper transition functions between cell cycle phases, than tumour cell populations.

Finally I will present a prospective view, adapted to personalised medicine, on therapeutic optimisation in oncology, which is based on physiological modelling throughout of the targets (cell populations in the whole body) and of the control means (fate of drugs, from their infusion in the general circulation until their molecular action at the cell and tissue level). To make these views more complete, I will also present extended principles of drug delivery optimisation, presently using only toxicity constraints on healthy cells, but also in the future, at a different time scale, simultaneously using drug resistance constraints on tumours with a cell Darwinian point of view.

Poster Session; Friday, July 1, 20:00

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Control of Chlamydia from a public health viewpoint

Infection with *Chlamydia trachomatis* poses a significant public health problem in the UK and worldwide. Left untreated the infection can cause further problems in individuals, including PID, epididymitis, and infertility. People with Chlamydia infection, (or other bacterial STIs) are also more likely to be infected with HIV through sexual contact. We have been comparing the efficacy of random screening, contact tracing, and combinations of the two with respect to controlling Chlamydia levels in a population in which the infection is already endemic. Our model system involves a pair approximation approach to mimic sexual contact structure and we explore the impact of changes in key control parameters over timescales of relevance to public health policy makers. In particular we use our model analysis to answer the question: what combination of screening and contact tracing should be employed to minimise prevalence of Chlamydia over realistic time intervals?

Population Dynamics; Friday, July 1, 14:30

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Emerging spatio-temporal patterns in a model of insect invasion

Recent empirical studies of insect invasions have provided evidence for invasive waves with endogenously generated variance in spread rates. Integrodifference equations provide a general framework to model the spread of an invasive species when the species has distinct growth and dispersal phases. Many insects from temporate climates satisfy this description. In this talk I will present an integrodifference model of insect host-parasitoid co-invasion which exhibits endogenously generated variance in spread rate. The emerging spatio-temporal patterns which form in the wake of the pulsed wavefront may provide insight into the mechanisms that lead to collapse and generation of insect outbreaks at the landscape scale.

Vector-borne diseases; Tuesday, June 28, 14:30

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A Model for Chagas Disease with Vector Consumption and Transplacental Transmission

Chagas disease is caused by the parasite Trypanosoma cruzi, which is spread primarily by domestic vectors in the reduviid family, and affects humans and domestic mammals throughout rural areas in Central and South America. An epidemiological model for Chagas disease in a hypothetical village setting will be presented. The model consists of a nonlinear coupled system of four differential equations, one of which has a delay, that describes the rate of change of the total number of the vectors, infected vectors, infected humans, and infected domestic mammals. In addition to birth, death, and parasite transmission due to vectors, the model takes into account insecticide spraying, transplacental transmission, and consumption of the vector by domestic mammals. Steady state analysis of the model with constant coefficients provides a stability condition on the model parameters. In representative examples, the theory and computer simulations reveal that the endemic equilibrium is locally asymptotically stable.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents II; Wednesday, June 29, 08:30

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Simulating the decline of HCV infected hepatocytes by mathematical modelling allows for individual tailoring of Peg-IFN+RBV therapy and for a better selection of the candidates to the new direct antiviral agents.

Background. We have already shown in a retrospective study that modelling infected cells dynamics by ALT and HCV RNA decline during the first 4 weeks of therapy warrants accurate prediction of treatment outcome and offer the possibility to compute individual treatment duration. We compared in a randomised controlled trial the duration and the efficacy of the new model tailored (MT) schedule vs the traditional Guide Line (GL). Patients and methods. 100 consecutive patients stratified by previous therapy (38 nave, 62 retreated), HCV genotype (60 G1-G4 and 40 G2-G3)and peg-IFN type (60 2a and 40 2b), randomly received GL or MT schedules. GL pts were treated 24 weeks if G2-G3 and 48 weeks if G1-G4 applying week 12 stopping rule in G1 non responders (NR). In MT patients ALT and HCV RNA were measured at day 0-2-4-7-14-21-28 to compute the number of infected cells at the end of therapy (Ieot), treatment was stopped at week 6 if computed Ieot at GL duration $>$ 5000 (NR), otherwise tailored to achieve Ieot $<$ 250. Results. Ieot could be computed in 42 (84%) MT patients, the remaining 8 pts showed ALT or HCV-RNA data that did not fit into the model, thus they were treated with GL schedules and not included in this analysis. Therapy was withdrawn/modified because of side effects in 13 (26%) MT and in 9 (18%) GL pts. Therapy was discontinued at week 6 because of NR in 11 (22%) MT pts and at week 12 in 8 (16%) GL pts. The SVR rate in those who completed therapy was 85% according to the MT (mean duration 32 weeks, range:13-56) and 82% according to the GL (mean duration 38 weeks, range:24-48). Treatment duration in SVR pts ranged between 18-55 weeks in 7 G1 pts, 13-21 weeks in 3 G2 pts and 21-56 weeks in 5 G3 pts. Mean duration for SVR of GL schedules was 21% longer in responder patients and 100% in NR. Conclusions. The prospective application of our model confirmed the wide diversification of the treatment duration required for SVR, as predicted by our previous retrospective study, and allowed in clinical practice a fine personalization of the antiviral treatment at the single patient level. Tailoring treatment to

Ieot<250 showed SVR rates comparable to those of the standard schedules (85% vs 82%) but with a significant reduction of non-effective and non required treatments. Use of a model computed Ieot threshold with high chance of SVR to predict treatment duration might be very helpful for decision making after a lead in phase of Peg-IFN+RBV therapy when the direct antiviral agents will be available, thus optimizing the cost-effectiveness of the new antiviral therapies.

Multiscale modelling of biological systems: the Chaste framework;
Tuesday, June 28, 11:00

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Using a cell-vertex model to study the role of differential adhesion in the intestinal crypt

A cell-based vertex model in Chaste was used to study differential adhesion and cell positioning in the intestinal crypt. The results were compared to the ones obtained using a different modelling framework, namely the Potts model.

When directly comparing the models simulations we see that both models agree with experimental data in transit time, migratory velocities and migratory patterns of cells. However, this is not the case when comparing the boundary between differentiated and transit amplifying cells: while using the Potts model a sharp boundary can be observed, using the vertex model such boundary is not seen.

Our results suggest that different modelling frameworks can give different answers when studying the same phenomenon, reinforcing the importance of testing in more than one modelling platform in order to obtain robust results.

Structure and Dynamics of Biochemical Reaction Networks I; Tuesday, June 28, 14:30

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Multistationarity in mass action networks by linear inequality systems

Ordinary Differential Equations (ODEs) are an important tool in many areas of Quantitative Biology. For many ODE systems multistationarity (i.e. the existence of at least two positive steady states) is a desired feature. In general establishing multistationarity is a difficult task as realistic biological models are large in terms of states and (unknown) parameters and in most cases poorly parameterized (because of noisy measurement data of few components, a very small number of data points and only a limited number of repetitions). For mass action networks establishing multistationarity hence is equivalent to establishing the existence of at least two positive solutions of a large polynomial system with unknown coefficients. For mass action networks with certain structural properties, expressed in terms of the stoichiometric matrix and the reaction rate-exponent matrix, we present necessary and sufficient conditions for multistationarity that take the form linear inequality systems. Solutions of these inequality systems define pairs of steady states and parameter values. We also present a sufficient condition to identify networks where the aforementioned conditions hold.

Immunology; Wednesday, June 29, 17:00

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Continuous-time branching processes to model viral load in treated HIV+ individuals

We will discuss a continuous-time, multi-type branching model of HIV viral dynamics in the blood stream. We are motivated by observations of viral load in HIV+ patients on anti-retroviral treatment (ART). ARTs very effectively limit viral replication. However, while on ARTs, an HIV+ individual's viral load remains non-zero, and blood tests show occasional viral blips: short periods of increased viral load. We hypothesize that this low viral load can be attributed to activation of cells latently infected by HIV before treatment initiation. Blips then represent small-probability deviations from the mean. Modeling this system as a branching process, we derive equations for the probability generating function. Using a novel numerical approach we extract probability distributions for viral load yielding blip amplitudes consistent with patient data. We then compute distributions on duration of these blips through direct numerical simulation. Our stochastic model of latent cell activation reproduces features of treated HIV infection. It can be used to provide insight into variability of treatment outcomes for HIV+ individuals not available in deterministic models.

Population Dynamics; Wednesday, June 29, 11:00

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Development of structure sensitivity analysis methods

Most of the time, sensitivity analyses performed on mathematical models are limited to those concerning the parameters. Though, it has been shown that the mathematical formulation of the biological processes that one wants to model can also be very important for the dynamics of ecological systems. For instance, several authors have highlighted that the choice of the functional response formulation, which gives the consumption rate of predators as a function of prey density, can have a strong impact on predator-prey models behavior and stability. This is referred by [**1**] as a new type of model sensitivity, called the structure sensitivity of the model.

The formulation of biological processes can be very complex and it is not rare to find several possible mathematical expressions to model one process. Indeed, the process studied is often difficult to measure in the natural medium and it is approximated by functions estimated from laboratory or *in situ* experiments. These functions are considered as a good approximation of the phenomenon observed in natural systems, which is of course questionable since it has been demonstrated that natural systems are much more heterogeneous than simplified laboratory systems.

In this context, we have decided to develop some simple mathematical methods that will help modelers to detect and to measure if their system is sensitive to the formulation of the process studied. We argue that this type of analysis is essential if one wants to be able to use and comment informations obtained from model simulations. We show an example of application by investigating the effects of the functional response formulation on a chemostat-type predator-prey model dynamics. We find that the system does exhibit structure sensitivity, which is even stronger than system parameters sensitivity.

References.

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Evolutionary Ecology; Wednesday, June 29, 11:00

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Space, coexistence, and mutual invasibility

Two possible conditions that will lead to two species coexisting are: (i) there is a stable equilibrium point where both densities are nonzero; and (ii) either species can invade the other when rare. For many simple models these two conditions are equivalent, but this need not be the case. Unfortunately, a dearth of exact analytical methods hampers the exploration of this question for spatial, stochastic systems. However, asymptotically exact results can be computed in the limit where interactions take place on a large but finite length scale [**1**]. Here, I study a spatial, stochastic Lotka-Volterra competition model, which is selectively neutral except for the spatial kernels that describe within- and between-species interactions [**2**]. The equilibrium stability eigenvalue gives a wealth of (asymptotically exact) results for when coexistence is to be expected. However, the invasibility eigenvalues give different preditions. I argue that this is because exponential growth is not an appropriate description of successful invasion in spatial systems. This means that approximation methods for computing invasion eigenvalues can give misleading results in evolutionary studies of spatial systems.

References.

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Poster Session; Friday, July 1, 20:00

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The Utility of Thornthwaite and Hamon Models for Potential Evotranspiration and Drought Index Calculation: the Case of Wild Common Bean

Potential Evotranspiration (PET) is a theoretical value that aims to characterize the quantity of water that will flux from the soil-biosphere system towards the atmosphere as a consequence of evaporation and transpiration, based on the supposition that available water is infinite. In this research, an agroecological diversity study based on PET was conducted on 104 wild common beans to estimate drought tolerance in their natural habitats. Our wild population samples covered a range of mesic to very dry habitats from Mexico to Argentina. Two PET models which considered the effects of temperature and radiation were coupled with the precipitation regimens for each collection site during the last fifty years. We detected a broader geographic distribution in wild common beans than in cultivated ones. Furthermore, we found that wild accessions were distributed among different precipitation regimens following a latitudinal gradient and that agroecological diversity was structured into natural populations. Habitat drought stress index based on the Thornthwaite potential evotranspiration is the most promising predictor of drought tolerance. This resource should be coupled with considerations about population structure as a consequence of the evolutionary history and diversification process suffered by the species. Finally, this modeling tool suggests that information from wild common bean accessions should be taken into account in order to exploit variation for drought tolerance in order to minimize significant depletion of the yield components.
Key words: Bioclimatic variables, potential evotranspiration models, PET, precipitation, Thornthwaite estimator, Hamon estimator

Cell and Tissue Biophysics; Friday, July 1, 14:30

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Modelling Insulin Action on Glucose Transporters

The application of insulin to a cell causes membrane-embedded glucose transporter proteins to be transported to the cell surface. An experimental technique that is ideally suited to investigate this dynamic process is total internal reflection microscopy of single cells, where fluorescent markers are attached to the molecules and movements recorded. To create software capable of annotating the recordings automatically, ideal mathematical models are required. Features of the models and software are outlined and compared with biological recordings.

Multiscale modelling of reaction kinetics in biology; Tuesday, June 28, 14:30

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A constrained multiscale approach to modelling biochemical systems

It is well known that intrinsic noise can play a significant role in biological systems. Stochastic descriptions of these types of systems give far more accurate representations of the true dynamics. Exact methods for the stochastic simulation of these systems exist, but can be very computationally expensive, particularly in the presence of multiple timescales. Many different methods exist for reducing the system to one which is only concerned with the slowly evolving variables.

In this talk we introduce the Conditional SSA (CSSA), a method for sampling directly from the conditional distribution on the fast variables, given a value for the slow variables. Using this, we go on to describe the Constrained Multiscale Algorithm (CMA), which uses simulations of the CSSA to estimate the drift and diffusion terms of the effective dynamics of the slow variables. We show how this approach can give accurate estimates for quantities of interest, such as average period of oscillation in biological processes. This is joint work with Radek Erban and Kostas Zygalakis (Oxford), and Ioannis Kevrekidis (Princeton).

Modeling of immune responses and calcium signaling I; Tuesday, June 28, 17:00

Markus Covert
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Heterogeneous cellular responses via noisy paracrine signals

The mammalian immune response is a striking example of coordination between individual cells. We previously discovered that the response of wild-type murine embryonic fibroblasts (MEFs) to lipopolysaccharide (LPS) depends on paracrine secretion of tumor necrosis factor (TNF). We then demonstrated in single cells that the low concentration of the paracrine TNF signal results in two qualitatively different responses to LPS: roughly one-half of the cells exhibit a transient NF-kappaB response, while the other half exhibit a persistent response with NF-kappaB remaining in the nucleus for hours. Only cells that sense the low TNF concentration and therefore respond to the paracrine signal exhibit the persistent response. The ability of a low concentration signal to create qualitatively different subpopulations of cells in response to one stimulus led us to ask, how does a single cell respond to low concentrations of TNF? To answer this question, we measured NF-kappaB activity in thousands of living cells under TNF doses covering four orders of magnitude to determine the range of individual cell responses which occur in a population, and what effect these responses might have on NF-kappaB dependent gene expression.

Structure and Dynamics of Biochemical Reaction Networks I; Tuesday, June 28, 14:30

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Persistence and the Global Attractor Conjecture: The Big Picture

We discuss the long-term behavior of population systems, and in particular of chemical reaction systems modeled by mass-action kinetics. We especially focus on the property of "persistence", and its connections to other dynamical properties of these systems. A system is called persistent if no positive trajectory has a limit point on the boundary of the positive orthant. Persistence is important in understanding properties of biochemical networks (e.g., will each chemical species be available indenitely in the future), and also in ecology (e.g., will a species become extinct in an ecosystem), and in the dynamics of infectious diseases (e.g., will an infection die o, or will it infect the whole population). We describe two important open problems for mass-action systems: the Persistence Conjecture and the Global Attractor Conjecture. The Persistence Conjecture says that weakly reversible mass-action systems are persistent, independent of the values of the reaction rate parameters. A proof of the Persistence Conjecture would also imply the Global Attractor Conjecture, which says that complex balanced systems have a global attractor. We explain the relationship between these conjectures, and other recent results. This is joint work with Casian Pantea and Fedor Nazarov.

Cellular Systems Biology; Tuesday, June 28, 14:30

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Multiscale Modelling of Red Blood Cell Production using Continuous and Hybrid Models

This presentation will be devoted to multiscale mathematical modelling of erythropoiesis, the process of production and regulation of red blood cells. It lies upon works recently published [1, 2, 3, 4], in collaboration with N. Bessononv (Institute of Mechanical Engineering Problems, St Petersburg, Russia), I. Demin (Novartis Pharma, Basel, Switzerland), O. Gandrillon (University Lyon 1, France), S. Genieys (INSA de Toulouse, France), P. Kurbatova (University Lyon 1), S. Fisher (INSA de Lyon, France), L. Pujo-Menjouet (University Lyon 1) and V. Volpert (University Lyon 1, France), within the INRIA Team Dracula (Lyon, France).

Erythropoiesis is a complex process, involving cells with different maturities, from very immature stem cells to circulating mature red blood cells. It is regulated both at the intracellular level and at the cell population scale. We propose two complementary approaches for a multiscale model of erythropoiesis [1, 2, 4], in which we describe together erythroid progenitor (immature red cells) dynamics and intracellular regulatory network that determines erythroid cell fate. The intracellular regulation model is based on several proteins inhibiting and activating one an other, under external actions of growth factors that influence their production. The levels of these proteins will decide of cell self-renewal, differentiation or death by apoptosis. Erythroid progenitors dynamics are either described with an individual-based model as discrete elements [1] or with structured models, either compartmental models (systems of ordinary differential equations) [2, 4] or partial differential equations [3]. In both cases, nonlinearities are considered in the models to account for cell fate regulation.

Analysis of the continuous models is performed and simulations are carried out to confront the models to experimental data of anemia (blood loss). The IBM is also confronted to experimental data, and this allows concluding on the roles of the different feedback controls and the relevance of such models, in order to provide more insights into the regulation of erythropoiesis.

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Modeling and analysis of tumor invasion I; Tuesday, June 28, 11:00

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Multiparameter Computational Modeling of Tumor Invasion

Clinical outcome prognostication in oncology is a guiding principle in therapeutic choice. A wealth of qualitative empirical evidence links disease progression with tumor morphology, histopathology, invasion, and associated molecular phenomena. However, the quantitative contribution of each of the known parameters in this progression remains elusive. Mathematical modeling can provide the capability to quantify the connection between variables governing growth, prognosis, and treatment outcome. By quantifying the link between the tumor boundary morphology and the invasive phenotype, this work provides a quantitative tool for the study of tumor progression and diagnostic/prognostic applications. This establishes a framework for monitoring system perturbation towards development of therapeutic strategies and correlation to clinical outcome for prognosis.

Poster Session; Friday, July 1, 20:00

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A mathematical model of calcium dynamics in airway smooth muscle cells including store-operated calcium entry

One of the principal causes of airway narrowing in asthma is the contraction of smooth muscle cells lining the conducting airways. This contraction is regulated by changes in intracellular calcium concentration ($[Ca^{2+}]_i$). The mechanism controlling $[Ca^{2+}]_i$ primarily involves agonist-induced release of calcium from internal stores. Appropriate refilling of these stores is achieved via calcium influx from the extracellular medium into the cytoplasm, which is then pumped back into the stores by sarcoplasmic/endoplasmic reticulum calcium APTase (SERCA). However, in contrast to other types of muscle cells, calcium influx in airway smooth muscle cells (ASMC) occurs mainly through non-voltage-dependent pathways. In particular, store-operated calcium entry (SOCE), in which calcium influx is triggered by store depletion, has been shown to play an important role. Therefore, in order to account for the characterics of calcium influx observed in human ASMC subject to SERCA block or agonist stimulation [1,2], we develop a mathematical model of calcium dynamics in ASMC that includes SOCE. Preliminary simulations and phase-plane analysis of the model indicate that either direct SOCE into the internal stores, in addition to cytosolic SOCE, or desensitization of cytosolic SOCE by $[Ca^{2+}]_i$, is required to account for the experimental responses reported in [1,2].

This modelling work is part of a larger project aiming at developing a multiscale model of airway hyper-responsiveness in asthma, from the molecular mechanisms of airway contraction at the cellular level to the biomechanics of the whole tissue [3,4].

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Cellular Systems Biology; Saturday, July 2, 11:00

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Cell signaling network unit dynamics

Cells use a dense network of signaling pathways to decide how to respond to various external stimuli. Several dynamic aspects of complex pathways have been already described. Here we show that simple generic motifs of signaling pathways (without any feedback) could show some interesting dynamics. We investigated the dynamics of the simplest dynamical elements in biochemical networks: we analyzed the response dynamics of a signaling protein when it enters the signaling pool in one state (modified or unmodified) and exits in both of these states. When the exit rates of these two states are comparable, a persistent stimulus results in step responses and can produce ultrasensitivity, however, when the exit rates are imbalanced, the signaling protein gives transient responses to persistent stimuli. Such adaptive behavior of signaling pathways could be used by many organisms. We also investigated the dynamical features of phosphorelays: phosphorelays are extended two-component signaling systems found in diverse bacteria, lower eukaryotes and plants. We found that the intermediate layers of phosphorelays can display ultrasensitivity that could result in tolerance of pathway cross-talk. Furthermore, it leads to a high signal to noise ratio for the relay output. We show that these features of phosporelays might be employed by the sporulation network of B. subtilis.

Epidemics; Saturday, July 2, 08:30

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Models of infectious disease control with limit treatment resource

The number of patients need to be treated may exceed the carry capacity of local hospitals during the spreading of a severe infectious disease. We propose an epidemic model with saturation recovery from infective individuals to understand the effect of limited resources for treatment of infectives on the emergency disease control. It is shown that saturation recovery from infective individuals leads to vital dynamics, such as bistability and periodicity, when the basic reproduction number $\mathbb{R}_0$ is less than unity.

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Mathematical modeling of biomechanical regulation in bone tissue (Session I); Wednesday, June 29, 08:30

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A Computational Model of Bone Resorption Behavior

Bone resorption by osteoclasts plays a fundamental role in the bone remodeling cycle which serves the purpose of repairing micro-damage and/or achieving mineral homeostasis. This process is also essential in growth and remodeling of bone, where it is tightly coupled to bone formation by osteoblasts. In order to study the static and dynamic behavior of bone resorption, a computational model of bone resorption has been developed using a cellular automaton method and its hybrid method with finite element calculation. In the model, essential features of bone resorption include the interaction of osteoclasts with the bone matrix and with other osteoclasts, and a recruiting signal for osteoclasts from osteocytes that can sense the change in mechanical properties of the bone matrix such as strain and strain-energy density. The computational model provides a theoretical tool to address various questions on bone resorption in terms of the shape and size of resorbed bone. From the simulations of the computational model of bone resorption, it is found that the process of bone resorption is strongly affected by the strength of interactions between osteoclasts with the bone matrix and with other osteoclasts, external mechanical loads, and velocity of a blood vessel.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits I; Wednesday, June 29, 14:30

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Vasculogenesis and collective movement of endothelial cells

The early vascular network is one of the simplest functioning organs in the embryo. Its formation involves only one cell type and it can be readily observed and manipulated in avian embryos or in vitro explants. The early vascular network of warm-blooded vertebrates self-organizes by the collective motility of cell streams, or multicellular "sprouts". The elongation of these future vascular network segments depends on a continuous supply of cells, moving along the sprout towards its tip. To understand the observed self-organization process, we investigate computational models containing interactions between adherent, polarized and self-propelled cells. By comparing the simulations with data from in vivo or simplistic in vitro experiments, we explore the role of active migration, tip cells, invasion of the ECM, and cell guidance by micromechanical properties of adjacent cell surfaces.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents II; Wednesday, June 29, 08:30

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Modeling hepatitis C virus (HCV) RNA kinetics during treatment: in vitro and in vivo

In the last decade HCV kinetic modeling in vivo has played an important role in the analysis of HCV dynamics and the effects of antiviral therapy and they have suggested mechanisms of action (MOA) for both interferon-alpha (IFN) and ribavirin. While we still do not fully understand the MOAs of IFN and ribavirin, understanding the observed HCV RNA profiles during therapy with new direct acting agents (DAA) against HCV will shed light on HCV-host interaction, the dynamics of infection and the MOA of antivirals. The new cell-culture systems (in vitro) that allow the study of HCV replication, infection and treatment at the molecular level will provide valuable insights into HCV-host-drug dynamics within infected cells; a feature that has been considered as a black box. Recent experimental data (in vitro and in vivo) and modeling efforts in the presence of IFN/ribavirin/DAAs will be presented.

Developmental Biology; Thursday, June 30, 11:30

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Analytical modeling of Dpp wt profile and *tkv* clones in *Drosophila* wing imaginal discs

Morphogen concentration gradients in developing organisms or tissues provide positional information which can induce patterning and space-dependent cell fates [1]. A well known example is Decapentaplegic (Dpp), involved in the patterning of *Drosophila* wing imaginal discs, which forms a concentration gradient along the Anterior-Posterior axis [2].
In a recent work [3], we developed and compared to experimental data a 1D analytical model describing the Dpp steady state gradient profile and *tkv* mutant clone effects. In this model, we identify three distinct Dpp components: external Dpp, Tkv-bound Dpp and internalized Dpp. We assume that the external Dpp diffuses from a finite-size production region and can bind to the Tkv receptors. The bound Dpp can unbind or be internalized. The internalized Dpp can be degraded or transported cell by cell by transcytosis. We consider that transcytosis is receptor-mediated and we model it in a pure diffusive way. Assuming a large number of free receptors allows for the linearization of the corresponding differential equations, from which we obtain simple analytical expressions for each Dpp component.
In the *tkv* clonal regions, the number of receptors as well as the receptor-mediated transcytosis are affected. We consider loss-of-function (LOF) experiments, with no receptors inside the clone, and gain-of-function (GOF) experiments, with a $n-$fold increase of receptors.
An extensive qualitative analysis of LOF experiments and quantitative data extraction from the GOF images allows to (i) constrain the parameters space and find a set of optimal parameters (ii) understand which of the external diffusion or

transcytosis is the dominating mechanism in the Dpp gradient formation (iii) obtain the relative abundance of external, Tkv-bound and internalized Dpp. All the experimental data and theoretical results are reported in [3].

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Cellular Systems Biology; Tuesday, June 28, 17:00

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Minimal modeling of two-oscillator circadian systems under conflicting environmental cues

Multiple coupled oscillators have been presumed to constitute the circadian system of many organisms. In some cases the different oscillators are driven by diverse environmental cues (zeitgebers), as suggested by the light- versus food-entrainable oscillators in mice and the light- versus temperature-entrainable oscillators in Drosophila. In order to survey the spectrum of dynamics that could emerge from the interaction of potentially conflicting zeitgebers with a multi-oscillator circadian system, we assume a minimal model consisting of two mutually coupled oscillators, each being exclusively driven by a periodic environmental signal. Mathematically we represent the circadian system by 2 mutually coupled phase oscillators [1], A and B, each with an arbitrary individual period. As the two environmental signals are assumed to have the same period (24 h) and are only separated by a phase shift DELTA, the environment can be represent by a third phase oscillator, which is unidirectionally coupled to oscillators A and B, respectively, with the DELTA being reflected in a delayed coupling to oscillator B. Performing numerical studies of the system as a function of DELTA, and the balance of the environmental and intra-oscillator coupling strength, rich dynamic behavior like bistability and hysteresis, as well as loss of entrainment and quasi-periodicity is observable. Our study provides insight into the structure of the putative coupling network required to maintain the organism in a stable phase-relation with the environment, even in the face of contradictory signals. Furthermore, our results can indicate appropriate experimental strategies to evaluate the strength of inter-oscillator coupling and the relative zeitgeber strength, which have been performed in the past, but mostly lacked guidelines for correct design and interpretation of the results. We finally compare our minimal model with a more complex model, using limit-cycle oscillators [2], showing that the principal dynamics are not altered by the inclusion or exclusion of more details.

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Algorithm for Searching for Approximate Tandem Repeats based on the Burrows-Wheeler transform

Genomic sequences tend to contain many types of repetitive structures of different length, either interspersed or tandem. Tandem repeats play an important role in the gene expression and transcription regulations. They can be used as markers for DNA mapping and DNA fingerprinting. Some, when occurring in increased, abnormal number, are known to be the cause of inherited diseases. All functions of tandem repeats in genomic sequences are still not well defined and understood. However, growing biological databases together with tools for efficient identification of these repeats may lead to discovery of their specific role or correlation with particular symptoms or diseases.

Perfect tandem repeat consists of successive duplications of some motif. Typically tandem copies are approximate due to mutations. Hence approximate tandem repeat (ATR) can be defined as a consecutive, inexact copies of some motif. In our considerations we are assuming that two such successive repeats must be of equal lengths and can differ only by an established number of mismatches. Dissimilarity of these two approximate copies is measured using Hamming distance between them. We are interested in finding approximate tandem repeat when each repeated motif is similar enough to the adjacent duplicate.

Algorithm presented is an enhancement of a method for finding perfect tandem repeats in DNA sequences based on Burrows-Wheeler transform (BWT). It uses its intermediate results, groups of particular sequences repeated within the whole input string, to find candidates for double ATR — that is the first stage of searching. The second stage consists of investigating found candidates and accepting or rejecting them as a pair of ATRs. Finally, in last stage, located double ATRs are extended to contain as much successive, similar copies, as possible.

In the first stage the input string is converted according to BWT. This, together with some auxiliary arrays, allows to make use of the alphabetically sorted array of input string suffixes, without the need of storing the whole suffix array structure. The algorithm finds the range of positions of the repeated pattern in the suffix array. It starts with the empty pattern P and recursively appends, in front of P, characters from the considered alphabet. This approach uses the results from the previous iteration to calculate a range of positions for a longer pattern and it is done in a constant time, according to the idea of Ferragina and Manzini. Two sequences from the range of repeated patterns are considered a candidate for a double approximate tandem repeat if they lay close enough to each other within the input string, in particular, if it is possible that they will form an approximate

tandem repeat with established, maximum dissimilarity. To limit the number of redundant candidates the algorithm makes use of the property of two strings of length n and with Hamming distance h between them, which states that two such strings have always a common, matching substring at corresponding positions of length $\lfloor \frac{n}{h+1} \rfloor$ at least. Hence, repeated patterns of length d are used to search only for ATRs of length n that satisfies the equation $d = \lfloor \frac{n}{h+1} \rfloor$ for all acceptable h. Additionally, as positions of previously found ATRs are known, qualifying as a candidate the ATR discovered before is avoided.

In the next stage Hamming distance between found pairs of candidates is measured (checking all possible alignments of found candidates) and if it satisfies the assumptions, the double approximate tandem repeat is reported. In the third, final stage, Hamming distance is measured between marginal motif of found ATR and a neighboring string. As long as it is not greater than the assumed maximum, the ATR is extended in that direction.

The developed algorithm exploits the advantages offered by the BWT algorithm and the suffix array data structure to return ATRs from the input string, assuming that any two consecutive copies within ATR differ at most by a provided Hamming distance.

Acknowledgement: This work was supported by the European Union from the European Social Fund.

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Models in Spatial Ecology; Tuesday, June 28, 17:00

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Repopulation of Ambystoma tigrinum in the West Texas playas in the period following Antevs Altithermal: a mathematical model

We consider a population of amphibians in transient wetlands. The effect of predation, migration and finite resources is examined through a series of models based on differential equations. Logistic growth coupled with predation with satiation can, depending on parameters, produce an Allee effect in an isolated habitat. In particular, a population that might thrive in isolation may go extinct if migration becomes an option and an equilibrium of populations in a coupled system does not necessarily lead to stable nonzero populations when migration stops. We show that under some circumstances periods of migration followed by periods of isolation is a faster way to repopulate a system than a single long period of migration. We apply this model to the Ambystoma tigrinum population of the highland playas of west Texas to show that in a given rainy period it is unlikely that migration will occur except to nearest adjacent ponds. Coupling this result with rainfall data gives a rough probability for migration in a given rainy season. Field data give an indication of extinction rates for individual playas. Coupling these two probabilities in a percolation process on a finite grid gives an indication of how many years are required to restock a whole system of playas from a single populated pond. We show under what assumptions it is possible for the system of about 20,000 playas to be restocked from a single source by Ambystoma tigrinum in the interval since the intense dry period known as Antevs Altithermal.

Poster Session; Friday, July 1, 20:00

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Hyphal tip morphogenesis

Tip growth is a mechanism by which cells can expand in a preferred direction. It is the defining feature of filamentous organisms such vegetative fungi and actinomycete bacteria. The ability to extend by apical growth allows these organisms to optimally explore and exploit the complex environments that they normally inhabit. Mathematical modelling of tip growth is a mature subject. However, recent advances in imaging and genetic manipulation has brought new impetuous to this area, as the mechanisms by which cell wall building material is brought to the tip and subsequently used to extend the hypha, are now beginning to be revealed. However, there are still many open questions regarding the organisation of these complex processes. In particular, how the biomechanics of the cell wall-plasma membrane complex and vesicle supply centre (Spitzenkorper) interact is still largely unknown. We discuss models that treat the cell-wall development as a consequence of either geometry or elasticity and detail what progress can be made regarding tip morphologies from these basic assumptions.

Modelling biofilms: from gene regulation to large-scale structure and function; Wednesday, June 29, 17:00

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Cell differentiation in bacterial biofilms

It has been long understood that isogenic (genetically identical) cells in complex living organisms can perform different, but co-ordinated roles. This is called cell differentiation and until recently, it was thought that this behaviour was restricted to multi-cellular organisms. However, through recent technical advances it has been shown that simple, single-celled organisms such as bacteria, also display cell differentiation and so to some extent can behave as "multi-cellular collectives". It has been postulated that this within-species variation may be essential for survival in a changing environment.

One of the most striking examples of bacterial cell differentiation is within a *biofilm*: a multicellular sessile community of bacteria encased within a self-produced polymeric matrix. It is thought that over 90% of bacterial colonies in the natural environment exist in this form. Biofilms are important in all sectors of our economy with examples ranging from human health (e.g. they form the basis of chronic infections) to bioremediation (e.g. they are required for the effective treatment of sewage). The Gram positive bacterium *Bacillus subtilis* is extensively used in an industrial context to produce enzymes for cleaning products and has growing potential as an alternative and environmentally friendly pesticide. It has recently been shown that within biofilms of *B. subtilis*, only a subpopulation of the isogenic cells produce the extracellular matrix which surrounds all of the cells, while a different subset retain their flagella (and therefore remain motile) and a further subset will undergo sporulation. We discuss a regulatory network that may shed some light on component processes in cell differentiation in *B. subtilis*. In particular we focus on the phosphorylation of the response regulator DegU and its control of cell fate, detailing how a non-unimodal distribution of "on" cells within a population does not necessarily come from a classical bistability in the underlying dynamics of the regulatory network.

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The impact of social structure on spatially explicit epidemiological models

We investigate the role that social structure plays in influencing the spread of infection both in spatial and non-spatial epidemiological models. Social hierarchy is introduced into such models through covariates which affect individuals fecundity, giving rise to realistic population distributions. The effect of correlations between these covariates and the disease prevalence is examined through analytical and numerical approaches. Heterogeneous distributions of sizes of the various subpopulations, arising from the non-uniform fecundity, tend to increase disease prevalence compared to homogeneous models, and these differences are larger when spatial structure is taken into account. These findings have implications for epidemiological models, and for the deployment of disease control strategies.

Delay Differential Equations and Applications II; Saturday, July 2, 08:30

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Mathematical model of bioenergetic process in green plants with delayed argument

In this presentation the system of ordinary differential equations which describe the bioenergetics of green plants is constructed. This model is the mosification of presented in [1] We use three variables in the proposed model:

- x - the part of biomass of green plants participating in bioenergetic processes;
- y - the level of ATP i.e. the mass of this compound;
- z - the level of non-organic phosphorus taking part in bioenergetic i.e. the total mass of anions PO_4^{3-} absorbed from soil after dissociation of phosphates.

We consider the following nonlinear system of first order equations with delayed argument describing the bioenergetic processes in green plants

$$\left\{\begin{array}{lcl} x'(t) & = & \varphi(t)x(t) - c_1(x(t)y(t))^\gamma \\ y'(t) & = & c_2x(t)z(t)(Ax(t-\tau) - y(t-\tau))^+ - c_3(x(t)y(t))^\gamma \\ z'(t) & = & H(x)c_4(c_5x(t) - z(t)) - c_6x(t)z(t)(Ax(t-\tau) - y(t-\tau))^+ \end{array}\right. .$$

We present proofs of the existence and the uniqueness of the solution of the problem and results of computer experiments.

References.

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Ecology and evolution of infectious diseases; Friday, July 1, 14:30

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Optimal control of drug resistant pathogens and the mixing versus cycling controversy

The evolution of drug resistance presents a major challenge for the control of infectious diseases. Numerous recent simulation studies suggest that deploying drugs at an intermediate level in the population can sometimes minimize the total size of infectious disease outbreaks. In this talk I will revisit this issue from the standpoint of optimal control theory. I will demonstrate that the optimal drug deployment strategy is, in fact, one that uses a maximal treatment level but that times the treatment appropriately during the outbreak. From this conclusion I will then go on to consider the optimal deployment of two drugs. Again, optimal control theory will be used to shed light on recent controversies about drug mixing versus drug cycling. I present analytical results demonstrating how some situations lead to mixing being optimal and others lead to a form of cycling being optimal. These results help to partially resolve some discrepancies among other studies.

Cancer; Friday, July 1, 14:30

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Mathematical Modelling of Cancer Growth and Spread: The Role of Enzyme Degradation of Tissue

Metastatic spread of cancer is the main cause of death in patients suffering from the disease - cancer cells from a primary tumour break away from the central mass and are disseminated throughout the body where they re-grow to form secondary tumours or metastases. A crucial aspect of metastatic spread is the process of local invasion of the surrounding tissue. The cancer cells achieve this by the secretion of certain enzymes involved in proteolysis (tissue degradation), namely plasmin and matrix metalloproteinases (MMPs). These overly-expressed proteolytic enzymes then proceed to degrade the host tissue allowing the cancer cells to spread throughout the microenvironment by active migration and interaction with components of the extracellular matrix such as collagen.

Here, we present a mathematical model of cancer cell invasion of a host tissue at the macro-scale (cell population) level. The model considers cancer cells and a number of different matrix-degrading enzymes (MDEs) from the MMP family and their interaction with, and effect on, the extracellular matrix (ECM) using systems of reaction-diffusion-taxis partial differential equations in an attempt to capture the qualitative dynamics of the migratory response of the cancer cells, with a specific focus placed on the membrane-bound MMPs. We use mathematical analysis and computational simulations of the equations in both one- and two-space dimensions to predict the spatio-temporal evolution of the cancer cell density, the concentration levels of the various enzymes and the density of the extracellular matrix. The model exhibits either travelling-wave solutions of cancer cells, which can be used to determine the maximum speed of invasion into the tissue, or very dynamic and heterogeneous spatio-temporal solutions, which match experimentally and clinically observed results for aggressive invading carcinoma.

Multi-scale mathematics of the liver: From intracellular signaling to intercellular interaction; Wednesday, June 29, 08:30

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From hepatocyte polarization to canalicular network formation: a multiscale approach

The generation and maintenance of hepatocyte polarity is crucial for the proper functioning of the liver, and is important in development, as well as liver regeneration. It is well-known that the complex polarity of hepatocytes is characterized by the existence of multiple basolateral and apical/canalicular poles per cell. Yet, it remains unclear what molecular and cellular interactions regulate the generation of segregated membrane domains, and how this affects the morphology of the hepatic epithelium and the formation of bile canulicular network.
To investigate the feedback between the molecular and cellular interactions, we have developed a multiscale modeling environment called Morpheus. This modeling and simulation framework facilitates the integrative modeling of multiscale cellular systems, and includes solvers for discrete and continuous models, a XML-based modeling language, and a graphical modeling interface.
To study the generation and consequences of hepatocyte polarity, we established a hybrid model consists of two modules. The molecular interactions between Rho GT-Pases and phosphoinositides (PIPs) are modeled using a reaction-diffusion (PDE) formalism. Anisotropic adhesion and bile secretion between cells are represented in a cellular Potts model. The integration of the modules is based on cell-cell and cell-matrix signals that trigger polarization of membrane proteins, and the downstream effects of membrane domains on the formation of tight junctions and bile secretion at the apical/canalicular domain. Our results are compared to quantitative data on the polarity and tissue morphology of murine hepatocytes in *in vitro* sandwich cultures.

Mathematical modelling of physiological processes in patients on dialysis;
Saturday, July 2, 11:00

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Compartmental modeling and adequacy of dialysis

In compartmental modeling the patient body may be considered as a single compartment, two compartments (intracellular and extracellular or perfused and non-perfused) or more compartments, as appropriate to the kinetics of investigated solute. Then the analysis of solute kinetics can be used for the description of dialysis and provide support for the assessment of its efficiency. Two compartment variable volume urea kinetic model, based on ordinary differential equations, was used to simulate numerically different dialysis modalities: 1) conventional hemodialysis (HD) with three dialysis sessions per week, 2) daily HD with 6 short sessions per week, 3) nocturnal HD with 6 long sessions per week, 4) continuous ambulatory peritoneal dialysis (PD) with four exchanges of dialysis fluid per day and 5) bimodal dialysis, i.e., a combination of 5 days on PD and two HD sessions. The volumes of extracellular (Ve) and intracellular (Vi) compartments were related to total body volume V as Ve(t) = 1/3V(t) and Vi(t) = 2/3V(t), respectively. The obtained urea concentration, mass and distribution volume profiles in patient body and solute concentration, mass and dialysate volume profiles allow to calculate the following dialysis adequacy indices, DAI: 1) fractional solute removal, FSR; and 2) equivalent continuous clearance, ECC. FSR is defined as total solute mass removed from the body normalized by solute mass in the body. ECC is defined as solute removal rate over solute concentration in the extracellular compartment of patient body. In general, there are four variants of DAI linked to the variability of solute concentration, mass and fluid volume during intermittent dialysis treatment with different time intervals between treatments. FSR and ECC are related to 1) peak, 2) peak average, 3) time average and 4) treatment time average reference values of mass and concentration, respectively. The system of DAI was applied 1) to compare conventional, daily and nocturnal HD and continuous ambulatory PD, i.e., treatments with different dialysis dose and time schedules, 2) to calculate the efficiency of bimodal dialysis, 3) to assess the contribution of residual renal function and dialysis into the overall efficiency of the treatment, and 4) to determine the dialysis dose in metabolically unstable patients. The results of this investigation are important for practical applications of dialysis. Using compartmental models and solute kinetic analysis we were able to evaluate dialysis adequacy, FSR and ECC, for simulated dialysis modalities in anuric and non-anuric patients taking into account their metabolic state.

Poster Session; Friday, July 1, 20:00

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Computer modeling of insulin secretory granules' dynamics in pancreatic betacell

Insulin is the body's glucose lowering hormone which is stored in dense-core secretory granules in pancreatic beta-cells. Glucose-induced insulin secretion follows a two phase time course: one rapid and transient phase and a week but sustained phase. Loss of first phase in insulin secretion results in Type 2 Diabetes, a metabolic disorder which is rapidly increasing worldwide. Therefore it is important to understand the cellular mechanism underlying biphasic insulin secretion. Total number of granules, size distribution and spatial distribution of granules in a typical betacell are important in the proposed models for stimulated insulin secretion from betacells. In this project we develop an in-silico model based on experimental results to find the true size distribution (TSD), 3D density profile and total number of granules (N) in a typical betacell. Then we make an agent-based model for granules dynamics inside the cell and try to find the mechanism and explanation behind the two-phase insulin release.

Developmental Biology; Friday, July 1, 14:30

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Manipulating auxin transport: different strategies leave different signatures

Auxin is a key hormone in plant development. Among its roles is the determination and maintenance of root meristem identity. When a root forms a lateral organ, differentiated cells turn into a *de novo* meristem, with the aid of auxin.

From a developmental perspective, Legume roots are a particularly interesting example: they can sprout two different lateral organs: lateral roots and nitrogen fixing root nodules. Both of these are formed in the same region of the root, the differentiation zone. In both cases auxin accumulation is found at the location of the organ primordium. The primordia, however, originate from different cell layers and the organs are induced in different ways. This implies that the mechanism behind the local auxin accumulation most likely differs between the two cases.

Inspired by this, we analyzed the general characteristics of three plausible generic strategies for increasing the local auxin concentration: increasing influx, decreasing efflux and local production.

Each strategy results in a pattern with its own characteristic signature. This holds in a simple 1D model, but also shows up in a more complex root-like environment. Returning to the legumes: are the differences large enough to explain the early differences between both lateral organ primordia?

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A model of host response to a multi-stage pathogen

Pathogens that traverse different stages during their life cycle or during an infection process have been studied since the late nineteenth century. The most prominent genus is Plasmodium, causer of Malaria. Other important examples are Trypanosoma and the family of herpes viruses. Our focus is on the herpes virus Epstein-Barr (EBV), which is known to cycle through at least four different stages during infection within the human body. One remarkable characteristic of infections with many of such pathogens is *life-long persistent infection*.

The main goal of this work is to study the properties of the immune response to such a pathogen using mathematical modeling. In particular, we are interested in the existence and properties of steady-state behavior corresponding to life-long persistent infection. Our mathematical approach is based on standard ODE models of viral infection. For the postulated system of ODEs, we were able to characterize the equilibria in full generality regarding the number n of stages the pathogen cycles through. To establish the stability properties of the models' equilibria, we successfully applied techniques from modern control engineering.

If the pathogen is able to establish infection, (i.e., the basic reproductive number R_0 satisfies $R_0 > 1$), the model's parameters induce a partial order on the pathogen's stages. This binary relation $j \succ k$ is based on comparison of the rate at which stage j produces stage k with the rate at which stage k is lost to death and transformation into the next stage $k+1$. We say stage j *starves* stage k if immune regulation at stage j deprives stage k of sufficient population to support immune regulation. A stage k is called *starvable* if there is another stage j such that $j \succ k$. If no such j exists, k is called *unstarvable*. One of our main results is the fact that, generically, the system has a unique (local) asymptotically stable fixed point, namely, the one at which all unstarvable stages are regulated and all starvable stages are unregulated. In this sense, the immune regulation of unstarvable stages is sufficient to immunologically control the starvable stages. At steady state, immune regulation is only required against those stages that are produced with relatively higher yield.

This puts within reach a principled quantitative explanation of chronic infection with pathogens such as EBV, including the pattern of regulation (which is known to vary from person to person in the case of EBV), the sizes of the infected populations and the host response.

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Poster Session; Friday, July 1, 20:00

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Analysis of Feedback in GAL Signalling Cascade

The GAL network cascade in yeast (*Saccharomyces cerevisiae*) contains dynamic molecular interactions. The complex interplay of galactose, Gal3p, Gal80p and Gal4p regulate the transcriptional activity of enzymes in galactose utilization. Mathematical models have been proposed to understand such biological signalling processes. Further studies suggested that the models exhibit bistability/multistability due to the systems' positive feedback loop, ultrasensitivity, etc. In this study, an ODE model in which the feedback possesses a sigmoidal characteristic is used. We are interested to investigate how robustly positive feedback loop gives rise to bistability depending on whether it is mediated by stoichiometric complexes of signalling proteins, enzymes, or transporter molecules. In particular, we will examine how feedback in GAL signalling pathway can be used to apprehend the enhancement of cellular memory.

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Information, human behaviour and disease; Saturday, July 2, 11:00

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Effects of Behavioral Changes in Smallpox and Influenza Models

Communicable diseases are highly sensitive to how rapidly people reduce their contact activity patterns and to the precautions that the population takes to reduce the transmission of the disease. Recent experiences with the H1N1 pandemic show that an outbreak of a deadly disease would generate dramatic behavioral changes. However, models for infectious diseases have focused on analyzing the impact of traditional intervention strategies such as isolation and vaccination. In this talk I will present a model in which some individuals lower their daily contact activity rates or wear masks once an epidemic has been identified in their community. I will demonstrate that even gradual and mild behavioral changes can have a dramatic impact in slowing the epidemic and reducing the total number of cases. I conclude that for simulations of infectious diseases to be useful, they must consider the impact of behavioral changes. This is especially true if the model predictions are being used to guide public health policy.

Poster Session; Friday, July 1, 20:00

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3D image reconstruction of biological tissues

To analyse the movement and reaction of drugs in tissues, a detailed knowledge of the tissue structure is needed. To acquire a better understanding and provide a model for mathematical analysis and simulations, we construct a 3D-model from given image stacks showing various tissues. This model builds the foundation for particle simulations and narrows the gap from a discrete to an experimental approach. Furthermore the model serves as a verification method for simulation data and provides feedback to refine the simulation process.

The image recognition is implemented using OpenCV, which is the standard library for computer vision and comes with a variety of efficient algorithm useful to identify the different tissue structures. With the use of an image stack the distinguished tissue structure can be constructed to a geometrical model. For verification and better understanding of the results we generate a 3D visualisation using OpenGL. Statistical data can also be calculated using the generated model, for instance cell volume fraction or mean cell density.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits II; Wednesday, June 29, 17:00

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Two examples of influence of cell-cell interactions on populations: migrating cancer cells and magnetic manipulation for tissue engineering

Cell interactions can have a strong influence on the behaviour of their population, qualitatively as well as quantitatively. Often, the link between the microscopic law of their interaction and the macroscopic behaviour is not straightforward, and requires computer simulations and/or analytic techniques which can be successfully borrowed from condensed matter physics.

Here we give two examples of experimental situations where a macroscopic mathematical model for the population of cells was derived (in a non-rigorous way) from postulated microscopic interactions. In both cases, the aim is two-fold. Since the models succeed in reproducing the experiments, they can make predictions about more complicated, or even unattainable, experimental conditions. On the other hand, in a context where the microscopic mechanisms at stake are difficult to investigate directly, the quantitative match of the macroscopic models with the experiments indicate that the underlying microscopic hypotheses may be true.

In the first experiment, the excluded volume and adhesion, or contact inhibition, interactions between migrating cancer cells governs the way they collectively spread, making it far from a simple diffusion. In the second one, heaps of cells were prepared using magnetic nanomanipulation. The shape of the heaps and their evolution depend on the contact interactions, and can be understood thanks to simulations and to a mathematical model.

Modeling of collective phenomena in biological systems; Saturday, July 2, 08:30

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Analyzing emergent behaviour in interacting cell systems

Examples of emergent behaviour in interacting cell systems are life cycles of bacteria and social amoebae, embryonic tissue formation, wound healing or tumour growth. Thereby, development of a particular spatio-temporal "multi-cellular" pattern may be interpreted as cooperative phenomenon emerging from an intricate interplay of local (e.g. by adhesion) and non-local (e.g. via diffusing signals) cell interactions. What are cooperative phenomena in interacting cell systems and how can they be studied by mathematical models and computer simulations?

Typical modelling attempts focus on a macroscopic perspective, i.e. the models (e.g. partial differential equations) describe the spatio-temporal dynamics of cell concentrations. More recently, cell-based models have been suggested in which the fate of each individual cell can be tracked. Cellular automata are discrete dynamical systems and may be utilized as cell-based models.

Here, we analyze spatio-temporal pattern formation in cellular automaton models of interacting discrete cells. We introduce lattice-gas cellular automata and a cellular automaton based on an extended Potts model that allows to consider cell shapes. Model applications are bacterial pattern formation and tumour invasion.

DEUTSCH, A. AND DORMANN, S. (2005) Cellular Automaton Modeling of Biological Pattern Formation. Birkhauser, Boston

Modeling and analysis of tumor invasion II; Tuesday, June 28, 14:30

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Analyzing emergent behaviour in cellular automaton models of cancer invasion

Deciphering the principles of cancer invasion is crucial for the development of new therapy concepts. While molecular biology methods are required for a better characterization and identification of individual cancer cells, mathematical modelling and computer simulation is needed for investigating collective effects of cancer invasion. Here, we demonstrate how lattice-gas cellular automaton (LGCA) models allow for an adequate description of individual invasive cancer cell behaviour. We will then show how analysis of the LGCA models allows for prediction of emerging properties (in particular of the invasion speed). Furthermore, we propose that the transition to invasive tumour phenotypes in some brain tumours can be explained on the basis of the microscopic Go or Grow mechanism (migration/proliferation dichotomy) and oxygen shortage, i.e. hypoxia, in the environment of a growing tumour. We test this hypothesis again with the help of a lattice-gas cellular automaton. Finally, we will use our LGCA models for the interpretation of data from in vitro glioma cancer cell invasion assays.

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Epidemics; Wednesday, June 29, 08:30

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Coexistence of vertically and horizontally transmitted parasite strains in a simple SI type model

We study an SI type endemic model with one host and two parasite strains with complete cross protection between the strains. We assume that one strain is exclusively vertically transmitted and the other strain is horizontally (and possibly also vertically) transmitted. We assume that each strain reduces fertility and/or increases mortality of infected hosts. Our model consists of just three ordinary differential equations. We use the mathematical theory of persistence to show that the (exclusively) vertically transmitted strain that would go extinct by itself can persist by protecting the host against the more virulent horizontally transmitted strain [2]. There are two more interesting properties of our model. First, the ratio of horizontal to vertical transmission decreases if the coefficient of horizontal transmission increases, contrary to what one might expects [1]. Second, the equilibrium where both parasite strains coexist is always locally asymptotically stable if the horizontal transmission is of density-dependent (mass-action) type, but can loses its stability and gives rise to a limit cycle if the horizontal transmission is of frequency-dependent (standard) type [3].

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Poster Session; Friday, July 1, 20:00

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Turing Theory in an Epidemiological Model

Spatial models quantify disease spread in terms of epidemiological parameters (infection and recovery rates) that influence the speed of disease propagation *traveling epidemic fronts*. A recurrent assumption behind both type of models is uniformity in disease propagation. Such an assumption while unrealistic facilitates the mathematical analysis. In this dissertation the assumption of uniform mixing (*homogeneity*) is relaxed, spatial heterogeneity in the transmission process is allowed. A novel reaction diffusion model is introduced and used to identify necessary and sufficient conditions for the aggregation of individuals that may result in response to the introduction of a communicable disease. The methodology and techniques used in the analysis of this model, which exhibits diffusive instability, include Turing theory, which as far as I know, has not been used in this context.

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Optimal controls for enhancing natural response of the immune system in obesity-related chronic inflammation

Recent researches shows that the prevalence of obesity has increased by 70 percent over the past decade [2]. According to World Health Organization estimates, over 300 million adults are obese [4]. As the severity of the problem continues to grow worldwide, many scientific experts consider the obesity crisis a pandemic [3]. Chronic inflammation within fat tissue is now recognized as a contributor to the many ill health consequences that come with obesity, from diabetes to cardiovascular disease. The new discovery may therefore point to a targeted therapy designed to limit the health impact of the obesity epidemic, the researchers say. Unlike acute inflammation, which is the natural response to injury or infection, chronic inflammation results from a defective immune response. The excessive activity of pro-inflammatory cells and proteins can result in additional defects for surrounding tissues. These effects of chronic inflammation can lead to diseases such as cancer, kidney failure, atherosclerosis, and type 2 diabetes mellitus.

In this work, the optimal control theory is applied to an extended version of the model introduced by P. Díaz et al. in [1]. The model is defined by a system of ordinary differential equations and reflects the molecular and cellular interactions of the macrophages, T cells, chemokines, and cytokines that cause chronic inflammation, after the onset of adipocyte hypertrophy. The model does not account for the time period in which the subject becomes obese. In comparison with the model in [1], here a linear model for pharmacokinetics has been added. Seeking to maximize the effect of drug treatments to the model, we use a control representing the treatment. The optimal control is characterized in terms of the optimality system, which is solved numerically for several scenarios.

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Poster Session; Friday, July 1, 20:00

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Modeling Early Initiation Processes in Smoking-Induced Lung Adenocarcinomas

While most cancer models focus on the development of the tumor itself, our objective is to build a mathematical model of the early initiation processes of the development of lung adenocarcinomas induced by smoking. Our goal is to produce a model that is accurate enough to account for the major phenomenology involved in these initiation processes, that is able to reproduce all the experimental data, and that can explain the timings of tumorigenesis based on demographic differences.

We have approached the model building in four steps. First, the poorly understood biology was triaged to identify the key biological behaviors causing the phenotype transition from normal cells (prior to any smoke exposure) to the earliest phenotype that could be considered a neoplasm. Second, the biology was translated into a nonlinear ODE model that can reasonably explain the effects of smoking and that is neither too complex nor too simplistic. The resulting rate equations for the phenotype dynamics contain first and second order terms. The model is augmented with constraint functions that have a dual role they can be used for checking that the simulation results obey the modeling assumptions and they can be used in the optimization step to insure more reasonable parameters.

The third modeling step consists of the acquisition and analysis of quantitative biological data to calibrate the model. Because the amount of quantitative data within the scope of the model is limited, we have adopted a rigorous surrogate strategy. This allows us to use both clinical and animal data (including omics). The use of animal data requires care to make sure that both the dose and the age of the animals can be properly incorporated into a human model that extends across an entire adult lifespan. Finally, a strategy of constrained optimization is used to obtain a single set of model parameters that simultaneously provides a good fit to all the experimental data sets and accurately reproduces the key biological phenomena, without producing any unacceptable ones.

The model is currently being built and so far contains approximately 20 differential equations involving 50 parameters. We will discuss the model building process, some of the associated mathematical and computational challenges, the need for good data collection practices, and the value of a formal mathematical language for the expression of complex biological knowledge.

Neurosciences; Wednesday, June 29, 08:30

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The stochastic Morris-Lecar neuron model embeds a one-dimensional diffusion and its first-passage-time crossings

Stochastic leaky integrate-and-fire models, i.e. one-dimensional mean-reverting diffusions, are popular tools to describe the stochastic fluctuations in the neuronal membrane potential dynamics due to their simplicity and statistical tractability. They have been widely applied to gain understanding of the underlying mechanisms for spike timing in neurons, and have served as building blocks for more elaborate models. Especially the Ornstein-Uhlenbeck process is popular, but also other models like the square-root model or models with a non-linear drift are sometimes applied. However, experimental data show varying time constants, state dependent noise, a graded firing threshold and time-inhomogeneous input, and higher dimensional, more biophysical models are called for.

The stochastic Morris-Lecar neuron is a two-dimensional diffusion which includes ion channel dynamics. We show that in a neighborhood of its stable point, it can be approximated by a two-dimensional Ornstein-Uhlenbeck modulation of a constant circular motion. The associated radial Ornstein-Uhlenbeck process is an example of a leaky integrate-and-fire model prior to firing. A new model constructed from a radial Ornstein-Uhlenbeck process together with a simple firing mechanism based on detailed Morris-Lecar firing statistics reproduces the interspike interval distribution, and has the computational advantages of a one-dimensional model. The result justifies the large amount of attention paid to the leaky integrate-and-fire models.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents II; Wednesday, June 29, 08:30

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Modelling HCV kinetics in vitro yields estimates of the number of E2-CD81 complexes necessary for viral entry into target cells

Interaction between the hepatitis C virus (HCV) envelop protein E2 and the cell surface receptor CD81 is necessary for HCV entry into target cells. Blocking this interaction is therefore a promising strategy for therapeutic and preventive intervention. The minimum number of E2-CD81 complexes that must form across a virus-cell interface to facilitate virus entry, however, remains unknown. The recently developed cell culture systems that allow persistent HCV infection in vitro present data of the dependence of the susceptibility of cells to virus entry on the CD81 expression level on cells. We develop a mathematical model that quantitatively describes several independent experimental observations of viral kinetics in vitro and of the frequency of virus entry as a function of the CD81 expression level. Comparisons of model predictions with experiments yield estimates of the threshold number of E2-CD81 complexes necessary for virus entry. The threshold number depends on the affinity of the E2-CD81 complex and presents guidelines for the design and optimal usage of entry inhibitors and vaccines that target the E2-CD81 interaction.

Fractals and Complexity I; Wednesday, June 29, 14:30

Radu Dobrescu
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Using a mix of cellular automata in tumor margin analysis

Cellular automata are classical examples of models for many complex systems related to biology, being suitable tools for modeling growth and diffusion phenomena, especially tumor growth, considering that they have in common with tumors the concept of cell and local interaction. The goal in obtaining a good tumor model with cellular automata, as in any other model, is a better understanding of tumor dynamics and the developing of better techniques for the prediction of their evolution in real instances. The theoretical ingredients of this experiment are mixed cellular automata, the fractal dimension of the structure generated by an automaton (estimated by the box counting dimension), the frontier fractal dimension between two mixed cellular automata (estimated by the compass dimension) and the Langton's Lambda parameter of a cellular automaton.

References.

[1] B. Pfeifer, K. Kugler, M.M. Tejada. A cellular automaton framework for infectious disease spread simulation. The Open Medical Informatics Journal, 2008; 2: 70-81

Immunology; Wednesday, June 29, 14:30

Marina Dolfin
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A phenomenological approach to the dynamics of clonal expansion and immune competition of T cells

This presentation deals with a model of the dynamics of clonal expansion and immune competition of T cells [**1**] based on the approach of continuum mechanics. Field equations are mathematically constructed in the macroscopic framework of the thermodynamic theory of reacting fluid mixtures [**2, 3**], adapted to the case in which proliferative events occur [**4, 5**]. The introduced mathematical model is inspired by the experimental observation that during the treatment of type I hypersensitivity with the Specific ImmunoTherapy, the relative fraction of allergen specific Th1 cells increases [**6**] and its principal scope is to individuate key parameters and to evaluate their effect upon the domination of Th1 cell population over the Th2 one and viceversa.

References.

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[5] N. Bellomo, N.K. Li, P.K. Maini, *On the foundations of cancer modelling: selected topics, speculations and perspectives* Mathematical Models and Methods in Applied Sciences **18** (2008) 593–646.
[6] Personal communication of Prof. S. Gangemi of the Policlinico Hospital of the University of Messina to the author.

Bioinformatics and System Biology; Wednesday, June 29, 14:30

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Light and temperature effects on the circadian clock

The circadian clock is endogenous 24h timer driving numerous metabolic, physiological, biochemical and developmental processes. The clock has a complex interaction with its environment as it responds to light and temperature cues. It can be entrained to daily cycles of light and temperature, yet it also remains very robust to their stochastic fluctuations. Another key striking feature of the clock is that it can maintain nearly constant period over a broad range of physiological temperatures (a feature called temperature compensation). These properties enable the clock to do a variety of functions: it can be used to predict transitions at dusk and dawn, measure day length, and it allows an organism to respond accurately to seasonal rhythms. Elucidating the interaction of the clock with its environment can help us gain greater understanding of the design principles of this important mechanism. Here I will present some recent work in this direction [**1, 2**].

References.

[1] M. Domijan and D.A. Rand, *Balance equations can buffer noisy and sustained environmental perturbations of circadian clocks* Interface Focus **1** 177–186.

[2] P.D. Gould , N. Ugarte, J. Foreman, M. Domijan, D. McGregor, S. Penfield, D.A. Rand, A. Hall, K. Halliday, A.J. Millar, *Photoreceptors contribute temperature-specific regulation to the biological clock in Arabidopsis*, preprint.

Analysis of mathematical models for cancer growth and treatment, Part I;
Tuesday, June 28, 11:00

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The noisy life of tumors

In this talk we shall survey some recent theoretical results of our group on how much and how noise can deeply affect both natural history of tumours and their therapies. In the first part we shall show how intrinsic noise might beneficial since it might trigger tumour suppression through evasion form immune surveillance. On the other hand, we shall show how extrinsic noise may be negative, since it might trigger, both in absence and in presence of therapies, bounded-noise-induced induced phase transitions leading to tumour expansion.

References.

[1] A. d'Onofrio, Phys Rev E (2010)
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[3] G. Caravagna, A. d'Onofrio, P. Milazzo and R. Barbuti, J Theor Biol (2010)

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Malay Banerjee
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The interplay between delays and bounded noises in immune reaction to tumors

In this talk we shall summarize some recent results concerning the subtle interplays existing between the statistical fluctuations of the baseline levels of immunity and the delays in the tumor-stimulated activation of the immune system. We set our analysis in the framework of the theory of bounded noises.

Bioimaging; Tuesday, June 28, 11:00

Alexey Doroshkov
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Analysis of leaf hairiness in wheat Triticum Aestivum L. using image processing technique

Leaf hairiness in wheat is of great importance for adaptation to environmental factors including protection from pests. For example, this trait is the characteristic of a number of drought resistant wheat cultivars referred to the steppe ecological group. Study of leaf hairiness morphology and identification of the corresponding genes will allow obtaining the varieties which are resistant to hard climatic conditions and certain pests. To identify the genes responsible for the leaf hairiness, mass analysis of a great number of plants belonging to different hybrid populations is needed, accompanying with a laborious manual job. Furthermore, the more accurate description of the morphological properties of the trait for correct determination of phenotypic classes is timely. We developed the computerbased technology for descriptions of quantitative traits of leaf hairiness. It contains the LHDetect program with the feature of image processing [1,2]. Using the LHDetect one can count the trichome number, the mean length of the trichomes, and evaluate the trichome length distribution vector for each leaf sample. In the investigation, we used the LHDetect program for determining the morphological properties of leaf hairiness on a number of wheat genotypes. The technology appeared to be the effective approach for a large scale analysis of leaf hairiness morphological peculiarities in individual plants. In according with genotyping this approach can be useful for quantitative trait loci (QTL) mapping. In this study we carried out the detailed morphology analysis of leaf hairiness in 8 wheat cultivars: Golubka, Saratovskaya 29, Rodina (almost glabrous leaf), Rodina introgression line 102/00i (genome contains Aegilops speltoides gene, responsible for trichomes, line has well-haired leaf), Houng mang may, Janetzkis probat, Chinese synthetic and Diamant 2. Chosen cultivares represent a wide range of leaf hairiness morphology: the trichome density, length and distribution pattern greatly varied. Golubka cultivar plants was grown in the various conditions. It was shown that drought stressed Golubka plants form more trichomes on the leaf surface, but they are significantly shorter than those from plants grown in a favourable conditions. There are at least two possible explanations of the observations. First, much more trichomes are needed to form the microclimat in the drought conditions. Second, plant cells cant produce enough turgor pressure to form a long trichomes while the drougt stress.

References.

[1] Using the computer-based image processing technique in genetic analysis of leaf hairiness in wheat Triticum aestivum L./ A.V.Doroshkov, M.A.Genaev, T.A.Pshenichnikova, D.A.Afonnikov //the 7-th international conference on bioinformatics of genome regulation and structure/ systems biology, june 20-27 2010 Novosibirsk, Russia.

[2] WheatPGE system for analysis of the relationships between phenotype, genotype and environment in wheat/ M.A.Genaev, A.V.Doroshkov, D.A.Afonnikov //the 7-th international conference on bioinformatics of genome regulation and structure/ systems biology, june 20-27 2010 Novosibirsk, Russia.

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Not Missing at Random and Combined Odds Ratios from Mixture Models

Longitudinal studies and surveys often deal with incomplete observations. The validity of inference depends on the missingness mechanism [Little J.A, and Rubin, D.B., 2002]. When the missing data mechanism depends on observed data only, estimation of means and/or regression coefficients requires adjustment but is possible without further information. If the missingness mechanism depends on unobserved data, unbiased estimation requires further information. The information from random sub-samples of subjects whose responses are obtained, can be used to model the data using selection, shared parameter or pattern mixture models [Allison, 1994], which are identifiable in this case. However, the parameters obtained may not be the ones of interest to an investigator. A separate regression fit to responders and nonresponders will result in two regression coefficients when a single coefficient for the whole population is of interest. Multiple imputation [Rubin, D.B. 1987, Glynn etal, 1993] can lead to standard statistical analysis. Very large surveys can have more than 50% non-response. A naive approach using multiple imputation results in data sets with more than 50% imputed values. We will discuss logistic regression for a mixture model and compare it to multiple imputation when missingness depends on the unobserved data., The methods are illustrated with the Project Talent data set. The original survey was very large and baseline information is available for all participants. Study attrition exceeds 50% but random sub-samples of nonrespondents have almost complete follow-up.

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From one to many: Cell-based modeling of collective, emergent behaviors in biology -I; Tuesday, June 28, 11:00

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Possible cell behavior strategies to escape biomechanical constraints in liver regeneration and tumor growth

In this talk we will show how cells can escape possible biomechanical constraints. We consider the examples of the growing monolayers and multi-cellular spheroids, as well as the proliferation and regeneration pattern in liver after drug-induced damage and after hepatectomy. For each example we compare experimental results with the simulation results of single-cell-based models. Our model of the center-based type considers each cell as an individual unit parameterized by cell- biophysical and cell-biological quantities. Cell migration is mimicked by an equation of motion for each cell, representing all forces on that cell and including the cells micro-motility. Part of the models is parameterized from image analysis of either bright field or laser scanning micrographs for quantitative comparison with data. We demonstrate that the growth kinetics of monolayers and multi-cellular spheroids can be consistently explained if proliferation is controlled not only by molecular factors but also by a biomechanical proliferation control. The same type of proliferation control is able to ensure that unrealistically compressed cell volumes during regeneration after partial hepatectomy in liver does not occur, and that during tumor growth in liver vessels are not pushed out of the tumor cell mass. After drug induced liver damage cells around the so called central veins show massive necrosis. The central vein forms the center of a liver lobule, the repetitive functional unit of liver. Healthy cells must move actively to escape unrealistic compressions. In the absence of such a mechanism, the experimentally observed regeneration and proliferation pattern cannot be reproduced. The models of regeneration of liver after drug induced damage and after partial hepatectomy made predictions that could subsequently be validated.

References.

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Multi-scale mathematics of the liver: From intracellular signaling to intercellular interaction; Wednesday, June 29, 08:30

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Prediction and validation of an order principle to restore tissue architecture in liver regeneration after drug-induced damage: from experiments to modeling and back

Not much is known about how cells coordinately behave to establish functional tissue structure and to restore micro-architecture during regeneration. Research in this field suffers from a lack of techniques that permits quantification of tissue architecture and its development. To bridge this gap we have established a procedure based on confocal laser scans, image processing and three-dimensional tissue reconstruction, as well as on quantitative mathematical modeling. To illustrate our method we studied regeneration after toxic liver damage. We have chosen the example of the regenerating liver, because liver function depends on the complex micro-architecture formed by hepatocytes (the main type of cells in liver) and micro-vessels (sinusoids) that ensures optimal exchange of metabolites between blood and hepatocytes. Our model of regeneration after toxic damage captures hepatocytes and sinusoids of a liver lobule during the regeneration process. Hepatocytes are modeled as individual agents parameterized by measurable biophysical and cell-biological quantities. Cell migration is mimicked by an equation of motion for each cell subject to cell-cell-, cell-extra-cellular matrix-, and cell-sinusoid-forces, as well as the cell micro-motility. We demonstrate how by iterative application of the above procedure of experiments, image processing and modeling a final model emerged that unambiguously predicted a so far unrecognized mechanism, the alignment of daughter hepatocytes along the closest sinusoids as essential for liver regeneration. In absence of this mechanism, the simulated tissue architecture was in dis-agreement with the experimentally obtained data and no other likely mechanism could replace it. To experimentally validate the model prediction, we three-dimensionally analyzed the orientation of daughter hepatocytes in relation to the sinusoids. The results of this analysis clearly confirmed the model prediction.

References.

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Multiscale modeling of biological systems: from physical tools to applications in cancer modeling I; Saturday, July 2, 08:30

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Multi-scale modeling of cells: concepts and open questions

The analysis of tissue organization and tumor growth is inherently of multi-scale nature. Extracellular signal molecules, metabolites, mutations may due to cascades of molecular intermediates modify the behavior and the physical properties of a cell resulting in re-organization processes on the tissue and organ level. Vice-versa, changes on the level of the tissue can feed back to the molecular regulation processes. Limits in computation time requirements and the great complexity of cells and tissues make it impossible to simulate the interplay of the different scales ranging from molecules to whole organs in great detail. On the other hand, many details on smaller scales have only small or no effects on processes on larger scales. In this talk we discuss different individual-based models to tissue organization including hybrid and multi-scale models.

(1) In the first part we introduce individual-based model concepts and demonstrate how they can be used to explain growth in biological models of tumor development, namely, monolayer, multi-cellular spheroids, and Xenografts (Drasdo et. al., J. Stat. Phys. 2007 and refs therein, Radszuweit et. al., Phys. Rev. E, 2009). We consider two model types: cellular automaton models and center-based models. The first model is parameterized by rules while the latter model is parameterized by measurable quantities, and directly represents physical forces between the cells, and between cells and extra-cellular structures. We will critically discuss advantages and pitfalls of the different model types and show how they can be linked to extracellular molecular concentrations to hybrid models.

(2) In a second step we show how intra-cellular, molecular core modules can be embedded into a single-cell-based model to a multi-scale model. We consider several examples: the integration of the beta-catenin core module to mimic the epithelial-mesenchymal transition during cancer invasion (Ramis-Conde et. al., Biophys. J. 2008), intravasation, the process by which a tumor cells enters a blood vessel (Ramis-Conde et. al., Phys. Biol. 2009), mesenchymal stem cell differentiation

(Krinner et. al., Cell Prol. 2009; BMC Syst. Biol. 2010), and the change of cell metabolism during liver regeneration after drug-induced damage. (3) Finally we show how individual-based models can be used to guide the development of continuum models considering growth of disperse and compact tumor phenotypes (Byrne and Drasdo, J. Math. Biol. 2009).

Evolutionary Ecology; Wednesday, June 29, 14:30

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Do bacteria form spores as a bet-hedging strategy in stochastic environments?

Many bacteria form spores to survive extreme conditions, such as lack of nutrients, periods of drought, or extraordinary high or low temperatures. Detailed observations by microbiologists have revealed that even in isogenic populations there is substantial intra-individual variation in the timing of sporulation initiation. This has led to the hypothesis that sporulation is a 'bet hedging strategy', which has evolved to cope with unpredictably varying environments. The idea behind this is that early sporulators have an advantage if the environment gets worse, whereas late sporulators can profit more quickly from improving environments. Genotypes that produce individuals of different types therefore 'spread their risks'. We will present a model for studying the evolution of sporulation strategies in environments where new resources arrive at stochastic times. Based on this model we make predictions about the conditions under which bet hedging sporulation strategies might indeed evolve. The problem is complicated, since it involves density dependent processes (due to resource depletion) as well as environmental fluctuation.

Keywords: Evolutionary modeling; Bed-hedging strategy; Stochastic environments; Sporulation.

References.

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Poster Session; Friday, July 1, 20:00

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Mathematical modelling of adult GnRH neurons in the mouse brain

Gonadotropin-releasing hormone (GnRH) neurons are cells in the hypothalamus that produce GnRH, one of the major hormones that controls fertility and reproduction. However, despite their importance, little is known about the mechanisms by which GnRH is produced. GnRH neurons exhibit complicated membrane potential dynamics, in the form of electrical bursting, and this bursting is closely coupled to the dynamics of intracellular calcium (Ca^{2+}) in ways that are not yet well understood.

A mathematical model has been constructed to help understand the mechanisms underlying the observed behaviours of GnRH neurons, and how electrical bursting synchronizes with transients in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$). Simulations show that the model is consistent with all the crucial experimental data. Most importantly, the mathematical model predicted the existence of particular $[Ca^{2+}]_i$-activated potassium (K^+) channel ($sI_{AHP-UCL}$), which was then confirmed experimentally. In contrast to the apamin-sensitive $[Ca^{2+}]_i$-activated K^+ channels (sI_{AHP-SK}), which control both the structure of firing within bursts and the interburst intervals, $sI_{AHP-UCL}$ solely determines the interburst dynamics.

The work has been published in Lee et al., 2010 and Duan et al., 2011.

References.

[1] Kiho Lee, Wen Duan, James Sneyd, Allan E. Herbison, *Two slow calcium-activated after-hyperpolarization currents control burst firing dynamics in gonadotropin-releasing hormone neurons* The Journal of Neuroscience **30(18)** 6214–6224.

[2] Wen Duan, Kiho Lee, Allan E. Herbison, James Sneyd, *A mathematical model of adult GnRH neurons in mouse brain and its bifurcation analysis* Journal of Theoretical Biology **276** 22–34.

Poster Session; Friday, July 1, 20:00

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Chaos and crises in a model for cooperative hunting

In this work we investigate the population dynamics of cooperative hunting extending the McCann and Yodzis model for a three-species food chain system with a predator, a prey, and a resource species. The new model considers that a given fraction σ of predators cooperates in prey's hunting, while the rest of the population $1-\sigma$ hunts without cooperation. We use the theory of symbolic dynamics to study the topological entropy and the parameter space ordering of the kneading sequences associated with one-dimensional maps that reproduce significant aspects of the dynamics of the species under several degrees of cooperative hunting. Our model also allows us to investigate the so-called deterministic extinction via chaotic crisis and transient chaos in the framework of cooperative hunting.

Poster Session; Friday, July 1, 20:00

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Spatio-temporal modeling of *Aedes albopictus* dispersal in Réunion Island. Application to the release of Sterile Insects.

This work is part of a project, called the SIT-project, that aims to develop biological control tools to prevent or stop a Chikungunya epidemic. Chikungunya is somehow a uncommon disease and before the huge epidemic in Réunion island and in India in 2006, our knowledges on this virus were small. Recently, in September 2010, a few cases of Chikungunya appeared in South of France, indicating that Chikungunya is not only a tropical disease but can potentially appear in Europe. The appearance of Chikungunya is strongly connected with the spreading of one of its principal vector, *Aedes albopictus*. This mosquito is now well established in the South of Europe. In [1] and [2], we were mainly concerned on the modeling of the epidemic and on the use of chemical vector control tools, like adulticides and larvicides, and mechanical control, which consists in reducing the breeding sites. Unfortunately, using chemical control tools, in Réunion Island is not really a good idea. First, because Réunion Island is a hot spot of endemicity, and second because mosquito can develop a resistance to insecticides. In a recent paper, we have developed a new model on the use of the Sterile Insect Technique (SIT) as an alternative to insecticides [3].

All published models are temporal models, i.e. they don't take into account the spatial component. Using the previous works, we began to fill this gap. Using mark-release-capture experiments, we have developed a system of partial differential equations (PDES) in order to model the spreading/displacement of an *Aedes albopictus* mosquito population. In a first approach, we have splitted the females in two biological stages: one representing the female looking for breeding sites, and the other representing females looking for blood meal. This led to a system of two coupled partial differential equations. Then, we have considered a full model with more compartments including the aquatic stage, imature females, female looking for blood meals, female looking for breeding sites, and males, for mating. These led to a system of coupled advection-reaction-diffusion PDES. Taking into account entomological knowledges, we have included biological facts into the equations in order to be as realistic as possible. We developed appropriate numerical methods in order to get realistic numerical simulations to be able to compare with "experiments" in the fields.

The main application of this work is to optimize vector control, using releases of sterile males combined with mechanical control.

References.

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Vector-borne diseases; Tuesday, June 28, 14:30

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Chikungunya: an unusual vector-borne disease. Overview and new research trends.

In 2006 Réunion Island faced a huge Chikungunya epidemic. Since then, in 2007, and more recently, in september 2010, a few cases of Chikungunya appeared in Italy and in South of France. Since the explosive epidemic in Réunion Island, our knowledges on the Chikungunya virus and its principal vector, *Aedes albopictus*, have increased (see [6] for instance). In some sense, Chikungunya is an unusual vector-borne disease: it has been proved that a mutation in the virus in 2005 has led to an increase in the probability of transmission from human to mosquito, and had also a strong impact on the life-span of infected mosquitoes [6], which may explain the explosive epidemic in 2006 in Réunion Island. All these biological assumptions have been taken into account in the models studied in [2,3]. After some theoretical works [1, 2] on the modeling of the epidemic and on the use of chemical vector control tools, like adulticides and larvicides, we recently have studied the "Pulsed" Sterile Insect Technique (SIT) as a biological alternative to insecticides, because mosquito can develop a resistance to insecticides [3]. Moreover SIT is known to be a species-specific environmentally nonpolluting method. In particular, we showed that frequent and small releases of sterile males can be efficient to control an epidemic, but only if it is considered early in the epidemic.

All published models are temporal models, i.e. they don't take into account the spatial component. Based on [2], we have filled this gap, considering a patchy model in order to take into account human displacements between cities in Réunion Island [**1**]. We have computed the Global Basic Reproduction Number, $\mathcal{R}_{0,G}$, for the patchy model, and we have showed that even if locally $\mathcal{R}_0$ is less than 1, $\mathcal{R}_{0,G}$ can be greater than 1, indicating that population displacements could have an effect on the global dynamic of the outbreak. For practical purposes, we show that vector control in cities where $\mathcal{R}_0$ is large, could be efficient to control globally the epidemic.

Finally, based on field experiments, we have include the spatial component in the modelling of the mosquito population. This leads to a complicate system of non linear partial differential equations [5]. The final aim is to "optimize" locally vector control by reducing the breeding sites or/and by using the Pulsed SIT. We will illustrate the presentation with numerical simulations.

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Multiscale modelling of biological systems: the Chaste framework;
Tuesday, June 28, 11:00

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Modelling the Effect of the Actin Basket and Basement Membrane in the Deformation of the Colonic Crypt

The role of the basement membrane is vital in maintaining the integrity and structure of an epithelial layer, acting as both a mechanical support and forming the physical interface between epithelial cells and the surrounding connective tissue. The function of this membrane is explored here in the context of the epithelial monolayer that lines the colonic crypt, a test tube shaped gland responsible for renewing the intestinal surface through a coordinated sequence of cell division, migration and death. It is believed that in the first step in colorectal carcinogenesis, crypts acquire genetic mutations that disrupt the normal patterns of cell proliferation and migration, which can lead to crypt buckling and fission. To identify mechanisms responsible for this, a model of the crypt with a realistic, deformable geometry is required, which takes into account the role of the surrounding tissue stroma in maintaining crypt homeostasis throughout these cell events.

A model is proposed here to directly address these criteria. An off-lattice cell-centre modelling approach is adopted, with cell-cell connectivity defined by a Delaunay triangulation, and polygonal cell shapes realistically prescribed by the dual Voronoi tessellation. As such, cell centres are defined by nodes that are free to move in space, which are connected to neighbouring cells along the lines of the triangulation. A novel method for modelling the role of the basement membrane beneath a growing epithelium is presented, which subsequently allows the desired crypt geometry to develop, rather than to be imposed. Further to this, the model takes into account the continuous meshwork of actin that forms a basket below each crypt base, and which provides stability to this region.

Results from *in silico* simulations show that homeostasis of the growing epithelial monolayer can be achieved and sustained within this modelling framework, and the necessary balance of interactive cell forces, cell migration and cell death are presented. This work forms the basis for investigation of the deformation of the crypt structure that can occur due to proliferation of cells exhibiting mutant phenotypes, experiments that would not be possible *in vivo* or *in vitro*.

This model is proposed as the foundation of a realistic representation of growth of an epithelial sheet in a deformable environment. Whilst it is applied here specifically to the colonic crypt, the basic principles extend to other biological epithelia, such as the interfollicular epidermis, or the olfactory mucous membrane. Thus, this work and the results presented, hold potential for future research in other biological contexts.

Poster Session; Friday, July 1, 20:00

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A discrete simulation of protein movement and protein-protein interactions in a biological membrane

The membrane is a complex and dynamic system that plays a major role in the metabolic processes of organisms. The lateral organization and dynamics of proteins in the membrane are important factors in controlling membrane bioactivity. Simulations of the membrane, which strive to maintain biological realism, enable us to investigate these processes. The purpose of this work is to explore time and length scales that are not accessible to all-atom, or even coarse-grained, molecular dynamics (MD) simulations that are currently undertaken. Here we present a novel simulation method for a system of synthetic membrane peptides, WALP-23, in a DPPC phospholipid bilayer.

We are able to investigate many of the features that are observable in MD simulations, but at a fraction of the computational cost. The ability to simulate longer time and length scales also enables us to investigate aspects of the simulated system that we would be unable to investigate with MD. We can look at the longer-term evolution of protein clusters, investigating their mobility, lifetime and rates of coalescence. We are also able to look at the larger-scale structures that form, allowing us to make comparisons with experimental data from techniques like atomic force microscopy.

We employ an off-lattice model, with the membrane represented as a two dimensional sheet and the proteins described by the position of their centre of mass. The simulation uses stochastic Brownian dynamics to model the motion of the proteins through a lipid continuum. Forces between proteins, mostly a result of the hydrophobic mismatch between the protein and the bilayer, act along the line of centres. The influence of the surrounding lipids on each protein is manifested both in the stochastic nature of the Brownian motion, and in their contribution to the inter-protein forces.

We use MD simulations to characterise the force between proteins. The inter-protein force for a pair of WALP-23 proteins in a DPPC bilayer can be measured whilst varying the separation of their centres of mass. The benefit of this approach is that the inter-protein force includes contributions from different sources. Some of these, such as the hydrophobic mismatch, would be difficult to characterise without such a calculation. By improving the parameterization process and looking at more protein species we can work towards a more varied and realistic membrane simulation.

Modeling of immune responses and calcium signaling III; Wednesday, June 29, 17:00

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Modelling the spatio-temporal organisation of intracellular calcium signalling : from mechanism to physiology

Signal-induced Ca2+ oscillations have been observed in many cell types and play a primary role in cell physiology. They mediate vital physiological processes such as secretion, gene expression or fertilization. Specificity in the physiological responses is ensured by the high level of spatio-temporal organization of Ca2+ dynamics in the form of stochastic sub-cellular increases, regular oscillations and intra- or intercellular Ca2+ waves. In this talk, I'll illustrate on some specific examples how the interplay between experiments and modelling can help uncovering the molecular mechanisms responsible for the spatio-temporal organization of intracellular Ca2+ dynamics and for their physiological role. The peculiarities of the Ca2+ oscillations induced by stimulation of mGluR5 will be presented in more details.

Crowd Dynamics: Modeling, Analysis and Simulation (Part 2); Wednesday, June 29, 14:30

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Kinetic modelling of opinion leadership

We propose a kinetic model for opinion formation in the presence of strong opinion leaders. Our approach is based on an opinion formation model introduced in Toscani (2006) and borrows ideas from the kinetic theory of mixtures of rarefied gases. Starting from microscopic interactions among individuals, we arrive at a macroscopic description of the opinion formation process which is characterized by a system of Fokker-Planck type equations. We discuss the steady states of this system and present numerical results.

Cell migration during development: modelling and experiment; Saturday, July 2, 08:30

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Models of neural crest cell migration during development

Elucidating the mechanisms underlying the cell movement and rearrangement that turn a clump of cells into a functioning organism requires close collaborations between experimentalists and mathematical modellers. One such important phenomenon is that of neural crest cell migration during embryogenesis. A two-dimensional individual-based model for the migration of cranial neural crest cells in the developing chick embryo has been formulated. The model consists of multiple agent types and predicts the responses of cells to an underlying chemoattractant which is used up by the cells. The model is used to make predictions which are then tested experimentally. This talk will outline the stages of the modelling process, demonstrating how repeated cycles of model construction, experimental validation and testing are vital for furthering our understanding in the area.

Plants, growth and transport processes II; Tuesday, June 28, 14:30

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The mechanics of plant root growth

Many growing plant cells undergo rapid axial elongation with negligible radial expansion. Growth is driven by high internal turgor pressure causing viscous stretching of the cell wall, a complex structure containing stiff cellulose microfibrils, embedded within a pectin ground matrix and linked through a network of hemicellulose crosslinks. This microstructure produces non-linear anisotropic mechanical behaviour, and can be manipulated under enzymatic control to alter the cell growth rate. We first present a theoretical model of a growing cell, representing the primary cell wall as a thin axisymmetric fibre-reinforced viscous sheet supported between rigid end plates. Asymptotic reduction of the governing equations, under simple sets of assumptions about the fibre and wall properties, yields variants of the traditional Lockhart equation, which relates the axial cell growth rate to the internal pressure. The model provides insights into the geometric and biomechanical parameters underlying bulk quantities such as wall extensibility and shows how either dynamical changes in wall material properties or passive fibre reorientation may suppress cell elongation. We then investigate how the action of enzymes on the cell wall microstructure can lead to the required dynamic changes in macroscale wall material properties, and thus demonstrate a mechanism by which hormones may regulate plant growth. Using knowledge gained from the single cell model, we consider a mathematical model of hemicellulose crosslink dynamics incorporating both strain-enhanced breakage and enzyme-mediated breakage and reformation. The relationship between stress and strain-rate is shown to exhibit the characteristic yielding-type behaviour seen experimentally. The model shows how this stress strain-rate relationship is modified in the presence of enzymes and predicts the distribution of crosslinks and stress within the cell wall.

Modeling of immune responses and calcium signaling V; Saturday, July 2, 11:00

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Three pool model of self sustained calcium oscilations

In addition to energy production, mitochondria are involved in crucial cellular signaling processes. They are one of the most important organelles responsible for the Ca^{2+} regulatory pathways in the cell. Several mathematical models explaining these mechanisms were created but only few of them describe an interplay between calcium concentration in endoplasmic reticulum (ER), cytoplasm and mitochondria (see e.g. [1]). Experiments measuring calcium concentrations in mitochondria and ER suggest the existence of cytosolic microdomains with locally increased calcium concentration (CMDs) in the nearest vicinity of the outer mitochondrial membrane. CMDs allow Ca^{2+} to be taken up by mitochondria rapidly and form a steep concentration gradient. Such microdomains have been described lately as a MAM - mitochondria-associated ER membrane. To simulate calcium oscillations more accurately, we propose a model with an additional direct calcium flow between ER and mitochondria which takes into account recently discovered specific physical connections between these two organelles. For the proposed model we have shown the global existence of nonnegative solutions. We examined numerically the existence of stable limit cycles of Ca^{2+} oscillations, basin of their attraction, and the dependence of the cycles period on the parameters.

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Epidemic models: Networks and stochasticity I; Wednesday, June 29, 14:30

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Measuring and modelling changing social contact patterns

Social networks offer an attractive way of viewing patterns of human contacts; however, it is seldom (never?) possible to accurately measure an epidemiologically-relevant network in all its detail and complexity. In practice, therefore, models of disease spread are obliged to make a range of simplifications. One common simplification is to assume that patterns of contacts do not change over time; more ambitious models make plausible, though somewhat ad hoc, assumptions to capture the effects of, for example, school holidays. In contrast, we present an age-structured model of the spread of H1N1v influenza (swine flu) in the UK in 2009, parameterised using data from a social contact survey completed by an internet-based cohort throughout the course of the epidemic. We find that this simple model can provide remarkably satisfying representations of disease incidence data. We conclude that even when detailed social network data are unavailable all is not lost.

Modelling biofilms: from gene regulation to large-scale structure and function; Wednesday, June 29, 17:00

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A numerical method for a doubly degenrate diffusion-reaction model describing biofilm processes

Some biofilm systems and processes can be described by quasilinear parabolic equations with two non-Fickian diffusion effects: (i) degeneracy of the diffusion coefficients for vanishing biomass density, and (ii) a super-diffusion singularity when the maximum biomass density is reached. Phenomenon (i) guarantees a well defined interface between the biofilm and the surrounding aqueous phase that moves at finite speed, phenomenon (ii) ensures that the maximum biomass density is not exceeded. In numerical simulations both these aspects are not easy to deal with. We discuss a simple, yet relatively robust numerical method. We show that under this numerical realisation the effects of (i) and (ii) are maintained, we give a stability result, show convergence numerically by grid refinement, and discuss the parallel speed-up gained on OpenMP platforms.

Recent advances in infectious disease modelling II; Saturday, July 2, 14:30

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Using viruses to eliminate tumours: the role of multi-stability and multi-instability phenomena

Recent advances in virology, gene therapy and molecular and cell biology have provided insight into the mechanisms through which viruses can boost the anti-tumour immune response, or can infect and kill directly tumour cells. Here, we derive a mathematical model to investigate the anti-tumour effect of two viruses and their interactions with the immune cells. We then discuss the role of virus persistence on the elimination of tumour cells. To this end, we focus on multi-stability and multi-instability, two complex phenomena that can cause abrupt transitions between different states in biological and physical systems. In the context of cancer immunotherapies, the transitions between a tumour-free and a tumour-present state were so far associated with the multi-stability phenomenon. Here, we show that the multi-instability phenomenon can lead to the formation of a homoclinic bifurcation, which causes the system to switch from a tumour-present to a tumour-free state. This multi-instability phenomenon is driven by the persistence of the virus, while the multi-stability phenomenon is driven by the immune response.

Bridging the Divide: Cancer Models in Clinical Practice; Thursday, June 30, 11:30

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Modeling Remnant Ablation Protocols in Thyroid Cancer

Thyroidectomy of pediatric and adult patients with differentiated thyroid cancer is typically followed by radioactive iodine treatment to ablate thyroid remnants. A common protocol for this followup treatment is to give replacement thyroid hormone T_4 after surgery as the patient recovers, and then withdraw replacement hormone for 2-3 weeks to raise TSH levels to 30 mU/L or higher, as radioiodine uptake is improved when TSH levels are high. Patients may be quite sick and impaired during these several weeks, due to the severe clinically hypothyroid condition generated. To explore whether this protocol can be improved, we adapted a physiologically based ODE model of adult hypothalamic-pituitary-thyroid axis regulation to incorporate severe hypothyroid effects, as well as adjusting the parameters to model pediatric thyroid cancer using pediatric clinical data. We simulated a range of replacement protocols to establish withdrawal times needed to raise TSH levels > 30 mU/L, each for a range of tissue remnant percentages based on typical clinical remnants after thyroidectomy. We found that use of T_3-only after thyroidectomy, rather than T_4, can substantially reduce the withdrawal time needed prior to radioiodine ablation therapy, thereby decreasing patient morbidity.

Game theoretical modelling and optimization in evolution and ecology I;
Tuesday, June 28, 11:00

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More capital or income breeding optimal strategies for indeterminate growers in the seasonal environment

We use dynamic optimization algorithm to find adaptive schedules of energy allocation to growth and reproduction in the seasonal environment for an organism that can be capital or income breeder. Value of newborns in our model is related to the timing of reproduction. Our results show that the relationship between newborns value and storing reserves for reproduction can be highly negatively correlated. Importantly the reliance on reserves in reproduction may be optimal without the stochastic changes in environmental conditions usually assumed in the models of capital breeding evolution. Our results confirm also the idea that optimality of capital breeding strategy depends on efficiency of energy channeling from reserves to reproduction.

Epidemics; Saturday, July 2, 08:30

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Global properties of virus dynamics models with multi-target cells and delays

In this paper, we propose a class of virus dynamics models with multi-target cells and intracellular delays and study their global properties. We first study the global properties of a virus dynamics model with two target cells and delays. Then we introduce two new virus dynamics models with multi-target cells and delays. The first model is a $(2n+1)$-dimensional nonlinear delay ODEs that describes the dynamics of the virus, n class of target cells (uninfected cells) and n class of infected target cells. The second model generalizes the first one by assuming that the infection rate is given by saturation functional response. Two classes of time delays are incorporated into these models, (i) the times needed for newly infected cells to start to produce viruses, (ii) the time for newly produced virus to become infectious (matures). Lyapunov functionals are constructed to establish the global asymptotic stability of the uninfected and infected steady states of these models. We have proven that if the basic reproduction number R_0 is less than unity then the uninfected steady state is globally asymptotically stable, and if $R_0 > 1$ (or if the infected steady state exists) then the infected steady state is globally asymptotically stable.
Keywords: Global stability; viral infection; intracellular delays; direct Lyapunov method.

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Existence of Positive Almost Periodic or Ergodic Solutions for Some Neutral Nonlinear Integral Equations

As we all know, the existence of periodic solutions of functional differential equations (FDE) has great theoretical and practical significance and is one of the problems of great interest to scholars in the field. Since Yoshizawa [**2**] presented an excellent result for the existence of periodic solutions to FDE with bounded delay, Cooke and Huang [**3**], Burton and Hatvani [**1**] generalized Yoshizawa's result to FDE with infinite delay. We remark that, in the nature, there is no phenomenon which is purely periodic, this gives the idea to consider the almost periodic situation.

In this paper, we consider the following neutral nonlinear integral equation

$$x(t) = \gamma x(t-\sigma) + (1-\gamma)\int_{t-\sigma}^{t} f(s, x(s))\, ds, \tag{1}$$

where $0 \leq \gamma < 1$, $\sigma > 0$ and $f : \mathbb{R} \times \mathbb{R}^+ \to \mathbb{R}^+$ is a continuous map.

We give sufficient conditions which guarantee the existence of almost periodic solutions for Equation (1). We also treat the ergodic solutions that means the asymptotically almost periodic, the weakly almost periodic and pseudo almost periodic solutions. Hypotheses of our results do not impose that the function $f(t,.)$ is monotone. To state our results, we use a variant of Hilbert's projective metric on a subset of a space of continuous and bounded functions.

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Poster Session; Friday, July 1, 20:00

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Models for extinction in metapopulations

Standard metapopulation models assume a timescale separation between the local dynamics (fast), and the global dynamics, allowing for a much simpler treatment of the whole population. This assumption is however not realistic. With a Master equation we implement a metapopulation model with general within-patch dynamics. We implement a Fokker-Planck approximation, by means of expanding on the inverse number of patches, to describe the quasi-steady state and the size of typical fluctuations. We use also WKB theory in order to calculate the expected time to extinction for the population. We compare our results to numerical simulations, and lastly to the standard metapopulation model.

Heart rate dynamics: models and measures of complexity (part II);
Wednesday, June 29, 17:00

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Heart rate asymmetry and its reflection in HRV complexity measures

Heart rate asymmetry (HRA) is a physiological phenomenon by which the contribution of decelerations to short-term variability is greater than that of accelerations, and the contribution of accelerations to long -term variability is greater than that of decelerations. After shuffling the above differences vanish, so it was concluded that HRA depends on the structure of the RR intervals series. Complexity based measures, such as sample entropy or symbolic dynamics, try to quantify the structure of a dataset trying it on the continuum between perfect order and randomness. It is therefore interesting to see if the two approaches are related.

Materials and methods: 30-min ECG recordings were obtained from 200 healthy subjects, 87 women. Variance based asymmetry descriptors ($SD1_a$, $SD1_d$, $SD2_a$, $SD2_d$, $SDNN_a$, $SDNN_d$, $C1_d$, $C2_d$, C_d) and sample entropy (SampEn) as well as parameters of symbolic dynamics (V0, V1, V2, SymbEnt) were calculated for each of them. The associations between these parameters was studied with the use of the non-parametric Kendall correlation.

Results: The variance based HRA descriptors are not associated with SampEn. $C1_d$, $C2_d$ and C_d are statistically significantly correlated with SampEn for m=1 (τ=−0.3, −0.13, −0.12) and only $C1_d$ is correlated with SampEn for m=2 ($\tau = -0.25$). All variance parameters are correlated with the parameters of symbolic dynamic, negatively with V0 and positively with the remaining parameters. $C1_d$ is negatively correlated with V0 ($\tau = 0.3$) and positively with all the other symbolic dynamic parameters, a similar observation can be made of $C2_d$ and C_d, but the magnitude of the correlation coefficient is very small.

Discussion: HRA descriptors are associated with the studied complexity based parameters. The nature of this association is, however unclear, and needs further study.

Evolutionary Ecology; Wednesday, June 29, 14:30

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Dispersal polymorphism and species' invasions

The speed at which species range expansions occur has important consequences for the conservation management of species experiencing climate change and for the invasion of exotic organisms. Dispersal and population growth rate are known to affect the speed of invasion, however, little is known about what the effect of having a community of dispersal phenotypes is on the rate of range expansion. We use reaction-diffusion equations to model the invasion of a species with two dispersal phenotypes into a previously unoccupied landscape. These phenotypes differ in both their dispersal rate and population growth rate. We find that the presence of both phenotypes can result in faster range expansions than if only a single phenotype is present in the landscape. We show that typically the invasion can occur up to twice as fast as a result of this polymorphism. This has implications for predicting the speed of invasion of species, suggesting that speeds cannot just be predicted from looking at a single phenotype and that the presence of a community of phenotypes needs to be taken into consideration.

Poster Session; Friday, July 1, 20:00

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Mathematical modeling of bacterial attachment to surfaces: Biofilm initiation

The development of bacterial biofilm is a multi-stage process consisting of five stages, namely, initial attachment of bacteria to surfaces or interfaces, irreversible attachment, first maturation, second maturation and the detachment of bacteria. Our interest in this work, is to model the biofilm initiation. In the early stage at low bacterial density, we use a stochastic model to describe the bacterial movement towards the interfaces. Then when the density is significantly high we develop a non-linear system of partial differential equations of Keller-Segel type model to illustrate more biological facts such as chemotaxis and sensing chemicals production. The numerical simulations to the models show that the sensing chemicals are highly concentrated in the interfaces which attract more bacteria to the boundaries, and this makes a good agreement with the biological observations.

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Modeling Dynamics of Complex Biological Systems; Tuesday, June 28, 17:00

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Protein scaffolds can enhance the bistability of multisite phosphorylation systems

The phosphorylation of a substrate at multiple sites is a common protein modification that can give rise to important structural and electrostatic changes. Scaffold proteins can enhance protein phosphorylation by facilitating interaction between a protein kinase enzyme and its target substrate. In this work, we consider a simple mathematical model of a scaffold protein and show that under certain conditions, the presence of the scaffold can substantially raise the likelihood that the resulting system will exhibit bistable behavior. This phenomenon is especially pronounced when the enzymatic reactions have a Km larger than 10 micromolar. We also find that bistable systems tend to have a specific kinetic conformation, and we provide through mathematical analysis a number of necessary conditions for bistability, such as the presence of multiple phosphorylation sites and the dependence of the scaffold binding/unbinding rates on number of phosphorylated sites.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -II; Tuesday, June 28, 14:30

Heiko Enderling
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Emerging tumor morphologies from cancer cell interactions

We present a theoretical model of tumor growth based on the interactions of cancer stem cells and non-stem cancer cells. We show that tumor growth is driven by cancer stem cells and modulated by non-stem cancer cells. Intrinsic cell parameters yield different kinetics and population ratios, and a variety of tumor morphologies emerge.

The emergence of resistance in cancer using mathematical modelling;
Saturday, July 2, 08:30

Heiko Enderling
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Emergence of radioresistance through selection for cancer stem cells in solid tumors

Tumor growth and progression is a complex phenomenon dependent on the interactionof multiple intrinsic and extrinsic factors. Necessary for tumor development is a small subpopulation of potent cells, so-called cancer stem cells, which also produce a distinct population of non-stem cancer cells. Both populations compete with each other yielding interesting tumor dynamics. During radiotherapy treatment the intrinsic tumor dynamics are perturbed, resulting in selection and expansion of resistant cancer stem cells.

Cellular Systems Biology; Thursday, June 30, 11:30

Radek Erban
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Stochastic modelling of reaction-diffusion processes in biology

Many cellular and subcellular biological processes can be described in terms of diffusing and chemically reacting species. Several stochastic simulation algorithms (SSAs) suitable for the modelling of such reaction-diffusion processes have been recently proposed in the literature. In this talk, two commonly used SSAs will be studied. The first SSA is an on-lattice model described by the reaction-diffusion master equation. The second SSA is an off-lattice model based on the simulation of Brownian motion of individual molecules and their reactive collisions. The connections between SSAs and the deterministic models (based on reaction-diffusion PDEs) will be presented. I will consider chemical reactions both at a surface and in the bulk. I will show how the "microscopic" parameters should be chosen to achieve the correct "macroscopic" reaction rate. This choice is found to depend on which SSA is used. I will also present multiscale algorithms which use models with a different level of detail in different parts of the computational domain.

Reports from US - African BioMathematics Initiative: Conservation Biology; Saturday, July 2, 14:30

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A Bio-economic Model For Tropical Forest Harvesting and Habitat Loss

We plan to study the interaction between tropical forest harvesting and the habitat loss for the Bonobos and Pygmy Chimpanzees (Pan paniscus) living in the forest.

Starting from data collected for the Idanre Forest Reserve in the lowland rain forest zone of South -Western Nigeria (and literature review), we constructed an analytic model that classifies the trees into 6 size classes according to their diameter and captures the forest growth over time. Our model assumes linear dynamics and uses a Leslie-like matrix that was fitted to historical time series.

We modeled the economic aspects of the logging activity by introducing variable (dependent on the effort) and fixed (independent of the effort) costs, estimated from real world data. Moreover, to estimate the economic value of the trees in each size class, we constructed a function that relates the diameter to the volume, from which we obtain a monetary value by looking at market prices of tropical wood.

We plan to include a population dynamic model of the animal populations living in the area that is dynamically coupled to the growth processes of the forest. In particular, we plan to capture the effect of each size class on the carrying capacity of the Bonobos and Chimpanzees populations.

Our final goal is to quantitatively study the effect of harvesting policies in terms of economic benefits and on the population survival probability, in order to obtain insights on the structure of more sustainable logging practices.

Epidemics of Neglected Tropical Diseases; Wednesday, June 29, 11:00

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Modelling transmission of Chagas' disease

Chagas disease, also known as American trypanosomiasis, is a potentially life-threatening illness caused by the protozoan parasite, Trypanosoma cruzi (T. cruzi) which is found mainly in Latin America. The main mode of transmission of Chagas disease in endemic areas is through the bite of an insect vector called a triatomine bug. The disease may also be spread through blood transfusion and organ transplantation, ingestion of food contaminated with parasites, and from a mother to her fetus. Control measures are limited since vaccines to prevent the disease are not available, and drugs are effective only in the acute and early chronic phase of infection, but have adverse effects. Control measures include insecticides to kill the vector, screening blood donors, and treatment to patients in the acute phase. Recently, a controversial strategy, Zooprophylaxis, has been proposed for the control of vector transmitted diseases. This technique refers to the control of vector-borne diseases by attracting vectors to domestic animals in which the pathogen cannot amplify (a dead-end host).

In order to assess the efficiency of the different control measures for Chagas disease, in this work we develop a mathematical model considering four populations: humans, vectors, and susceptible and no susceptible domestic animals to Chagas infection. We obtain the basic reproductive number of the disease, and through it we evaluate the impact of the control measures.

Fluid-structure interaction problems in biomechanics; Saturday, July 2, 08:30

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A heart model in the whole circulatory system

We present a mathematical model of left heart governed by the partial differential equations. This heart is coupled with a lumped model of the whole circulatory system governed by the ordinary differential equations. The immersed boundary method is used to investigate the intracardiac blood flow and the cardiac valve motions of the normal circulation in humans. We investigate the intraventricular velocity field and the velocity curves over the mitral ring and across outflow tract. The pressure and flow are also measured in the left and right heart and the systemic and pulmonary arteries. The simulation results are comparable to the existing measurements.

Biofluids, Solute Transport, and Hemodynamics; Wednesday, June 29, 11:00

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A computational model of whole kidney oxygen regulation incorporating arterial to venous oxygen shunting

Background: Our understanding of renal tissue oxygenation is complicated by the ability of oxygen to diffuse directly from arteries to veins in the cortex; referred to here as arterial-to-venous (AV) oxygen shunting. Furthermore, changes in the delivery of oxygen in renal arterial blood, and in the consumption of oxygen by kidney tissue, affect the PO2 gradients driving AV oxygen shunting. To understand how AV oxygen shunting influences kidney oxygenation, we constructed a computational model of oxygen transport in the renal cortex. Methods: The model is based on a quantitative analysis of the three dimensional morphology of the rat renal circulation (1). It consists of a multiscale hierarchy of eleven counter-current vascular modules, representing the various branch levels of the cortical vasculature. At each level equations describing the reactive-advection-diffusion of oxygen are solved. Factors critical in renal oxygen transport incorporated into the model include: the parallel geometry of arteries and veins and their size, variation in blood velocity in each vessel, oxygen consumption and transport, and non-linear binding of oxygen to hemoglobin. Because quantitative information regarding the barriers to AV oxygen diffusion in the kidney is not available, the model was calibrated against published measurements of outer cortical microvascular PO2 and renal venous PO2 (2). As the outer cortex is the most well oxygenated part of the kidney, this approach provides a conservative estimate of the magnitude of AV oxygen shunting. Results: The model predicts that AV oxygen shunting is quantitatively similar to total renal oxygen consumption under basal physiological conditions. It is predicted that oxygen shunting increases as renal oxygen consumption increases or arterial PO2 increases, or when renal blood flow or hematocrit are reduced. Assuming the barriers for AV oxygen diffusion are quantitatively similar throughout the cortical circulation, the model predicts that AV oxygen shunting occurs mostly in distal vascular elements. Regardless, in severe ischemia or anemia, or when kidney oxygen consumption increases, AV oxygen shunting in proximal vascular elements may reduce the oxygen content of blood destined for the medullary circulation. Conclusions: Cortical AV oxygen shunting limits oxygen delivery to cortical tissue and stabilizes tissue PO2 when arterial PO2 changes, but renders both the cortex and medulla susceptible to hypoxia when oxygen delivery falls or consumption increases. The model also predicts how much kidney oxygen consumption must change, in the face of altered renal blood flow, to maintain cortical tissue PO2 at a stable level.

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Crowd Dynamics: Modeling, Analysis and Simulation (Part 1); Wednesday, June 29, 11:00

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Modeling the dynamics of a multi-component crowd via a two-scale approach, working in a setting of measure-theory, mixture-theory and thermodynamics

We present a strategy to describe the dynamics of crowds in heterogeneous domains. In this framework, the behavior of the crowd is considered from a two-fold perspective: both macroscopically and microscopically. This means that we are enabled to examine the large scale behavior of the crowd (where the crowd is essentially considered as a continuum), and simultaneously we are able to capture phenomena happening at the individual pedestrian's level. On both scales we specify mass measures and their transport, and we unify the micro and macro approaches in a single model. Thus we benefit from the advantages of working with a continuum description, while we can also tract (i.e. zoom in to) microscopic features. In this model we couple the measure-theoretical framework described above to the ideas of mixture theory in continuum mechanics (formulated in terms of measures). This allows us to define several constituents (read: sub-populations) of the large crowd, each having its own partial velocity field. We thus have the possibility to examine the interactive behavior between sub-groups that have distinct characteristics. We especially aim at giving special properties to those pedestrians that are represented by the microscopic (discrete) part in the model. In real life situations they would play the role of firemen, tourist guides, leaders, terrorists, predators (considering animals instead of people) etc. Since typically there is only a relatively small number of such people in a crowd, they are most naturally modeled as individuals on the micro-scale. However, we are not interested in the exact behavior of pedestrians in the rest of the (large) crowd, thus it suffices to simplify here, and model them as a continuum. By identifying a suitable concept of entropy for the system, we derive an entropy inequality. From this inequality restrictions on the proposed velocity fields follow. Obeying these restrictions in the modeling phase, we make our assumptions more feasible. Joint work with Adrian Muntean.

Ecosystems Dynamics; Tuesday, June 28, 11:00

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Modelling the mesopelagic ecosystem: how far details are important ?

The role played by carbon in the global change led researchers to focus on its cycle within the biosphere. Since 70% of the earth surface is covered by the ocean, understanding the remineralization processes occuring among oceanic realms is crucial. However our knowledge of the mesopelagic layer is still poor and if logistical issues can partially explain this lack, our limited capacity in modelling marine ecosystems are responsible as well. Thus we need to improve our way to model marine ecosystems and more precisely, how they behave. An analysis of the role played by details in ecological modelling is essential, and if some works have been done on simple model (Fussmann and Blazius, 2005; Poggiale et al., 2010), it appears interesting to study more complex systems, such as a mesopelagic model. A few models already exist (Anderson and Tang, 2010; Jackson et al.,2001; Stemmann et al., 2004) but none of them have used the DEB theory in their construction hypotheses, which leads in a complexification of the model at the physiological scale.

Since we aim to understand the role played by details in modelling the mesopelagic layer, we here work on both different level of physiological complexicity and trophic web organization. Thus, we have built 3 mesopelagic model of different trophic web complexicity, all using DEB theory and compare it to non-mecanistic approaches. Our results shows the details required in modelling the mesopelagic ecosystem and enhance our knowledge of trophic web modelling.

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Bridging Time Scales in Biological Sciences; Saturday, July 2, 14:30

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Efficient Simulation in Protein Modelling and Non-equilibrium Processes

The behavior of a molecule is described by the Boltzmann distribution in conformation space. In classical molecular dynamics a trajectory describes the time dependent dynamics of a protein. Thereby the time step is confined to the fastest oscillation of the covalent bonds and thus shortens the absolute simulation time. Contrary, events which are relevant for protein design, such as protein folding occur only after comparably long time. Thus we have a time gap, between the fastest simulation which determine the maximum possible simulation time and the rare events which have a great impact on the configuration of the protein. Additionally with increasing size of the molecule the dimension of the corresponding conformation space and thus the computational complexity growths.
Consequently one seeks for methods which extract the relevant information out of the simulation data with less computational complexity. This is the basic concept of the coarse graining techniques. These methods take advantage of the fact, that the rare events can be "detected" by mathematical methods. In the last few decades various coarse graining techniques have been developed in order to bridge this time gap in biological processes. Here, we focus on conformation dynamics, where in contrast to classical MD one is interested in the identification of metastable states and transition probabilities. Moreover meshfree methods are introduced for a suitable discretization of the conformation space in high dimensions.
On this basis, we focus on the force simulation of non equilibrium processes which play an important role in protein miss folding diseases such as Alzheimer's disease. Furthermore, we motivate how results from computer simulation and experimental data from laboratory can be combined in a meaningful way.

Modeling of immune responses and calcium signaling II; Wednesday, June 29, 14:30

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Rule-Based Modeling of Molecular and Cellular Processes

Cells possess complex sensory mechanisms that are governed by the biochemical interactions of proteins. A typical signaling protein possesses multiple interaction sites, whose activity can be modified both by direct chemical modification (termed "post-translational modification") and by the effects of modification or interaction at other sites (termed "allostery"). This complexity at the protein level leads to combinatorial complexity at the level of signaling networks - an individual protein has many potential states of modification and interaction, which gives rise to an ever-multiplying set of possible complexes and poses a major barrier to traditional methods of modeling and simulation [1]. Here, I will review major developments in modeling, both from my work and that of others, that have helped to tame these difficulties.

The need to simplify the development of signal transduction models and to expand their scope has motivated the development of rule-based modeling languages, such as BioNetGen [2] and Kappa [3], which provide a rich and yet concise description of signaling proteins and their interactions. Their success is demonstrated by the growing community of users and the substantial number of models that have been developed and published. While greatly facilitating the translation of knowledge about signaling biochemistry into models, however, rule-based languages do not directly address the combinatorial challenges involved in the simulation of such models, which arise from the size of the reaction network implied by the rules. For these, new agent-based stochastic simulation methods have been developed for rule-based models with computational requirements that are independent of the number of possible species (i.e., complexes) and proportional to the number of molecules (e.g., proteins) being simulated. In addition, general and efficient implementations are now available that enable the rapid simulation of rule-based models of virtually any complexity. NFsim is one such simulator that stands out because of its efficiency and the ability to course-grain complex interactions through the incorporation of high-level functions into the rate laws that govern rule application [4]. The use of stochastic simulations, however, exacerbates the already difficult problems common to all complex models of relating model parameters to model behavior and of estimating parameter values based on experimental observations and data. For these, new statistical model checking algorithms and tools have been developed that allow model properties to be determined from a minimal number of simulation runs [5]. Taken together, rule-based modeling languages and their associated tools address the issue of combinatorial complexity in cell regulatory networks, allowing the development, simulation, and analysis of models with unprecedented scope and detail and, we hope, predictive capability.

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Noisy Cells; Saturday, July 2, 14:30

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Random but reliable: Properties of spike sequences of IP3-induced Ca2+ signaling

Ca2+ is a universal second messenger in eucaryotic cells transmitting information through sequences of concentration spikes. A prominent mechanism to generate these spikes involves Ca2+ release from the endoplasmic reticulum (ER) Ca2+ store via IP3-sensitive channels. Puffs are elemental events of IP3-induced Ca2+ release through single clusters of channels. Intracellular Ca2+ dynamics are a stochastic system, but a complete stochastic theory has not been developed yet. As a new concept, we formulate the theory in terms of interpuff interval and puff duration distributions, since unlike the properties of individual channels, they can be measured in vivo. Our theory reproduces the typical spectrum of Ca2+ signals like puffs, spiking and bursting in analytically treatable test cases as well as in more realistic simulations. We find conditions for spiking and calculate interspike interval (ISI) distributions. Signal form, average ISI and ISI distributions depend sensitively on the details of cluster properties and their spatial arrangement. In difference to that, the relation between the average and the standard deviation of ISIs does not depend on cluster properties and cluster arrangement, and is robust with respect to cell variability. It is controlled by the global feedback processes in the Ca2+ signaling pathway (e.g. via IP3-3-kinase or ER depletion). That relation is essential for pathway function, since it ensures frequency encoding despite the randomness of ISIs and determines the maximal spike train information content. Hence, we find a division of tasks between global feedbacks and local cluster properties which guarantees robustness of function while maintaining sensitivity of control of the average ISI.

Modeling of immune responses and calcium signaling IV; Saturday, July 2, 08:30

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How does single channel behavior cause cellular Ca2+ spiking?

The behavior of signaling pathways is determined by the molecular properties of their components, feedbacks and self-organization among the participating molecules. But usually systems are too complex to understand in detail how cellular behavior relates to molecular behavior. Intracellular Ca2+ signaling offers an opportunity to understand that relation in detail, since it is comprised from relatively few different types of molecules. A well-studied system involves Ca2+ liberation through inositol trisphosphate receptor (IP3R) channels wherein the cellular dynamics emerge through a hierarchy of events. Opening of single Ca2+ channels can induce local Ca2+ release events evoked by channel clusters (called puffs), the combined action of which results in repetitive global cellular Ca2+ spikes. Although cellular behavior and single channel properties have been characterized in detail before, this study investigates statistical properties of the cluster dynamics by analyzing high-resolution data from TIRF microscopy in two mammalian cell lines. We find that interpuff intervals (IPIs) are significantly shorter than cellular interspike intervals (ISIs), that puff-activity is stochastic with a recovery time much shorter than the cellular refractory period, and that IPIs show no sign of periodicity. These results strongly suggest that Ca2+ spikes do not arise from oscillatory cluster dynamics, but that cellular repetitive spiking and its typical time scales arise from collective dynamics of the whole cluster array.

Population Dynamics; Tuesday, June 28, 11:00

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Asymptotic almost periodicity of competitive-cooperative systems with almost periodic time dependence

In this report, we are interested in the asymptotic almost periodicity for a positively bounded motion $\pi_t(x, g)$ by investigating its ω-limit set. We proved if $\omega(x, g)$ is hyperbolic, that is, the linearized equation about the flow on $\omega(x, g)$ has an Exponential Dichotomy on $\omega(x, g)$. Then $\omega(x, g)$ is 1-cover of $H(f)$, that is, $\pi_t(x, g)$ is asymptotically almost periodic.

Semigroups of Operators in Mathematical Biology II; Saturday, July 2, 11:00

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Wentzell semigroups in biology

In this talk we are going to introduce linear and nonlinear physiologically structured population models with diffusion in the size-space. We equip our model with Wentzell boundary conditions which can be recast as dynamic conditions on the boundary. We apply our model for a population in which individuals are structured with respect to a pathogen load which represents the continuous structuring variable. Then the compartment of uninfected individuals carries mass. For a much earlier attempt see: Waldstaetter et al. in SIAM JMA (1988). We will discuss existence and positivity of solutions and qualitative questions: such as existence of steady states and asymptotic behaviour of solutions. We will be working in the framework of the theory of strongly continuous semigroups and utilising some earlier results, see e.g. Favini et al. in J. Evol. Eq. (2002).

Analysis of mathematical models for cancer growth and treatment, Part IV; Wednesday, June 29, 08:30

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Evolution of tumor spheroids: adopting a Bingham scheme for the cell component

Avascular multicellular spheroids are the simplest form of tumours that can be studied experimentally under controlled conditions. They can be grown in suspensions (thus being subject to atmospheric pressure) or in a gel which offers some mechanical resistance to their expansion. They are made of proliferating cells, quiescent cell and of dead cells progressively degrading to liquid. The whole cell population is embedded in an extracellular fluid, which provides the mass required for cell replication.

During the last years it has become evident that, despite the advantage offered by the simple geometry, the problem of describing the growth (or even the steady state) of a multicellular spheroid is generally very complicated and requires the choice of constitutive equations for the mechanical behaviour of the system. A peculiar difficulty is originated by its composite nature. Various papers have been devoted to the problem of spheroids evolution, assigning an important role to the deformability of the system of mutually interacting cells by introducing interaction potentials (depending on the cell volume fraction) and constitutive laws that may include yield stress and elasticity (see [1]).

Here we want to present an evolution model in which the main assumptions are:

(i)the cell volume fraction in the viable region is constant,

(ii)the rheological properties of the set of cells in the viable zone are the ones of a Bingham fluid,

(iii)the only species considered in the cells metabolism is oxygen and the influence of metabolites is neglected.

Thus our model is in the context of the two-fluid approach. The inspiring criterion was to incorporate some physically relevant feature (as it can be the presence of intercellular links providing a stress threshold for flow), but introducing the minimum possible number of constitutive quantities. Formulating a Bingham-like scheme proved to be not so simple, since some classical models are not compatible with velocity fields that have necessarily to occur in the case of a growing spheroid. Thus this aspect of the analysis is particularly delicate. The spheroid evolution is followed from the initial fully proliferating phase, to the stage which includes a necrotic liquid core, possibly reaching an asymptotic equilibrium (the existence of

steady states has been studied in the same framework in the paper [2]). Despite the many simplifications (to which we add some less important assumptions, like the existence of interfaces separating the various classes of cells), the problem turns out to be considerably complicated. An existence theorem and numerical simulations will be presented.

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Modeling and analysis of tumor invasion II; Tuesday, June 28, 14:30

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Migration-Proliferation Dichotomy in Tumor Cell

Proliferation and migration dichotomy of the tumor cell invasion is examined within a two-state continuous time random walk (CTRW) model. The overall spreading rate of cancer cells is obtained by using a Hamilton-Jacobi formalism. Random switching between cell proliferation and migration is taken into account, and its influence on the front propagation rate is studied.

Cellular Systems Biology; Thursday, June 30, 11:30

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Enzyme sharing as a cause of multistationarity in signaling systems

Bistability, and more generally multistability, in biological systems is seen as a mechanism of cellular decision making. Compared to systems with a single steady state, the presence of multiple stable steady states provide a possible switch between different responses and increased robustness with respect to environmental noise. To understand cellular signaling, it is therefore of fundamental importance to know i) which systems can exhibit multistationarity and ii) what are the biological conditions enabling it.

Here, we consider biological systems where a signal is transmitted by phosphorylation. Kinases catalyze phosphorylation of (protein) substrates, and phosphatases catalyse dephosphorylation of the same substrates. Biological systems are known in which several different kinases phosphorylate a single substrate and others where a single kinase phosphorylate several different substrates. Furthermore, phosphorylation in more than one site can be carried out by a unique kinase or, as in the case of priming kinases, different ones. The same phenomena are observed concerning phosphatases and dephosphorylation.

The interplay between kinases, phosphatases and their substrates increases the complexity of signaling pathways. In this presentation we determine the emergence of multistationarity in small motifs that repeatedly occur in signaling pathways. Our simple modules are built on a one-site modification cycle and contain one or two cycles combined in all possible ways with the above features regarding the number of modification sites, and competition and non-specificity of enzymes, incorporated.

We conclude that

a) Multistationarity arises whenever a single enzyme is responsible for catalyzing the modification of two different but linked substrates.
b) The presence of multiple steady states requires substrate saturation and two opposing dynamics acting on the same substrate.
c) Multistationarity in some of the systems occurs independently of the reaction rates.

The mathematical modeling is based on mass-action kinetics. This implies that steady states are solutions to a system of polynomial equations in the chemical concentrations and enables the use of algebraic arguments as previously proven successful, e.g. [**1**], [**3**]. In particular, the conclusions are derived in full generality without restoring to simulations or random generation of parameters. See [**2**].

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Mathematical modeling of biomechanical regulation in bone tissue (Session II); Wednesday, June 29, 11:00

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A multiscale bone remodelling framework using the Physiome Project markup languages

Numerous computational bone models have explored remodelling and bone response at either the cell level, micro level or macro level (whole bone). However, there have been limited attempts to link information across these spatial scales [1]. Treatments such as milk-derived Lactoferrin therapy [2], have been shown to increase mineralised bone by modifiying the number of active bone absorbing cells (osteoclasts) and bone forming cells (osteoblasts). This, in turn, changes the micro bone architecture and the overall continuum strength observed at the whole bone level. A multiscale computational framework that passes information across the spatial scales will allow us to evaluate treatments and study disease progression. The focus of this study is to (i) outline the spatial linkages from the cell to the whole bone using the framework and markup languages developed for the Physiome Project [3]; and (ii) demonstrate this framework by looking at an anabolic treatment, Lactoferrin, and how it modifies osteoblast/osteoclast numbers, influences the strain pattern at the micro bone level and changes whole bone strength.

The multiscale modelling framework developed as part of the IUPS Physiome Project [4] was used to link the spatial scales. At the cell level the bone remodelling process describing the RANK-RANKL-OPG pathway [5] was implemented in the CellML markup language [6]. This describes the amount of osteoblasts (bone

forming) and osteoclasts (bone resorbing) cells in response to a healthy, diseased or treatment state. At the micro level a particulate method, 'Smooth Particle Hydrodynamics' (SPH) was used to model the micro strain of a bone cube (1mm x 1mm x 1mm) [7]. SPH has the ability to handle highly fragmenting solid structures, bone addition and removal. At the micro level a bone remodelling algorithm based on strain excitation adapted from the work of Prendergast [8] was used to add or remove bone in order to maintain bone density. At this level the osteon cortical pore structure was visible and the bone growth and resorption patterns based on the number of osteoclasts/osteoblasts lead to a changing architecture and overall bone strength. The macro model (whole bone) was a Femur geometry from the AnatML database, with material properties described using FieldML. A spatially varying density and Young's modulus was fitted from CT images using the CT number and a grey-scale mapping. The macro level models are physiologically loaded from muscle forces and ground reaction force data taken from gait experiments [9]. The whole bone model provides the boundary conditions for the micro models. The proposed computational framework has the potential to improve understanding of how cellular level changes influence whole bone strength.

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Epidemics; Thursday, June 30, 11:30

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Time-dependent discret, Ising-like model for SIS epidemic systems

Standard SIS (Susceptible-Infected-Susceptible), SIR and other similar epidemic systems are commonly modeled as mean field dynamic systems or simulated as different kinds of cellular automata. We model a SIS system as an asymmetric Ising model. In its simplest version, each individual is considered fixed to the nodes of a square lattice of linear size L and they interact with their nearest neighbors only. Then each individual is represented by a vector which may assume the values 1 (susceptible) or -1 (infected) and the probabilities of a susceptible to become infected and an infected to recover depend respectively on the number of infected neighbors and a constant field H. Here we show that the SIS model is consistent with time dependent probabilities in a Glauber fashion, derive the classic mean-field equations and through extensive Monte Carlo simulations, we show how spatial heterogeneities arise naturally from the model.

Epidemics of Neglected Tropical Diseases; Wednesday, June 29, 11:00

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Modelling the dynamics of dengue real epidemics

The infectious diseases are still a relevant problem for human life. Nowadays, due to the intense flow of people around the world and within the cities, the understanding of their complex dynamics is a multidisciplinary issue. Concerning dengue, a vector transmitted disease, there is no vaccine against any of the four serotypes of the virus, although many efforts have been done in that direction. As a result, dengue transmission control is based on the control of the aquatic and adult mosquito forms. So far, the modelling of the dynamics of dengue may be very helpful for testing both the adopted vector control strategies and the action of future vaccines.

In South and North America, there are records of occurrence of all serotypes of dengue virus, while in Brazil, until now, only 3 serotypes (DENV1, DENV2 and DENV3) have been reported. However, Brazil is responsible for 80% of dengue cases in South America and 60% of notified cases around the world. The circulation of the three serotypes represent an important risk factor for the occurrence of dengue hemorrhagic fever (DHF). Although all the efforts applied by the Brazilian dengue control program to stop dengue transmission, it is still a relevant problem in the first decade of this century. Two factors had been associated to the failure of dengue control: the vector's adaptive capacity and the occurrence of new virus strains.

In this work we use a mathematical model for dengue transmission with the aim to analyze and compare two dengue epidemics that occurred at Salvador, Brazil in 1995-1996 and 2002. Using real data, we obtain the force of infection, Λ, and the basic reproductive number,R_0 for both epidemics. We also obtain the time evolution of the effective reproduction number, $R(t)$, which result to be a very asuitable measure to comparing the patterns of both epidemics. Based on the estimations of R_0 and $R(t)$ we show that control applied only on the adult stage of the mosquito population is not sufficient to stop dengue transmission, emphasizing the importance of the control applied on the aquatic mosquito phase.

Population Dynamics; Tuesday, June 28, 14:30

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Dengue Epidemics : *Urbi et Orbi*

Dengue is a viral disease which plagues most of the tropical regions of the world, mainly those with high humidity and dense population. Although the disease is not permanent (since it is through in about 3 weeks) and in most cases not fatal, nevertheless it has an enormous impact in the public health system and in the economic activity of the affected regions. The viral infection is only transmitted by infected mosquito *Aedes egypti* which only get the virus by biting infected humans. So, the dynamics of the dengue epidemics depends strongly on the human movement (the infected individuals) and on the existence of a large population of mosquitoes vectors. The coupling of both populations plus the movement of the human population is the basis for the the mathematical model that we present, where the vector population evolves locally (in urban areas) while the infected humans are responsible for the large distance phenomena (orbi). We have tested the model in the State of Sao Paulo-Brazil by devising a network consisting of its largest 60 cities linked by the highway traffic between them as a measure of their inter connections. At each city we have used a simple and homogeneous model of vector-epidemic dynamics. The simulation were made by starting a focus of infection in a far west city of the state (which is commonly observed) and the geographical and time evolution of the results are quite close to the data obtained from the State Health Department in the last decade. The main goal of this work is to have a reliable software to predict the evolution of an epidemic burst , detect its main spreading nodes so that the responsible public system can act sparsely (which is the only way it can afford to do) but quickly in order to block the further propagation of the infection.

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Unravelling laws of genome evolution with both mathematical and individual-based models

In order to investigate laws of evolution of genome organization over large evolutionary time scales, our lab has developed an individual-based model simulating Darwinian selection and most of mutations and rearrangements undergone by a chromosome during asexual reproduction. In particular, the length of the chromosome and the number and lengths of genes are free to vary. It was shown that evolutionary success depends not only on the fitness but also on an appropriate trade-off between genome robustness and variability. This indirect selective pressure regulates the amount of coding DNA, but also, more surprisingly, the amount of non-coding DNA, if large rearrangements are taken into account. The higher the spontaneous rate of duplications and deletions, the more compact the genome in the surviving lineages [1].

This phenomenon is reminiscent of the error-threshold effect described by Eigen in the quasispecies theory [2, 3], where the per-digit mutation rate q sets a maximum number of digits ν that can be reproducibly preserved: $\nu < -\frac{\ln(\sigma_0)}{\ln(q)}$, where σ_0 is a parameter quantifying the fitness superiority of the fittest sequence. If the mutation rate is increased beyond this limit, then the population structure breaks down, and the population disperses over sequence space. However, this effect was mostly studied in the special case where all sequences have an equal length and only point mutations can occur. In these conditions, the maximum chain length ν_{max} applies only to the segments that contribute to fitness [3], and thus cannot directly explain our results regarding the amount of non-coding DNA.

The computational model cannot be considered as an analytic proof of the observed relation. Here, we combine the intuition and power of this model with a mathematical analysis. By relaxing Eigen's hypotheses, we developed simpler dynamical models that exhibit essentially the same behavior as the original computational model as far as genome length and coding/non-coding ratio is concerned. These models yield a better insight on the impact of essential parameters and

provide valuable feedback for computational simulations. In return, these computational improvements lead to new relations and limits that can be investigated mathematically, closing the emulation loop.

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Analysis of mathematical models for cancer growth and treatment, Part II; Tuesday, June 28, 14:30

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Optimal control scenarios in cancer treatment strategies

Models depicting cancer dynamics are investigated with the inclusion of optimal control strategies to minimize the cancer cells, toxicity of the drugs, and the cost associated with the regimen. The ordinary differential equation models coupled with state constraints will be studied and some numerical results will be discussed.

Regulatory Networks; Saturday, July 2, 11:00

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Modeling and Estimation of Gene Regulatory Networks and Environmental Stress Response

This talk investigates the dynamics of gene regulatory networks governing cold shack response in budding yeast, Saccharomyces cerevisiae, through the use of a differential equation model. The inverse problem of determining model parameters from observed data is our primary interest. We fit the differential equation model to microarray data from a cold shock experiment using a Bayesian maximum likelihood approach, and we discuss future efforts involving gene deletion experiments and related modeling problems.

The emergence of resistance in cancer using mathematical modelling;
Saturday, July 2, 08:30

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Cancer drug treatment is unnatural selection

Targeted drug treatment reduces the tumour volume, but there is almost always recurrence even under chronic treatment. We show that the tumour population is heterogenous. Then the drug treatment is a selection process, targeting specific subpopulations. If treatment is stopped, phenotypic drift causes reversion towards the original wild-type population.

Our model is a discrete population of cells, the individual equivalent of an ODE. The cells each have a distinct phenotype. This phenotype determines their fitness. The fitness changes under drug conditions: we define a fitness landscape for both drug and drug-free conditions.

Experimentation shows evidence of only partial reversion to wild-type. We extend the complexity of the fitness landscape to multiple fitness "wells". Reversion after drug treatment only fills one of the wells. The overall behaviour matches experimental observations.

Our model concept extends to considering alternative treatments. Temporal variation appears unhelpful but well-chosen combination therapies could be effective. This approach gives a quantitative predicrtion of treatment strategies.

Multiscale modelling of biological systems: the Chaste framework;
Tuesday, June 28, 11:00

Dr Alexander Fletcher
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Modelling biological systems in Chaste: an overview

Computational models of a variety of biological processes have been implemented within the Chaste framework (http://web.comlab.ox.ac.uk/chaste). In this, the second talk of the mini-symposium, we provide an overview of this work, focusing in particular on models of the intestinal crypt. We discuss how multiscale modelling may be used to gain insight into processes such as crypt homeostasis, monoclonal conversion and the effect of dysregulated proliferation and adhesion on crypt dynamics. We also demonstrate how the generality of the Chaste framework allows a quantitative comparison to be made of different cell-based modelling frameworks. We conclude with a discussion of other biological systems that are being modelled within Chaste.

The emergence of resistance in cancer using mathematical modelling;
Saturday, July 2, 08:30

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Modeling diversity in drug-resistant populations using multitype branching processes

I will discuss a continuous-time birth-death process model of tumorigenesis where resistance mutations confer random additive fitness (birth rate) changes sampled from a mutational fitness distribution. We investigate the overall growth rate and diversity of the resistant population in the asymptotic limit, and the dependence of these features on parameters of the fitness landscape. We study the generation of resistance from both exponentially increasing sensitive cell populations (pre-treatment) and exponentially declining populations (during treatment). Using experimental data, we apply this model to study characteristics of a drug-resistant subpopulation at the time of diagnosis of chronic myeloid leukemia, and discuss implications for treatment strategies. (Joint work w/R. Durrett, K. Leder, J. Mayberry. F. Michor)

Recent advances in infectious disease modelling I; Saturday, July 2, 11:00

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Reducing HIV Reservoirs by Induced Activation of Latently Infected Cells

Treatment of patients infected with HIV is effective at lowering the serum viral concentration to below the limits of detection, but the virus persists in reservoirs of latently infected cells, such as resting memory T cells. Because the latent pool may serve as a source for reemergence of the virus after the cessation of treatment, speeding its decay is a necessary step toward eradication of HIV from the patient. One strategy for reducing the latent pool is to artificially activate memory T cells.

We present a model of viral infection including anti-retroviral therapy and activation of latently infected cells. We explore the relative roles of homeostatic proliferation and transient viremic events in maintaining the latent pool. Using this model, we evaluate the potential use of artificial activation to enhance HIV treatment.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents II; Wednesday, June 29, 08:30

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Modeling Early Events in Hepatitis Delta Virus Infection

Delta hepatitis virus (HDV) is a dependent satellite virus of hepatitis B virus. HDV relies on surface proteins produced by HBV to create new virus particles, but also has an inhibitory effect of HBV replication and the two species compete for common resources inside the cell. Understanding this dependence and competition could provide targets for antiviral therapies to eliminate or prevent chronic HDV superinfection.

By exploring the early events in HDV replication, we explain the dynamics of viral release from newly infected hepatocytes, including a delay in the initiation of viral release and a precipitous decline in production after 12 days. We further explore the consequences of these dynamics for the establishment of chronic hepatitis delta in the cases of coinfection and superinfection.

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The surprising complexity of signal processing in clock neurons

Neurons within the suprachiasmatic nucleus (SCN) of the hypothalamus act as the central daily pacemakers in mammals. Within these neurons, a molecular circadian clock is closely coupled to the neurons electrical activity to process timekeeping signals from the external world, and to determine the signals the neurons will send to the rest of the body. This is one of many emerging examples of how neuronal firing influences, and is influenced by, intracellular biochemical systems.

For as long as these neurons had been studied, they had been assumed to encode the time of day indicated by their internal molecular clock by the rate at which they fire action potentials. Here, I will present analysis of mathematical models that suggests much more complex coding, largely based on a balance between calcium and sodium dynamics. Bifurcation analysis of a mathematical model we have developed of neurons which control daily timekeeping in mammals suggested a variety of electrical states, including depolarized low amplitude membrane oscillations and depolarization block. These states were confirmed experimentally by colleagues. Further simulations suggest that rest membrane potential may be more important than spike rate for signaling in clock neurons. This suggests a new modeling paradigm when considering signaling from membrane to DNA and back.

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Automatic Classification of Vulture Behavior using Machine Learning Algorithms Applied to Accelerometer Data

Accelerometer data has been shown to be an effective tool for identifying certain animal behaviors. In this talk, I present the use of tri-axial accelerometer data as a predictor of seven ground-truthed Griffon vulture (Gyps fulvus) behaviors: active flight, eating, laying down, passive flight, preening, running, and standing. Five different machine learning algorithms were trained and validated on subsets of over nine-hundred observations, each 16 to 25 seconds in length. Prior to classification, summary statistics for the accelerometer data were calculated and used as inputs into the machine learning algorithms. The algorithms tested were Linear Discriminate Analysis, Classification and Regression Trees, Random Forests, Artificial Neural Networks, and Support Vector Machines. Of these methods, the Random Forest predictors were found to be the most accurate while Linear Discriminate Analysis predictors were the least accurate. Classification accuracies for all predictors were in the 80% to 90% range. Using results of the machine learning algorithms we determined the importance of the different summary statistics for the classification effort. Generally, measures of variance were found to be more important than measures of central tendency or correlation.

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Efficient reannotation system for verifying genomic targets of DNA microarray probes

Systems for data cleaning for supporting analysis of results of DNA microarray experiments are becoming important elements of bioinformatics aspects of gene expression analysis [1]. It has been demonstrated that data cleaning at the level of microarray probes, based on most recent knowledge on genomic data, can substantially improve results of predictions of molecular classifiers. However, due to the difficulty of the whole genome browsing projects, available services and data for reannotation of microarray probes are still quite sparse. In our research we have created an efficient reannotation tool by combining the well known gene search tool BLAT [2] with appropriately designed database and tools for operations on it.

We show properties of our tool by using two Affymetrix chips HG U133A and HG 1.0 ST. In the Affymetrix microarrays, the gene intensity is calculated on the basis of gene probes consisting of 25-mer oligo-nucleotides. For many reasons, in many cases, the calculated value does not match the real expression. These reasons include single nucleotide polymorphism, adjusting the probe to another gene or intron. Our task was to check how many probes can truly determine gene expression. We have developed a database which contains information about how the probes are aligned to the latest human genome. Using those matches to the genome, for each probe we found mRNA and EST sequences. In our presentation we compare reannotation results for analyzed Affymetrix chips, based on two different built of Human Genome, HG18 and HG19. Improving the quality of data can be further verified by comparing the misclassification rates for classification of microarray data obtained using the official affymetrix CDF files and CDF file created by us. The information obtained from reannotations can help to update the CDF files, and can significantly improve the quality of classification.

Acknowledgements. This work was supported by the European Community from the European Social Fund.

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Connecting microscale and macroscale models of cellular migration;
Tuesday, June 28, 17:00

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Discrete and continuum modelling of growth and signalling in biological tissue

In the recent work [1], we examined methods for deriving continuum approximations of one-dimensional individual-based models (IBM) for systems of tightly adherent cells, such as an epithelial monolayer. Each cell occupies a bounded region, defined by the location of its endpoints, has both elastic and viscous mechanical properties and is subject to drag generated by adhesion to the substrate. The evolution of the discrete system is governed by a system of differential-algebraic equations. This IBM is then approximated by a system of partial differential equations in the limit of a large number of cells. We consider two different techniques: the usual continuum approximation which is appropriate when cellular properties vary slowly between neighbouring cells, and a multiple-scales approach which is appropriate when cellular properties are spatially periodic (so may be heterogeneous, with substantial variation between adjacent cells). In the latter case, the relationship between mean cell pressure and mean cell lengths in the continuum model is found to be history-dependent when cell viscosity is significant. We apply this model to examine the acceleration of a wound edge observed in wound-healing assays.

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Population Dynamics; Wednesday, June 29, 17:00

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Hybrid modelling of cell migration: coupling individual-based models with partial differential equations

Two approaches to mathematical modelling of cell migration are often used in the literature: (i) individual-based (agent-based) models, which describe the behaviour of each cell, and (ii) macroscopic partial differential equations (PDEs), which are written for cell concentrations. A widely studied example of cell migration is chemotaxis, where cells move according to extracellular chemicals that can be altered by the cells themselves. In this case, systems of coupled PDEs are used to model the concentrations of cells and external chemicals. A more detailed description is given by hybrid models that couple an individual-based model of cells with PDEs for extracellular chemicals. In this talk, we will give an overview of hybrid models used in the literature. Examples will include chemotaxis of bacteria and eukaryotic cells. We will analyse similarities and differences between hybrid models and macroscopic PDEs.

Bridging the Divide: Cancer Models in Clinical Practice; Thursday, June 30, 11:30

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Therapeutic approaches to brain cancer

The standard treatment of newly diagnosed glioblastoma, the most aggressive brain cancer, is surgical resection followed by radiation and chemotherapy. This treatment, however, has failed to signi

cantly extend the patient's life expectancy which is typically one year. By the time the disease is diagnosed, tumor cells have already migrated to other parts of the brain. Based on clinical data, we shall evaluate dierent combination protocols of resection, radiation and chemotherapy that may increase a patient's survival time. We shall also consider viral therapy, currently at the preclinical stage, and the eect of drugs that slow down glioma cell migration. The mathematical models used in our analysis are based, primarily, on systems of partial dierential equations.

Analysis of mathematical models for cancer growth and treatment, Part I;
Tuesday, June 28, 11:00

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The development of fingers in solid tumors

We consider a solid tumor in a region which is modeled either as a porous medium (by Darcy's law) or as fluid-like tissue (by Stokes equation). We assume that the proliferating and dying cells move around with velocity v in a way that keeps their density constant in the tumor region $D(t)$. The nutrient concentration and the velocity v satisfy a system of PDEs in $D(t)$. The aggressivity of the tumor is represented by a parameter μ which relates nutrient concentration to proliferating rate of cells. It is shown that there is a stationary spherically symmetric solution of radius R which depends on some of the model parameters but not of μ. We prove that this solution is asymptotically stable for $\mu > \mu_*$ and there exist infinite number of branches of stationary solutions with arbitrarily large number of fingers, indicating the onset of metastasis. We also prove that the fluid-like tumor develops more fingers than the tumor with porous medium consistency.

Cell and Tissue Biophysics; Thursday, June 30, 11:30

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On a parabolic model for particle alignment

In [1] we proposed a model for the initiation on cell polarization at the first steps of cellular motion. Now, numerical simulations indicate the emergence of shocks in the solution to these equations which may be interpreted as fronts of active barbed ends of actin filaments being established in the cell.

The original model included the description of actin monomers and filaments without taking into account the mutual alignment of the latter. In order to understand the effect of aligning filaments we deduced from the given model a simple parabolic system describing the motion of oriented particles with fixed velocity, undergoing diffusion and mutual alignment. This system, consisting of no more than two equations, may be used to model different kinds of aligning particles, e.g. myxobacteria.

For this model we analyze the stability of the totally symmetric state which corresponds to a non polarized cell against small perturbations. Here, the influence of different types of alignment terms will be discussed. We furthermore derive traveling wave solutions to the system and show how they emerge numerically from small initial data. We will thus observe polarization fronts developing from an initially almost symmetric state.

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Information, human behaviour and infection control; Saturday, July 2, 08:30

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Modelling the Influence of Human Behaviour on the Spread of Infectious Diseases

People can protect themselves against being infected by a disease by changing their behaviour in response to an outbreak, for example, through wearing face masks or reducing their number of infectious contacts. This type of behavioural change can affect the epidemiology of the disease itself. Here, I will discuss different ways to model the influence of human behaviour on the spread of infectious diseases, as well as challenges therein. As an example, I will present a model in which individuals are influenced by their peers as awareness of the presence of a disease as well as the disease itself spread in the social networks of influence and disease.

Undergraduate Biomathematics Education Beyond BIO 2010 (Part I);
Wednesday, June 29, 14:30

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Agent-based models of interacting populations

Agent-based models, also called individual-based models, are computer-based models that simulate the actions and interactions of autonomous agents that represent the individuals of the population. These models are powerful simulations that can capture the emergent phenomena of a natural system. These types of models have been applied to many different areas of research such as ecology, e.g., white-tailed deer and panther populations in South Florida, and epidemiology, e.g., human disease outbreaks in a realistic urban area. One of the most beneficial aspects of these models is that they are easily understood and explainable to both math and biology students. A framework for teaching how to develop an agent-based model and examples of such models will be presented.

Reports from US - African BioMathematics Initiative: Conservation Biology; Saturday, July 2, 14:30

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Overview: Reports from US - African BioMathematics Initiative: Conservation Biology

How do you combine the expertise of graduate students trained as mathematicians and conservation biologists, from two continents, to explore important questions in African conservation biology? This question was at the heart of the formation of the US-African BioMathematics Initiative: Conservation Biology, a jointly funded enterprise of the Center for Discrete Mathematics and Theoretical Computer Science (DIMACS), the Mathematical Biosciences Institute at Ohio State University (MBI), the Society of Mathematical Biology (SMB), the London Mathematical Society (LMS), and the US National Science Foundation (NSF). Two advanced studies institutes, or ASIs, with guest lecturers, a follow-up workshop and fieldtrips to see, first-hand, the local conservation needs in question, were held in South Africa (2010) and Kenya (2011).

Researchers working in the fields of mathematical modeling and conservation biology provided a series of lectures in population viability analysis, global climate change, harvesting, disease modeling, conservation genetics, remote sensing, reserve design, agent-based modeling and practical concerns in real-world conservation and management. These lectures established a common background among the students, while examining the range of fields pertinent to research into questions in mathematical modeling in conservation biology. These lectures were augmented with computational exercises, in multiple software platforms, giving students hands-on experience and coded examples to build on. Students from the US and ten African countries from the fields of mathematics, ecology, conservation biology, and wildlife and natural resource management came together for an intense week of training, reinforced and implemented in group projects.

Projects were formulated, conceived and chosen by the students, with guidance from the mentors. They included: agent-based modeling of anti-poaching strategies amongst villages with human-elephant conflict, modifying epidemiological models of bovine tuberculosis in African buffalo to understand directed culling efforts in the face of different transmission scenarios, modeling population viability and management of impacts on the flamingoes in Lake Nakuru, spatial modeling of landscape fragmentation and elephant movement corridors in Kenya, to name a few. Projects were initiated at the institutes, and plans for continuing work, through email and other means of communications were formalized and approved by faculty mentors.

This mini-symposium is a product of the initiative that was not part of the original prospectus for funding. The initiative funded a follow-up institute to the originally planned single combined institute and workshop. Faculty who would otherwise not have met each other have been inspired to collaboratively apply for funding to continue teaching these institutes, and to conduct joint research in the

future. A minimum of three publications and 5 talks are resulting from student projects formed at these institutes, so far, and established connections to the South African Wildlife College (SAWC) and Kenya Wildlife Services Training Institute (KWSTI) at Naivasha are spawning new ideas and project bases.

Turing !! Turing?? on morphogenesis via experimental and theoretical approaches; Wednesday, June 29, 17:00

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Aspects of Turing's Pattern Formation Mechanism On Growing Domains

The prospect of long range signalling by diffusible morphogens initiating large scale pattern formation has been contemplated since the initial work of Turing in the 1950s and has been explored theoretically and experimentally in numerous developmental settings. However, Turing′s pattern formation mechanism exhibits sensitivity to the details of the initial conditions suggesting that, in isolation, it cannot robustly generate pattern within noisy biological environments. Aspects of developmental self-organisation, in particular a growing domain, have been suggested as a mechanism for robustly inducing a sequential cascade of self-organisation, thus circumventing the difficulties of sensitivity. This proposition is explored in detail for generalisations of Turing's model which include further biological aspects, for example, the inclusion of gene expression dynamics or intrinsic noise.

Poster Session; Friday, July 1, 20:00

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Evolution of protein targeting via endomembrane system to primary plastids

Before 1.5 billion years ago a heterotrophic eukaryotic ancestor of glaucophytes, red algae, and green plants engulfed cyanobacteria, which then were transformed into primary plastids with two envelope membranes. Gene transfer from the cyanobacterial genome to the host nucleus fostered the integration of the endosymbiont and the host but it is still not clear how protein products of the transferred genes were initially transported back into the ancestral primary plastid. At present, almost all proteins encoded by the host nucleus are imported into primary plastids post-translationally using N-terminal transit peptides and the Toc and Tic translocons. Because these translocons consist of many specialized protein subunits, it is hypothesized that the protein import into the ancestral plastid proceeded by a simpler pathway based on the host endomembrane system involving the endoplasmic reticulum (ER) and/or the Golgi apparatus (GA). In accordance with this hypothesis, five known proteins with N-terminal signal peptides, which are directed to primary plastids in vesicles derived from the endomembrane system, could be considered relics of this primordial import pathway. To test if it is true, we performed phylogenetic analyses as well as applied other bioinformatics tools specialized in the prediction of N-terminal targeting signals. Our analyses show that all nuclear-encoded plastid-targeted proteins with signal peptides are of the eukaryotic (not cyanobacterial) origin and that their homologs are equipped with signal peptides responsible for their co-translational import to the ER. This indicates that only a limited subset of host proteins, normally targeted to different secretory compartments, exploited their signal peptides to reach higher plant primary plastids via the endomembrane system. Thus, currently known plastid proteins with signal peptides cannot be considered a relic of the primordial plastid vesicular trafficking. The protein import into primary plastids was dominated right from the beginning by the gradually evolving Toc-Tic-based pathway while the vesicular trafficking to primary plastids evolved secondarily long after the primary endosymbiosis and probably only in the land plant lineage.

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AR-Sieve Bootstrap Method and Its Application in Biological Time Series

The problem of estimating characteristics of time series is considered. The bootstrap procedure, introduced by Bühlmann (1997), based on the method of autoregressive process sieve is used. AR(p(n)) model is fitted to the observed data and a bootstrap sample is generated by resampling from the centered residuals. The autoregressive sieve bootstrap is alternative method to the approach based on asymptotic theory. The AR-sieve bootstrap method was applied to medical data: Heart Rate time series.

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Mathematical modelling of physiological processes in patients on dialysis;
Saturday, July 2, 11:00

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Modeling of glucose-insulin system in patients on dialysis

One of the most common causes of end-stage renal disease (ESRD) worldwide is diabetes mellitus. According to the US Renal Data System in 2005 above 44% of new ESRD patients were diabetics. The process of regulation of glucose concentration in blood is complicated and can be substantially affected by uremia and dialysis, which both may have an impact on secretion and clearance of glucose and insulin, and on insulin resistance leading to hypo- or hyperglycemia. Low levels of blood glucose may cause shock and death, while too high levels are toxic. Thus, it is essential that glucose levels must be tightly regulated and an analysis of the effects of dialysis (peritoneal dialysis with glucose-based solution and hemodialysis) on plasma glucose and insulin concentration is of great importance. A mathematical model describing glucose-insulin regulation was based on the models proposed by Stolwijk and Hardy (1974) and Tolic et al (2000). Two different sources of glucose were taken into account: hepatic glucose production and an external source (e.g. food digestion, intravenous glucose infusion or transport between dialysis fluid in the peritoneal cavity and blood). There are three types of glucose utilization: 1) glucose leaves blood to enter most cells through facilitated diffusion (insulin independent glucose utilization), 2) in certain types of cells (e.g. muscle and adipose tissue) insulin helps to stimulate the facilitated diffusion process (insulin dependent glucose utilization), 3) glucose can be also excreted by the kidneys. As regards insulin, two sources are taken into account: pancreatic insulin production controlled by the glucose concentration and external source of insulin (e.g. injection). Insulin is degradated through a reaction involving the insulinase at a rate proportional to insulin concentration in blood. All these assumptions are used in the mass balance equation describing the blood concentration changes of glucose and insulin during dialysis (peritoneal dialysis and hemodialysis). The clinical parameters of the

glucose-insulin system, insulin sensitivity index and glucose effectiveness at basal and zero insulin (GEZI) were also estimated using clinical data from: 1) six hour peritoneal dialysis dwells with glucose 3.86% solution performed in 13 stable, fasting, non-diabetic patients, and 2) hemodialysis with a bolus of 33% glucose infused into blood in 8 stable, non-diabetic maintenance hemodialysis patients during their regular dialysis treatment. Computer simulations based on the model were performed for each patient and each dialysis session to estimate the model parameters. The mean values and standard deviations of the parameters were calculated and compared for both studies. There were statistically significant differences between hemodialysis and peritoneal dialysis patients especially in the parameters describing insulin regulation such as the insulin catabolism rate and the maximal level of insulin generation. Clinical and modeling results demonstrated high interpatient variability in glucose and insulin concentration profiles during a peritoneal dwell and during hemodialysis, and in the parameter values of the glucose-insulin system. The proposed model was able to adequately reproduce the clinical data on glucose and insulin transport and plasma levels and to distinguish patients with and without abnormalities in glucose regulation.

Cancer; Saturday, July 2, 14:30

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Phenotypic inheritance transforms heterogeneity in tumor growth

Cell-to-cell variation is seen in almost all aspects of cancer from initiation to invasion and subsequent metastasis. Our current understanding at the genetic scale gives little information on translating to actual changes in cell behavior, which will ultimately dictate tumor aggressiveness and treatability. Cell behavior can be described in terms of phenotypic traits, e.g., proliferation, migration, and apoptosis rates. Because these traits vary across a tumor population a useful way to represent them is in terms of distributions. How traits are passed on as cells divide and compete for space and resources affects how the trait distributions evolve.

An off-lattice cellular automata model is built where cells are either initiated as a tight cluster, to simulate a growing tumor mass, or as a dispersed population, to represent a cell culture experiment. These initial spatial distributions give different outcomes and lead us to question how heterogeneity *in vitro* can be translated *in vivo*. We combine the model's trait distributions, repopulation times, and morphological features with biological data to analyze how treatment resistance emerges and how it might be regulated.

Bioinformatics and System Biology; Wednesday, June 29, 14:30

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Transcriptional regulation by histone modifications

Transcriptional regulation in cells makes use of diverse mechanisms to ensure that functional states can be maintained and adapted to variable environments. Among these mechanisms are cis-regulatory modules and chromatin modifications. Unraveling the hierarchy of these different layers of regulation represents a challenge of Molecular Systems Biology. We here introduce a mathematical model of genome-wide transcriptional regulation governed by histone modifications. This model describes the binding of protein complexes to DNA which are capable of reading and writing histone marks. Cooperative molecular interactions between the protein complexes, the DNA and the modified histones create a regulatory memory and allow for switch-like changes of the expression state of the genome. We provide analytical results on the dependence of the regulatory states on i) the (de-) modification activity of histone (de-)methylases, ii) the accessibility of the DNA-binding regions of the protein complexes and iii) the number of histones that act cooperatively; and discuss the impact of the cellular environment on these properties. We demonstrate that according to our model proliferation activity per se can switch expression states of the genome as a consequence of suppressed inheritance of the histone marks. We apply our model to transcriptional regulation by trxG- and PcG-binding to DNA. By analysing ChIP-seq data of mouse ESC we provide evidence for cooperative modes of histone modifications. Thereby, our data suggest a threshold length of the cooperative chromatin regions of about 10kb which agrees with the loop length of an un-interrupted chromatin fibre. Our results provide new insights into genome-wide transcriptional regulation by histone modifications and represent a first step towards simulation studies on changes of the epigenome during ageing and disease.

Medical Physiology; Tuesday, June 28, 11:00

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A mathematical model for glucose and insulin dynamics with direct connection to the β-cell cycle

The term diabetes mellitus describes a group of metabolic diseases with persisting hyperglycemia as the main symptom. Interest is increasingly focused on the understanding and treatment of the disease because of its rising prevalence and the variety of severe complications. Recent experimental results indicate the relevance of the β-cell cycle for the development of diabetes mellitus.
We investigate the dynamics of the interplay of glucose, insulin and the β-cell cycle with a mathematical model of ordinary differential equations. The basis of the system is built by three different models. To analyze the dynamics of insulin the work of Grodsky [1] introducing a packet hypothesis for insulin storage has been modified. This has been connected with the dynamics of glucose (Topp et al. [2]) and a model for the β-cell cycle based on Daukste et al. [3]. The advantage of the system consists in its explicit incorporation of the β-cell cycle with insulin directly enhancing the replication rate of the cells.
In the presentation, the model and its development will be introduced as well as its capability of accounting for metabolic failures in the progression to diabetes.

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Analysis of mathematical models for cancer growth and treatment, Part II; Tuesday, June 28, 14:30

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Vascularization and chemotherapy: inferences from a simple model

Most of the models of chemotherapy are currently developed making only reference to the population of cancer cells. We propose to model chemotherapy taking into account the mutual interaction between tumor growth and the development of tumor vasculature. By adopting a simple model for this interaction, and assuming that the efficacy of a drug can be modulated by the vessel density, we studied the constant continuous and bolus-based chemotherapy, and combined therapies in which a chemotherapeutic drug is associated with an antiangiogenic agent [1]. The model allows to represent the vessel-disrupting activity of some standard chemotherapeutic drugs, and shows, in case of constant continuous drug administration, the possibility of multiple stable equilibria. The multistability suggests an explanation for some sudden losses of control observed during therapy, and for the beneficial effect of vascular "pruning" exherted by antiangiogenic agents in combined therapy.

References.

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A reinforced random walk model for studying the acute inflammatory response

The theory of reinforced random walks (RRWs) provides a natural framework for modelling the movement of individuals. RRWs are in particular suitable for modelling cell motility in response to one or more control substances [1]. In the past RRWs have been used to model angiogenesis and solid tumour growth and metastasis [2, 3].

In this work we have developed a spatio-temporal mathematical model consisting of a system of diffusion-advection-reaction equations, to capture some aspects of tissue inflammatory response. Two sorts of cell movement mechanisms are considered: 1. Chemotactic as the major physiological effect that leads the movement of leukocytes towards the site of infection/inflammation, 2. Leukocytes' random motility described via diffusion process. The proposed model accounts for (1) antigen recognition, (2) the effector function (activation/inhibition), (3) innate immune response, (4) elimination of antigen and resolution of the infection and (5) returning the immune cells back to a steady state. In case of a persistent source of antigen, i.e. chronic infection, it is observed that the immune response reaches an equilibrium level. 2-D Matlab simulations have enabled us to visualise the dynamics of the immune cells and chemicals.

Our simulations could provide insights for better understanding complex diseases associated with chronic inflammation like cancer and autoimmunity.

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Poster Session; Friday, July 1, 20:00

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Specialist-v-generalist host-parasite interactions: influence on the stochastic dynamics of bacteria-phage infection

The main models of the genetics underlying host-parasite infections are the matching-alleles (MA) and the gene-for-gene (GFG) models. These can be interpreted as two extremes of a continuum that ranges from one-to-one specific matching in all host-parasite pairs (MA) to many-to-one generalist interactions in some of these (GFG). We have incorporated this variable degree of generalism into a simple epidemiological model of the infection of bacteria by lytic phages, adopting a fully stochastic description of the population dynamics and analyzing the different dynamical regimes that appear along the MA-to-GFG continuum.

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Computational Model of Targeted Drug Delivery via Low-Temperature Sensitive Liposomes and image-guided focused ultrasound

The chemotherapeutic agent doxorubicin (DOX) is commonly used in cancer treatment, but causes dose limiting side effects. Various liposomal drug carriers were developed to overcome short plasma half-life and negative side effects of chemotherapeutic agents. Low temperature sensitive liposomes (LTSL) release their content only if exposed to a temperature above approximately 40 C and in contrast release a relatively small amount of drug at normal body temperature. The combination of LTSL with local heat generated by image-guided focused ultrasound enables non-invasively targeted drug delivery. We developed an axial symmetric computational model to simulate temperature, blood perfusion, and drug concentrations in different compartments of the model. The model describes the release of drug from the liposomes, transport mechanisms of the drug between different compartments and spatio-temporal drug and liposome concentrations. We compared two cases: Tissue heated to hyperthermic temperatures with a target temperature of 43C, and hyperthermia followed by a short high temperature exposure with a target temperature of 68 C of the same region. Blood perfusion was reduced of 7% of the baseline value within the heated area after hyperthermia, whereas it was completely eliminated inside the target region in case of the high-temperature exposure. Due to the eliminated blood flow drug is facilitated to remain trapped within the tissue. The plasma concentration of DOX reached a peak value of 12.1 g/g at t=3 min in both cases. The intracellular concentration of DOX during hyperthermia followed by short high temperature exposure was almost two times higher than hyperthermia alone with peak values of 18 g/g and 10 g/g, respectively. The complex interaction between thermal cancer treatments and locally induced chemotherapy agents, require a mathematical model to identify the relationship between heat exposure and pharmacokinetics in order to optimize drug delivery.

Mathematical models of gene regulation; Tuesday, June 28, 11:00

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Modelling delays induced by transcription and translation

Delays are always present In gene regulation and they are increasingly finding their way into models of gene networks . In this talk I will discuss sources of delays in gene regulation, and then concentrate on our recent attempts to model the processes of transcription and translation. The resulting models closely resemble old linear and nonlinear traffic models.

Poster Session; Friday, July 1, 20:00

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Boolean versus continuous dynamics on simple two-gene modules

We investigate the dynamical behavior of simple modules composed of two genes with two or three regulating connections. Continuous dynamics for mRNA and protein concentrations is compared to a Boolean model for gene activity. Using a generalized method, we study within a single framework different continuous models and different types of regulatory functions, and establish conditions under which the system can display stable oscillations. These conditions depend only on general features such as the ratio of the relevant time scales, the degree of cooperativity of the regulating interactions, and the logical structure of the interactions. Our results combine and generalize the findings of several disconnected previous studies.

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Modeling Dynamics of Complex Biological Systems; Tuesday, June 28, 17:00

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Macroscopic model of reversing self-propelled bacteria

Periodic reversals in systems of self-propelled rod shaped bacteria enable them to effectively resolve traffic jams formed during swarming and maximize their swarming rate. A connection is shown between a microscopic one dimensional cell-based stochastic model of reversing non-overlapping bacteria and a macroscopic non-linear diffusion equation for the dynamics of cellular density. Boltzmann-Matano analysis is used to determine the nonlinear diffusion equation corresponding to the specific reversal frequency. A combination of microscopic and macroscopic models are used for studying swarming rates of populations of bacteria reversing at different frequencies. Cell populations with high reversal frequencies are able to spread out effectively at high densities. If the cells rarely reverse, then they are able to spread out at lower densities but are less efficient at spreading out at higher densities.

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Mathematical and numerical modeling of cell membrane deformations as a consequence of actin dynamics

Actin is a molecule that exists in two different forms which can be monomeric as globular actin (G-actin) or assembled into the polar filamentous form (F-actin). It resides in the cell cytoskeleton and plays an important role in controlling cell motility and maintaining cell shape [3]. Cell motility consist of numerous highly coordinated events which involve a combination of chemical kinetics and physical forces, transport and movements of a polymer protein network interacting with a vast number of other proteins. These events can be treated mathematically by combining models of continuum mechanics and biochemical kinetics [2]. These models have proven to be useful for decoding cell motility processes [1]. The model we consider is a system that consists of a force balance equation and a reaction-diffusion equation describing the mechanical properties and biochemical kinetic of actin respectively. We solve the model equations by use of the moving grid finite element method whose key advantage is in its ability to treat moving boundary problems with pronounced curvature and is very beneficial in the accurate representation and approximation of the shape of the cell. Assuming slow domain evolution we validate the numerical results by comparing the finite element solutions to those predicted by linear stability theory. We show that the numerical scheme computes spatially inhomogeneous steady state solutions which coincides with those predicted by linear stability theory close to bifurcation points [4].
Far away from instability, we show that this model is able to describe the intracellular actin dynamics and the resulting shapes and movements of the membrane. In particular, by varying the pressure coefficient and the measure of the contractile tonicity parameter, the model behaviour gives uniform expansions, contractions and irregular deformations of the cell membrane with the cell centre staying mostly unchanged in the majority of the cases considered. The model also allow us to compare the actin distribution at the vicinity where large deformations occur and the results we obtain are found to be consistent with those observed experimentally.

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Can polyclonality prevent the outbreak of leukemia?

T cell receptor (TCR) polyclonal mature T cells are surprisingly resistant to oncogenic transformation through retroviral induction of T cell oncogenes. It has been shown that leukemia/lymphoma did not occur upon transplantation of polyclonal T cells into RAG1-1-deficient recipients, although the T-cells were transduced with high copy numbers of gammaretroviral vectors encoding potent T cell oncogenes [1]. Further studies demonstrated that the transplantation of T cells from TCR monoclonal OT1 mice that were transduced with the same protocol resulted in leukemia/lymphoma. The underlying mechanisms that prevent oncogenesis in the polyclonal situation and endorse the outbreak of leukemia in the monoclonal situation are currently unclear.

Using a mathematical modeling approach, we challenge the arising hypothesis that polyclonality induces competition within the T cell repertoire, which in turn suppresses the emergence of a leukemic clone. As a starting point, we developed a simple model of T cell homeostasis emphasizing the analogy of T cell homeostasis to species coexisting in ecological niches. The key assumption of the model is that T cell survival is critically dependent on the interaction of the clone-specific TCR with self-peptide-MHC-complexes (corresponding to environmental niches).

Based on our modelling results, we speculate about the cellular properties of the leukemic clone. Within our model framework, we are able to explain the observed phenomena under the following two assumptions about the cellular properties of the leukemic clone: (i) The leukemic clone is less competent than other T cell clones in acquiring survival stimuli from niches. (ii) Proliferation of the leukemic clone is less dependent on niche interaction. This is a plausible assumption as the transgenes are potent oncogenes capable of activating mitotic pathways.

From our results we conclude, that clonal competition is a possible mechanism to counterbalance clonal dominance. Our modeling results allow us to foster the design of further biological experiments. A future goal is to determine the minimum clonal complexity that is needed in order to control the leukemic clone under the given circumstances.

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Analysis of mathematical models for cancer growth and treatment, Part III; Tuesday, June 28, 17:00

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When do a low-grade glioma appear?

Gliomas are the most common tumour of the brain. The problem of WHO grade II and higher gliomas is the infiltration: it is not possible to see the whole tumour on a MRI examination because a part of it is underside the detection threshold [1]. Inevitably an anaplastic transformation occurs, that rapidly causes the demise of the patient.

A recent clinical study showed that the growth of low-grade gliomas appears linear, at roughly 2 mm/yr [2]. Is it possible to assume that it is always true ? Using this property, can we extrapolate the date of birth of gliomas ? To answer this questions, we use a diffusion-proliferation model, employed with success for high-grade gliomas [3]. It is a simple model (few parameters) that can explain the constant velocity of the front visible with MRI at large times.

This model is based on a partial differential equation where the concentration of tumour cells is determined by the migration and by the proliferation of the cells. We assume that the tumour is symmetric and begins with a single cell.

The model predicts the existence of a "silent period": the tumour is growing, but remains under the detection threshold and thus it is not visible. A consequence of this phase is that the extrapolation always underestimates the age of the tumour predicted by the diffusion-proliferation model.

We analyse data on real-life patients with the model. We estimate the age of the tumour at the time of the first MRI examination, the age of the patient at the onset of the tumour and the coefficients of diffusion and proliferation.

We also apply the model to patients who do not present symptoms, and we find, as expected, that the tumour age at time of MRI is smaller than in the case of symptomatic patients.

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Cancer; Saturday, July 2, 14:30

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The impact of phenotypic switching on glioma growth

Tumour growth is contingent on numerous intra-cellular and extra-cellular processes, such as an elevated rate of proliferation, evasion of apoptosis and angiogenesis [**1**]. Out of these, proliferation has traditionally been singled out as the most important, and has generally been the target of anti-cancer therapies. Recently, there has been a growing interest in the impact of cancer cell *motility*, and this is especially true in the case of glioblastoma, which generally exhibit diffuse morphologies stemming from the high motility of individual glioma cells.

In order to investigate this phenomenon, we propose a 3-dimensional cellular automaton model, which describes the growth of a glioma consisting of up 10^6 cells. In accordance with the *go or grow* hypothesis [**2**] each cell can be either in a proliferating or motile state. The switching between the states is achieved by means of a two-state Markov chain within each cell, characterised by two parameters p_m, the probability of remaining in the motile state, and p_p the corresponding parameter for proliferation. Simulating the cellular automaton and by sweeping the parameter space of the phenotypic switching model we find that the most invasive tumours (i.e. with the highest growth rate) occur at $(p_m, p_p) \approx (0.9, 0.9)$, i.e. they are characterised by both proliferative and motile behaviour, and by a high degree of phenotypic persistence. We also find that for each $p_p \in [0, 1]$ there is a $p_m \neq 0$ such that the growth rate is maximised.

These observations are in agreement with experimental results, where glioma cell lines with a lower proliferative capacity have been observed to rise to larger tumours when implanted in mice [**3**]. Further it suggest cancer cell motility as a potential target for therapy.

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Epidemiology, Eco-Epidemiology and Evolution; Saturday, July 2, 11:00

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Genomic mutation rates that cause extinction: general evolutionary predictions

When mutation rates are low, increasing the mutation rate can give rise to an increase in adaptation rate. If mutation rate is increased further, however, a point may be reached at which fitness declines despite continued adaptive and/or compensatory evolution. If fitness decline persists, it intuitively culminates in population extinction. Mathematical formalization of this criterion for extinction gives rise to a simple relation that puts a dynamic upper limit on viable mutation rates. The particular mathematical guise of this relation suggests encompassing generality, which we confirm using individual-based simulations. Additionally, we re-derive the classical "error threshold" formula and show, by proxy, that it is similarly general when used dynamically an attribute not previously recognized. Finally, we demonstrate the utility of the insights gained from these developments with an example application to immunology.

Stochastic models in computational neuroscience I; Wednesday, June 29, 14:30

Wulfram Gerstner
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Predicting action potentials and membrane potential of neurons

If neurons receive a current that is generated by a filtered point process, they fire spikes at specific moments in time, with little variation from one trial to the next.

In this talks I will discuss

(i) how to compare spike trains and measure reliability

(ii) how to extract adaptative currents from the data

(iii) how to systematicaly construct neuron models from simple models to more complex ones.

Philipp Getto
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A differential equation with state-dependent delay from cell population dynamics

The aim of this research is an analysis of the maturation process of stem cell populations. The regulation of this process leads to a description of the population dynamics as a differential equation with state-dependent delay, i.e., an object of great mathematical challenge. We show for this system well-posedness and give some results on the existence of equilibria.

Population Dynamics; Tuesday, June 28, 17:00

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A Biomass Flow Approach to Population Models and Food Webs

The dominant differential equation paradigm for modeling the population dynamics of species interacting in the framework of a food web retains at its core the basic prey-predator and competition models formulation by Alfred J. Lotka (1880-1945) and Vito Volterra (1860-1940) nearly nine decades ago. This framework lacks a trophic-level-independent formulation of population growth leading to ambiguities in how to treat populations that are simultaneously both prey and predator. Also, it does not fundamentally include inertial processes needed to account for the response of populations to fluctuating resource environments. Here I present an approach that corrects both these deficits and provides a unified framework for accounting for biomass transformation in food webs that include both live and dead components of all species in the system. This biomass transformation formulation (BTW) allows for a unified treatment of webs that include consumers of both live and dead material—both carnivores and carcassivores, herbivores and detrivores—and incorporates scavengers, parasites, and other neglected food web consumption categories in a coherent manner. I trace how BTW is an outgrowth of the metaphysiological growth modeling paradigm and provide a general compact formulation of BTW in terms of a live/dead/deficit-stress three-variable differential equation formulation for each species in the food web. I then illustrate the application of this new paradigm to provide insights into two-species competition in variable environments and discuss application of BTW to food webs that incorporate parasites and pathogens.

Population Dynamics; Saturday, July 2, 11:00

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Quantifying Stochastic Introgression Processes with Hazard Rates

Introgression is the permanent incorporation of genes from one population into another. It has become of particular concern with the advent of genetically modified crops, since the introgression of genetically modified crop genes into their wild relatives could have adverse effects on local biodiversity. Modeling introgression can become a difficult task, compounded by stochasticity on several levels, from the offspring distributions of certain plants, to different weather patterns. This talk outlines how a branching process based approach can be used to derive a measure of risk of introgression, the hazard rate, which is the probability per generation that introgression occurs given it hasn't occurred before. Methods to calculate the hazard rate with randomness on different levels, from individual to environmental, form the basis of the talk.

Heart rate dynamics: models and measures of complexity (part I);
Wednesday, June 29, 14:30

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Generalized multifractal analysis of heart rate variability recordings with a large number of arrhythmia

The regulation of human heart rate is the result of many inputs e.g. the activity of the sympathetic and parasympathetic nervous system, respiration and its control or such pathologies as ectopic activity or delayed conduction of cardiac tissue - each having its own characteristic time scale and magnitude. The MF-DFA (MultiFractal Detrended Fluctuation Analysis) method used by us allows to assess the effect of the different controls systems and pathologies. Because it requires stationarity the method is applied in the literature to heart rate variability recordings with less than 5% of arrhythmia.

We analyzed the published MF-DFA method, using synthetic data and chosen RR intervals series. We developed an original, generalized version of the MF-DFA method - multiscale multifractal analysis MMA. We found that the calculation of the $f(\alpha)$ curve is a major source of artifacts. We thus focused on the dependence of the local Hurst exponent h on the multifractal parameter q: $h(q)$ and we allowed it to depend on the scale s. In the standard MF-DFA the time scale s is fixed, somewhat arbitrarily (usually from 50 intervals up to 500). Thus, we obtained the $h(q, s)$ dependence - a surface - the shape of which tells us what is the magnitude of the fluctuations the RR intervals have in different time scales (different frequency bands). MMA was found to be immune to noise contamination of the data (we tested up to 50% of noise). It also allows to study heart rate variability with an arbitrary level of arrhythmia required for clinical applications.

We analyzed 51 24-hour recordings of heart rate variability (36 males age 16-64, 15 females age 11-57: 42 healthy persons, 9 cardiac arrest cases including 5 without organic heart disease). We did not remove arrhythmia from the recordings. We limited the study to the night hours to avoid arbitrary daytime activity. Our mathematical criterion was able to distinguish, in a blind test, healthy subjects from the high risk cardiac arrest cases including those without organic disease. The different peculiarities of each recording have a unique effect on the results of the multiscale MF-DFA analysis e.g. the occurrence of arrhythmia may readily be identified from the results. Thus, the new method allows to recognize and assign a complexity measure to features of the heart rate variability which hitherto went unnoticed when using standard, linear diagnostic methods and MF-DFA.

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Cell and Tissue Biophysics; Thursday, June 30, 11:30

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Mathematical modelling of foot-and-mouth disease virus infection of bovine epithelial cells.

Foot-and-mouth disease (FMD) is a highly infectious animal disease that affects cloven hoofed animals (including cattle, sheep and pigs) and causes acute clinical signs such as vesicular lesions in the foot and mouth, lameness, fever and pain; in more severe cases it can lead to death of young livestock. In areas where FMD is endemic, it is considered to be the main threat to animal health and economic development, while an outbreak of FMD in 2001 in the United Kingdom, a disease-free country, resulted in 6.5 million animals being slaughtered and losses of £6 billion. Persistence of FMD virus (FMDV) occurs in previously infected but apparently recovered animals, in the pharyngeal area, specifically in the dorsal soft palate [1]. These carrier animals are a possible source of virus transmission, and potentially facilitate viral mutations. In addition to the persistence of FMDV, the virus appears not to cause lysis in the dorsal soft palate, even though lesions appears on the tongue and coronary band.

Presented in this talk is a mathematical model which aims to test the hypothesis that it is the different structure of epithelial cells, rather than the intrinsic properties of the tongue and dorsal soft palate that determines the extent of FMDV lysis. A simple ODE compartmental model of Schley et al (2010) [2] considered static live cells and indicated that the dimensions of the epithelial tissues in the tongue and dorsal soft palate are important for cell lysis and FMDV persistence. Here, this has been extended to a spatially explicit system of partial differential equations that

describes the viral dynamics in the epithelial layers of both tissue types. The model accounts for the movement of cells through growth, and includes heterogeneity of the cell layers which form the epithelium. New experimental data, required to fit the model, has been collected and applied, together with existing results from the literature. We will present numerical results from a limit of the model, relevant on the timescale of the early infection stages before the immune response becomes effective and discuss key insights. A full active system which accounts for the formation of lesions is work in progress.

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Modeling and analysis of tumor invasion II; Tuesday, June 28, 14:30

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Modeling the mechanical behavior of cell aggregates and their invasion of mesothelial linings.

The transmigration across the mesothelial lining is a fundamental step in the process of cancer invasion and formation of metastasis. We reproduce in vitro trans-mesothelial migration of ovarian cancer cells, through a mathematical model that integrates: (a) an Extended Cellular Potts Model (CPM), that captures mechanisms of cellular adhesion, shape constraints, motion in response to chemo-attractants and degradation of extracellular matrix (ECM); (b) a continuous model for the diffusion and uptake of chemo-attractants, and for the release of matrix metalloproteinases (MMPs). Simulations are in good agreement with biological experiments (provided by N. Lo Buono and A. Funaro, Laboratory of Immunogenetics of the Molinette Hospital in Turin), showing that the overall process is strongly regulated by the activity of matrix metalloproteinases (MMPs) and by the interplay of adhesive properties between cells. In particular in the case of cellular aggregates the process is more destructive.
Indeed the ability of cells to form aggregates is fundamental in many biological processes and it seems promising to study spheroid mechanical behavior, because the response of soft biological tissues may serve as a parameter in the diagnosis of tumor metastatic potential. We study the mechanical behavior of multicellular aggregates, treated as porous materials, composed of cells and filled with water, to derive an elasto-visco-plastic model. The cellular constituent is responsible for the elastic and the plastic behavior (due to the rearrangement of adhesive bonds between cells). On the other hand, the liquid constituent is responsible of the viscous-like response during deformation. The model is used to describe the uni-axial homogeneous compression both when a constant load is applied and when a fixed deformation is imposed and subsequently released. Results are compared with the dynamics observed in mechanical experiments found in literature.

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Vector-borne diseases; Tuesday, June 28, 14:30

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Optimizing pathogen fitness: the role of the antigenic archive for African Trypanosomes

Antigenic variation processes play a central role in vector-borne infectious diseases and are likely to respond to host immune mechanisms and epidemiological characteristics. A key priority in disease control and understanding pathogen evolution is the investigation of mechanisms by which pathogens regulate antigenic diversity and how these affect larger-scale population processes. While the within-host population ecology of antigen switching pathogens is not a new topic, increasing access to genetic data provides us with a rapidly widening opportunity to understand the evolutionary ecology of antigenic variation. In this work, we study the interactions between the structure and function of the antigenic archive of the African Trypanosome, the parasite responsible for sleeping sickness. We show that the genetic architecture of the archive has important consequences for pathogen fitness within and between hosts. The optimality criteria we find for the antigenic archive arise as a result of typical trade-offs between transmission and virulence. Our analysis suggests that different traits of the host population can select for different aspects of the antigenic archive, reinforcing once more the importance of host heterogeneity in the evolutionary dynamics of parasites.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -I; Tuesday, June 28, 11:00

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Multi-scale, Multi-cell Computational Modeling of Choroidal Neovascularization in Age-Related Macular Degeneration

Choroidal neovascularization (CNV) of the macular area of the retina is the major cause of severe vision loss in patients with age-related macular degeneration (AMD) and the major cause of vision loss in adults in the developed world. In CNV, after choriocapillaries initially penetrate Bruch's Membrane (BrM), the invading vessels may regress or expand (CNV initiation). After initiation, during early and late CNV, the expanding vasculature usually spreads in one of three distinct patterns: in a layer between BrM and the retinal pigment epithelium (sub-RPE, occult or Type 1 CNV), in a layer between the RPE and the photoreceptors (subretinal, classic or Type 2 CNV) or in both loci simultaneously (combined pattern or Type 3 CNV). The factors determining both CNV initiation and progression are poorly understood. While most previous studies of CNV have assumed that it is primarily related to growth factor effects or to local holes in BrM, our simulations of a three-dimensional (3D) multi-cell model of the maculae of normal and pathological retinas successfully recapitulate the three clinically observed types of CNV, under the hypothesis that initiation and early and late CNV result from combinations of impairment of: 1) RPE-RPE epithelial junctions (i.e. the outer blood-retinal barrier), 2) the adhesion of the basement membrane of the RPE (BaM) to BrM, and 3) adhesion of the RPE to the photoreceptor outer segments (POS). Our key findings are that when an endothelial tip cell or immune cell penetrate BrM: 1) RPE with normal epithelial junctions and basal attachment to BrM and apical attachment to POS resists CNV, showing that higher rates of EC activation due to excess vascular growth factors by themselves are insufficient to produce CNV. 2) Similarly small holes in BrM do not, by themselves, initiate CNV. 3) RPE with normal epithelial junctions and normal apical RPE-POS adhesion, but weak adhesion of BaM to BrM (e.g. due to lipid accumulation in BrM) initially results in Type 1 CNV. 4) Normal adhesion of BaM to BrM, but reduced apical RPE-POS and epithelial RPE-RPE binding (e.g. due to inflammation) initially results in Type 2 CNV. 5) Simultaneous reduction in RPE-RPE epithelial binding and BaM-BrM adhesion results in early Type 1 or 2 CNV which often progresses to Type 3 CNV as neovascularization further perturbs RPE-RPE adhesion and BaM-BrM attachment. These findings suggest that previously neglected changes in adhesion rather than the more often hypothesized excess production of vascular growth factors dominate both CNV initiation and progression.

Developmental Biology; Friday, July 1, 14:30

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Pattern formation in reaction-diffusion systems with an external morphogen gradient

Gradients of signalling molecules are abundant in the early embryo. They are central to early development. The Turing mechanism in reaction-diffusion systems is a paradigm for pattern formation which has been proposed as an explanation for many developmental phenomena. We propose a generic model of a reaction-diffusion system consisting of an activator and an inhibitor molecule in the presence of a linear morphogen gradient. We assume that this morphogen gradient is established independently of the reaction-diffusion system. Hence it is referred to as an "external" morphogen. It acts by increasing the production of the activator proportional to the morphogen concentration. The model is motivated by several existing models in developmental biology in which a Turing patterning mechanism is proposed and various chemical gradients are known to be important for development. Mathematically, this leads to reaction-diffusion equations with explicit spatial dependence. We investigate how the Turing pattern is affected, if it exists. We also show that in the parameter range where a Turing pattern is not possible, the system may nevertheless produce "Turing-like" patterns. We also apply our general findings to a model of bone pattern formation in vertebrate limbs and show how they may shed light on some experimental findings concerning the action of the protein *Sonic Hedgehog*.

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Poster Session; Friday, July 1, 20:00

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The range of fluctuations of number of zinc ions depends on the ligand binding reaction rate constant and the initial concentration

The range of fluctuations of number of zinc ions depends on the ligand binding reaction rate constant and the initial concentration Wojciech Goch a), and Wojciech Bal b)

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We present the dependency of the range of fluctuations on the parameters of a reversible chemical association reaction in an equilibrium state. We derived the infinite system of equations describing the central moments from a set of equations called Chemical Master Equation. Next, we performed a series of numerical simulations in order to find appropriate assumptions in our model. Finally, by placing these assumptions into the equations, we derived the explicit formulas on the first two central moments. The second central moment determines the range of fluctuations of one partner of the reaction, thus, we are able to investigate the impact of the probability factor on the behavior of the system. We compared the obtained results with numerical simulations. The essential result is the mathematical formula describing the dependency of the range of fluctuations of the number of interacting molecules on the reaction rate constants and the initial concentrations. The mathematical model, as well as the method of the approximation, could be expanded to much more complicated systems. The method was tested on several experimental data available in literature for interactions of Zn(II) ions with biomolecules, including the reaction of formation of a zinc finger complex, for which K_d = k_off/k_on = 50 pM. For this particular example, the volume, in which the virtual experiment was performed, was V = 0.5 pL, initial concentrations of reagents were: [Zn] _Free =50 pM, [ZnP] = 50 M, [P] = 50 M and, as a result, the range of fluctuations of zinc ions was estimated to be ca. 26%, translating into the fluctuation of the Kd value in the range of 59% 190%.

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Strain dynamics and influenza drift

One of the most exciting current areas in infectious disease modelling is in bringing together the epidemic and evolutionary dynamics. Influenza drift is perhaps the most striking example of where the two processes must be considered together: epidemics give rise to new strains, which in turn permit new epidemics.

We will begin with a general introduction to models of multiple strains, and some of their challenges, both technical and in terms of capturing observed biological phenomena. In most population-based models of strain dynamics, the number of variables grows exponentially with the number of strains. We present two items of our recent work, each of which avoids this problem in one way or another:

1) The impact of evolutionary constraints on influenza drift: standard drift models assume influenza is free to mutate to escape host immunity. In practice, there may be some functional cost associated with these mutations, and this can be incorporated into a mathematical model. In contrast to unconstrained drift models, this system is bistable, exhibiting both drift-like patterns and single strain dynamics for the same parameter values. This raises some important questions for vaccination strategies.

2) Age-structure and immune history: although relatively simple assumptions about the acquisition of immunity capture well the general dynamics of influenza drift, recent outbreaks have highlighted the importance of considering the details of precisely how immunity is acquired by an individual over their lifetime. In particular, strains that infect us when we are young may be disproportionately important (e.g. through original antigenic sin), and the immune response may be weakened in the elderly.

Game theoretical modelling and optimization in evolution and ecology II;
Tuesday, June 28, 14:30

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Multiplayer evolutionary games: from selection to mutation

Evolutionary game theory is an abstract and simple, but very powerful way to model evolutionary dynamics. Even complex biological phenomena can sometimes be abstracted to simple two player games. But often, the interaction between several parties determines evolutionary success. In these cases, one can resort to multiplayer games. Public goods games are a special class of multiplayer games which have been studied in great detail. A general approach to multiplayer games has although has remained limited [**3**]. We extend the replicator analysis to general d player games with n strategies and comment on the maximum number of equilibria possible. Moving on to finite populations we provide general conditions for a strategy to be favoured by natural selection in a d player game with two strategies [**4**]. Another important evolutionary force is mutations, which has only recently yielded to analytical methods [**1, 2**]. We derive the composition of a d player, n strategy system in the mutation-selection equilibrium [**5**]. The average frequencies of the strategies at this equilibrium are obtained via recursions using coalescence theory [**6**]. Multiplayer multi strategy games offer the generality which helps us to apply them to diverse entities like from alleles to behavioural strategies.

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Poster Session; Friday, July 1, 20:00

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A stochastic modelling approache for bacterial cell-cell communication

Quorum sensing is a form of microbial communication via so-called autoinducers which regulates many bacterial processes. In an experiment, bacteria (*Pseudomonas putida*) were attached in a flow chamber. There, they grow in small microcolonies; the state of the bacteria (ON or OFF, influenced by the present autoinducer concentration) can be observed via Gfp (a fluorescence protein) by confocal laser scanning microscopy. We developed stochastic modelling approaches which allow to quantify e.g. rates of cell division, activation or detachment of the bacteria. The autoinducer production can also be considered in the model and depends on the the bacterial states in the microcolony. The model (a kind of extended birth-death process) can be adapted numerically to data of quite different situations: e.g. flow versus non-flow, and by that helps to understand better the steps of cell activation and how they can be influenced.

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Mathematical models of evolutionary dynamics of infectious agents;
Tuesday, June 28, 17:00

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Heterogeneity in antibody range is required for the antigenic drift of influenza A viruses

In this paper we explore the consequences for the evolution of a rapidly mutating virus of a heterogeneous immune response in the population. We show that several features of the incidence and phylogenetic patterns typical of influenza A may be understood in this framework. Limited diversity and rapid drift of the circulating viral strains result from the interplay of two interacting subpopulations with two different types of immune response, narrow or broad, upon infection. The subpopulation with the narrow immune response acts as a reservoir where consecutive neutral mutations escape immunity and can persist. Strains with a number of accumulated mutations escape immunity in the other subpopulation as well, causing larger epidemic peaks in the whole population, and reducing strain diversity. These recurrent larger epidemics have been identified in the data and associated in the modelling literature with "cluster jumps", or mutations whose antigenic effect is larger and generate strains for which the pool of susceptibles in the population is also larger. Our model reproduces the observed epidemic peak height variation and antigenic drift patterns without any assumption of punctuated antigenic evolution.

Poster Session; Friday, July 1, 20:00

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Modeling circadian clocks as coupled damped oscillators

Circadian rhythms represent one of the more conspicuous examples of biological rhythms. Manifested at the physiological, behavioral, and cellular levels, these 24-hour rhythms originate at the molecular level, through a complex gene regulatory network. In mammals, the circadian pacemaker is located in the suprachiasmatic nuclei of the hypothalamus (SCN). We have developed deterministic models using non-linear ordinary differential equations that account for the occurrence of autonomous circadian oscillations in single cells, for their entrainment by light-dark cycles, and for their phase shifting by light pulses. The model can be used to unravel the links between molecular alterations (e.g. mutations in clock genes) and clock-related physiological pathologies (such as sleep phase disorders). We have investigated the coupling between the SCN cells and proposed a synchronization mechanism based on neurotransmitter release. Numerical analysis of the model predicts that (1) efficient synchronization is achieved when the average neurotransmitter concentration dampens individual oscillators and (2) phases of individual cells are governed by their intrinsic periods. These results illustrate the possible interplay between the single-cell oscillator and the inter-cellular coupling mechanisms.

Regulatory Networks; Tuesday, June 28, 17:00

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Qualitative Control of a Bistable Genetic Network

The control of a generic model for a genetic network is studied using piecewise affine differential systems. The system is the well-known bistable switch with two genes and proteins x_1, x_2:

$$\begin{aligned} \dot{x}_1 &= u\kappa_1 s^-(x_2, \theta_2) - \gamma_1 x_1 \\ \dot{x}_2 &= u\kappa_2 s^-(x_1, \theta_1) - \gamma_2 x_2. \end{aligned}$$

where κ_i denote production rates, γ_i denote the degradation rate constants, and θ_i the threshold concentrations. The step function represents the inhibition of the expression of each gene by the other.

$$s^-(r, \theta) = \begin{cases} 1, & r < \theta \\ 0, & r > \theta. \end{cases}$$

This class of piecewise affine systems (PWA) was first introduced by [1], and is widely used for modeling genetic regulatory networks [2]. It is assumed that the state measurements of x_1, x_2 are qualitative (each variable is at high or low concentration) and that the possible input values of the control u are also qualitative (no control, high value or low value). The advantage of this approach is to obtain control laws which can be implemented in the laboratory, using only qualitative knowledge of the system's variables. Solutions are given for the problem of controlling the bistable switch to either of its three steady states [3].

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Multiscale modeling of biological systems: from physical tools to applications in cancer modeling II; Saturday, July 2, 11:00

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Homogenization of a reaction-diusion system modeling carcino- gens inside a human cell

We use a reaction-diusion model to describe the behavior of potentially cancer-causing chemicals inside a human cell. We show how periodic homogenization can be used to upscale rigorously the reaction-diusion equations in the cytosol as well as on the surface of the endoplasmic reticulum. The resulting macromodel is also suitable for direct implementation. Results of numerical simulations will be shown.

Heart rate dynamics: models and measures of complexity (part I);
Wednesday, June 29, 14:30

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Entropy-based measures of complexity in the assessment of heart rate variability: a clinical approach

Non-linear dynamics is a powerful approach to understanding physiological data but non-linear methods usually require long data sets. In 1991, Pincus et al. introduced Approximate Entropy, a measure of complexity which can be applied to short and noisy time series of clinical data [**1**]. Subsequently, other entropy-based methods with some improvements were added and presently there are many examples of their successful application in medicine. An overview of the most promising applications in heart rate variability assessment will be presented. Advantages and limitations of these methods from the physician's point of view will be discussed based on recently published papers and our own results.

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Immunology; Saturday, July 2, 08:30

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Generalised Stress: A unifying model for psychological stress and psychosomatic treatment

Mathematical description of the impacts of psychological stress and psychosomatic treatment on patients with serious immune-related diseases and conditions is both challenging and important for the development of new quantifiable and effective treatment approaches for a range of diseases and conditions, including cancers [1], myeloproliferative blood diseases [2], etc. The development of such quantitative mathematical models is impeded by the fact that the characterisation of psychological stress and psychosomatic treatment is often based upon subjective perceptions of the involved human subjects (including preservative cognition). In this paper, we introduce and justify a new model based on a concept of generalised stress that mathematically unifies psychological stress and psychosomatic (hypnotic) treatment. This model correlates the two independently and subjectively reported levels of psychological stress and psychosomatic treatment on two different arbitrary scales to an objectively measured physiological parameter platelet count. As a result, the two subjectively reported quantities are reduced to the same unit scale and mathematically unified into one new quantity called generalised stress. Excellent applicability of this model is demonstrated on an example of a 3.5 years longitudinal study of blood parameters in a patient with myelofibrosis, who was subjected to severe work-related psychological stress and psychosomatic (hypnotic) treatment. The stress and treatment were statistically shown to have a major (dominant) impact on blood platelet counts well described by an exponential dependence on cumulative levels of generalized stress. Only 12 % of the total variation of platelet counts could be attributed to factors other than psychological stress and psychosomatic treatment. The developed model will be instrumental for the quantified analysis of the impacts of psychological stress and psychosomatic treatment for patients with immune and blood disorders. It also demonstrates a unique role of platelets for neuroimmunological pathways for psychological stress and psychosomatic treatment.

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Ecosystems Dynamics; Tuesday, June 28, 14:30

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Pathogen exclusion in eco-epidemiological models

It is well known that external forcing (whether periodic or stochastic) can alter the conditions under which a population is excluded from or can establish itself within an ecological system. This phenomenon is largely understood when the forcing only has one component but less so when there are multiple components, especially when some are environmental while others are controls imposed by management to achieve its objectives. The problem of how to exercise these controls is of importance in eco-epidemiological systems where the pathogen is to be excluded, particularly so in wildlife systems that impinge on human health and livelihood. Much of the work in this area has focused on the dynamics of the underlying unforced and unmanaged system but progress has also been made on the effect of specific controls (e.g. culling, vaccination) in systems with periodic environmental forcing (e.g. on birth rate, infection transmission). In this paper we wish to add to the literature by taking an algebraic approach based on a quadratic approximation in the forcing strength, linking directly to the pathogen exclusion threshold through the rare invader approximation. This approach generates explicit formulae for the distortion in the pathogen threshold when the forcing is of moderate strength. We can then efficiently explore the behaviour of specific eco-epidemiological models and to make general statements about their behaviour. The algebraic analysis provides a sound basis to extend the analysis to large strength forcing by numerical simulation, of importance when the pathogen threshold reflects resonance in the resident subsystem and the subharmonics and chaos that increased forcing can create. Applications include the effect on threshold behaviour of added structure in epidemiological models and the effect of forcing on coexistence in the presence of apparent competition mediated by pathogen or predator.

Stochastic models in computational neuroscience I; Wednesday, June 29, 14:30

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Continuity across bifurcations of stochastic Morris Lecar output distributions

Using the stochastic Morris Lecar model neuron, type II, with ion channel noise,we investigate the inter-spike interval distribution as increasing levels of applied current drive the model through a sub-critical Hopf bifurcation. We show that the parameter of the exponential tail of the ISI distribution is continuous over the entire range of plausible applied current, regardless of discontinuities in the phase-portrait of the model. Further, we show that the seldom-considered distribution of number of consecutive spikes is geometric with associated parameter similarly continuous as a function of applied current over the entire input range.

Poster Session; Friday, July 1, 20:00

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Fractal Geometry: a helpful way for looking cancer complexity

Cancer research has undergone radical changes in the past few years. Amount of information both at the basic and clinical levels is no longer the issue. Rather, how to handle this information has become the major obstacle to progress. System biology is the latest fashion in cancer biology, driven by advances in technology that have provided us with a suite of omics techniques. It can be seen as a conceptual approach to biological research that combines reductionist (parts) and integrationist (interactions) research, to understand the nature and maintenance of entities. In geometrical terms, cancerous lesions can be depicted as fractal entities mainly characterized by their irregular shape, self-similar structure, scaling relationship and non-integer or fractal dimension. It is indubitable that The Fractal Geometry of Nature has provided an innovative paradigm, a novel epistemological approach for interpreting the anatomical world. It is also known that mathematical methods and their derivatives have proved to be possible and practical in oncology. Viewing cancer as a system that is dynamically complex in time and space will probably reveal more about its underlying behavioural characteristics. It is encouraging that mathematicians, biologists and clinicians contribute together towards a common quantitative understanding of cancer complexity.

Game theoretical modelling and optimization in evolution and ecology I;
Tuesday, June 28, 11:00

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Dynamic game for optimal resource allocation of annual plants and grazing consumers

In [**1**] authors have formulated a model of optimal resource allocation in annual plants with constant grazing pressure along a season of fixed length. The plant has two choices: either to invest nutrients in the vegetative part of the plant or in the reproductive part. This kind of problem has been stated and solved as a problem of optimal control using Pontryagin's maximum principle.

In our work we consider a similar model but we take into account that the grazing pressure on the plant varies in time and occurs due to the presence of consumers in the system. Consumers are also faced with an allocation dilemma between the investment of time in increasing their internal energy through grazing or in reproduction (see for details [**2**]). Hence we are dealing here with a dynamic game of two players which are known to be fairly advanced mathematical objects [**3**]. Its resolution address interesting questions such as the influence of an adaptive, rather than fixed, grazing pressure on plants phenology.

References.

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Analysis of mathematical models for cancer growth and treatment, Part IV; Wednesday, June 29, 08:30

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Mathematical Model of Doxorubicin Transport within Solid Tumours

The efficacy of treating tumours with chemotherapeutic agents, such as doxorubicin, is dependent on how much drug reaches the regions most distant from drug supply in sufficient concentrations. Primerau et al. [1] show that the concentration of doxorubicin decreases exponentially with the distance from the nearest blood vessel. It is therefore important to understand how drug penetrates through cancerous tissue and how the penetration depends on treatment constraints, such as the pharmacokinetic profile or the dose of the injection.

Evans et al. [2] develop a mathematical model for the drug penetration through a multicellular layer, incorporating the "flip-flop" mechanism as a form of transport to and from cells and a Pgp-pump mechanism, which is thought to be the leading mechanism for the increased drug resistance of cancer cells. Because the model is bespoke to a transwell geometry, it has been successfully validated by experiments and important transport rates have been estimated.

Building on the work of Evans et al. [2], a model is presented for a geometry closer to that encountered *in-vivo*: a cylindrical blood vessel surrounded by multiple layers of cancerous cells. Moreover, the limited amount of membrane proteins that facilitate the transport of the drug is incorporated into the model, leading to Michaelis-Menten transport terms. Using this model, the effect of different pharmacokinetic profiles representing bolus injections, repeated bolus injections of lower concentration and infusions over several hours are assessed for their ability to deliver drug to the outer layers in the most efficacious manner.

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Statistical methods in computational neuroscience II; Wednesday, June 29, 17:00

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Scales of Neuronal Data and the Problem of Interaction

Cortical information processing was suggested to be performed via functional groups of cells, called cell assemblies [**1**]. Theoretical work supported this idea by indicating that synchronous input to a neuron is much more effective in emitting a spike than uncorrelated input. Although this coding scheme was controversially discussed, first supporting indications for spike synchrony were published, soon after techniques became available to simultaneously record from more than a single neuron. Presence of excess spike synchrony was found to be dynamic and related to behaviorally relevant instances in time. As expressed by different recording techniques (e.g. action potentials, local field potential (LFP)), the brain exhibits interesting phenomena on several spatial and temporal scales. However, the relationship of the various measures of cortical activity now experimentally available is largely unknown. The characterization of the joint signature of cortical processing in functionally meaningful contexts provides insight into the relevant scales and the potentially hierarchical organization of brain processes.

The mechanisms underlying neuronal coding and in particular the role of temporal spike coordination are hotly debated. However, this debate is often confounded by an implicit discussion about the use of appropriate analysis methods. To avoid wrong interpretation of data, the analysis of simultaneous spike trains for correlation needs to be properly adjusted to the features of experimental spike trains. Neuronal spiking activity is typically not stationary in time, but neurons 'respond' by changes in their firing rates to external stimuli or behavioral contexts. Also, data are not stationary across trials, but the statistical features may change during the experiment. Parametric approaches may be applied to experimental data to account for these aspects, however, the data may also contain features (e.g. deviation from Poisson) that do not allow an analytical treatment or parametric testing. Ignorance of such features present in parallel spike trains are potent generators of false positives, but can be avoided by including those features in the null-hypothesis of the significance test. In this context the usage of surrogate data becomes increasingly important to deal with such complex data [**2**].

The assembly hypothesis implies that entities of thought or perception are represented by the coordinated activity of (large) neuronal groups. However, whether or not the dynamic formation of cell assemblies constitutes a fundamental principle of cortical information processing remains a controversial issue of current research. While initially mainly technical problems limited the experimental surge for support of the assembly hypothesis, the recent advent of multi-electrode arrays reveals fundamental shortcomings of available analysis tools. Although larger samplings of simultaneous recordings from the cortical tissue are expected to ease the observation of assembly activity, it implies on the other hand an increase in the number

of parameters to be estimated. It is usually infeasible to simply extend existing methods to such massively parallel data due to a combinatorial explosion and a lack of reliable statistics if individual spike patterns are considered. Due to limitations in the length of experimental data, in particular in respect to stationarity, all parameters of the full system cannot be estimated. Thus new concepts need to be developed and I will give a short review on the methods we developed that allow the analysis of massively parallel (hundred or more) spike trains for correlated activities [**3**].

Alternatively, one may directly observe a measure that reflects the activity of populations of neurons, as does the local field potential (LFP). It has been conjectured that LFP oscillations may represent an alternative network-averaged signature of assembly activations. With the aim to test this hypothesis we study and found that in different species and brain areas spikes are locked to the LFP and the locking may even increase with learning. Furthermore, we found that excess spike synchrony is much better locked to the LFP than chance synchronous events or individual spikes clearly indicating that significant excess spike synchrony reflects coordinated network activity on larger scales as expressed by the LFP [**4**].

In this presentation I will give an overview of the potential obstacles in the correlation analysis of parallel neuronal data and possible routes to overcome them.

References.

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Cell and Tissue Biophysics; Saturday, July 2, 11:00

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Role and activity of some chosen voltage-gated K+ and Na+ channels mathematical description and analyses.

Ion channels play crucial role in the process of conduction of electrical impulses, particularly in nerve and muscle cells. Channels are integral proteins immersed in the cells lipid bilayer, which itself has usually poor ionic permeation. Channels third order structure creates a transmembrane pore a passage for ions. As comes out from experiments, permeability of ions through channels fluctuates in time, and is determine by varying structure of the channel. Modulation of ionic flux is called gating, which may be driven by different stimuli like chemical species or variation of electric potential. It is interesting that even if channel is subjected to the constant, positive transmembrane voltage that should keep it open, its permeability decreases after short time channel inactivation. It is than clear that the voltage gating is not the only one mechanisms of gating present in ion channels. In this paper we will discuss, so called ball and chain model of inactivation addressed to potassium Shaker channel [1-3]. Polypeptide ball a part of the channels protein that is responsible for inactivation, is treaded as a Brownian particle tethered on polypeptide chain. Its wandering was described by means of diffusion (parabolic and hyperbolic operators) [4,5]. First passage time of the ball was calculated and compared with experimental data [2]. Second part of the paper is devoted to the sodium channel activity in rat prostate cancer cells as well as human breast cancer cells. Fractal methods were used to analyze quantitative differences in secretory membrane activities of two rat prostate cancer cell lines (Mat-LyLu and AT-2) of strong and weak metastatic potential, respectively [6]. Each cells endocytic activity was determined by horseradish peroxidase uptake. Digital images of the patterns of vesicular staining were evaluated by multifractal analyses: generalized fractal dimension (Dq) and its Legendre transform f(a), as well as partitioned iterated function system semifractal (PIFS-SF) analysis. These approaches revealed consistently that, under control conditions, all multifractal parameters and PIFS-SF codes determined had values greater for Mat-LyLu compared with AT-2 cells. This would agree generally with the endocytic/vesicular activity of the strongly metastatic Mat-LyLu cells being more developed than the corresponding weakly metastatic AT-2 cells. All the parameters studied were sensitive to tetrodotoxin (TTX) pre-treatment of the cells, which blocked voltage-gated Na+ channels (VGSCs). Some of the parameters had a simple dependence on VGSC activity, whereby pre-treatment with TTX reduced the values for the MAT-LyLu cells and eliminated the differences between the two cell lines. For other parameters, however, there was a complex dependence

on VGSC activity. The possible physical/physiological meaning of the mathematical parameters studied and the nature of involvement of VGSC activity in control of endocytosis/ secretion are discussed. Basically, the same sort of approach had been used to analyze the endocytic membrane activities of two human breast cancer cell lines (MDA-MB-231 and MCF-7) of strong and weak metastatic potential, respectively, were studied in a comparative approach [7]. Uptake of horseradish peroxidase was used to follow endocytosis. Dependence on ionic conditions and voltage-gated sodium channel (VGSC) activity were characterized. Fractal methods were used to analyze quantitative differences in vesicular patterning. Digital quantification showed that MDA-MB-231 cells took up more tracer (i.e., were more endocytic) than MCF-7 cells. For the former, uptake was totally dependent on extracellular Na+ and partially dependent on extracellular and intracellular Ca2+ and protein kinase activity. Analyzing the generalized fractal dimension (D(q)) and its Legendre transform f(alpha) revealed that under control conditions, all multifractal parameters determined had values greater for MDA-MB-231 compared with MCF-7 cells, consistent with endocytic/vesicular activity being more developed in the strongly metastatic cells. All fractal parameters studied were sensitive to the VGSC blocker tetrodotoxin (TTX). Some of the parameters had a "simple" dependence on VGSC activity, if present, whereby pretreatment with TTX reduced the values for the MDA-MB-231 cells and eliminated the differences between the two cell lines. For other parameters, however, there was a "complex" dependence on VGSC activity. The possible physical/physiological meaning of the mathematical parameters studied and the nature of involvement of VGSC activity in control of endocytosis/secretion are discussed.

References.

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Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents I; Tuesday, June 28, 17:00

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Determinants of the early hepatitis C viral decline after treatment initiation

The standard model of HCV infection and treatment (Neumann et al., 1998, Science 282(5386):103-107) has played an important role in the analysis of HCV RNA decay after the initiation of interferon (IFN)-based therapy. Using this model and assuming that IFN rapidly reduces the average rate of virion production, it has been possible to estimate the antiviral effectiveness of therapy, as well as to estimate the rate of HCV clearance rate. However it will be shown that this model cannot predict the early viral decline observed with some new direct-acting antiviral (DAA) agents if one uses the HCV clearance rate estimated during IFN-based therapy, which hints that the determinants of HCV decline under treatment may not be fully understood.

Indeed one limitation of the standard model is that the intracellular viral replication, which is directly targeted by DAA agents, is not taken into account. In order to provide a more comprehensive understanding of the determinants of the early viral decline after treatment initiation, a new multi-scale model that considers both intra- and extra-cellular level of infection will be introduced. Simulation studies will show that in the framework of this model, the analysis of HCV RNA decay allows to one to dissect the antiviral effectiveness in blocking different stages of viral replication. Based on data from several clinical trials, HCV kinetics under different classes of DAAs will be compared and the implications of this new approach for the estimation of the HCV clearance rate will be discussed.

Modeling and analysis of tumor invasion I; Tuesday, June 28, 11:00

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Lumped models for tumor progression

(Primary)tumors have been described mainly as localized entities which grow by mitotic duplication (with a given intrinsic maximal growth rate) in restricted conditions. Such restrictions will slow tumor growth rate until a proper value of carrying capacity is reached.

Some of the most popular scenarios, reflecting tumor growth in specific phases of development (avascular phase, 'multipassage'syngenic transplant in mice, development of the necrotic core, angiogenesis, invasive phase,..)can be satisfactorily described by means of the Phenomenological Universality (PUN) method, which assumes that the tumor volume V depends on the growth rate c(t), whose effective time derivative can be approximated by a series expansion in the variable c(t) itself:

dV/dt = c(t) V; dc/dt = -alpha c - beta c2 +...

Retaining only the constant term we get the unlimited growth U(0), while by considering the linear term the Gompertz law U(1) is obtained, accounting for a time-varying growth rate and a constant carrying capacity.U(2), which is the following term, corresponds to the so called West law, whose main characteristics is that of accounting for tumor vascularization through an 'optimal' fractal network. As a matter of fact, U(2) entails a variation in the overall tumor carrying capacity, that in a more general sense becomes not only dependent from the limiting volume for tumor development, but on the overall environmental conditions, including nutrients availability, switch to different metabolic pathways, hormonal influences and so on.

Provided the two main parameters, i.e. growth rate and carrying capacity, are modulated in time to properly account for the internal metabolism and the relationship between the tumor and its environment respectively, a full description of the 'natural history' of the tumor can finally be obtained. Comparison with available data and clinical description (e.g. for the case of prostate cancer) will help in finely modulating the model parameters. Even more interestingly, such a general model is suitable for 'theoretical' validation of therapeutic efficiency. The effect of therapy t(t), whose functional form can be expressed in terms of tumor radiosensitivity, drug resistance, etc., can be incorporated into Eqn. 1 by substituting c(t) with the difference c(t) - t(t). Spatially inhomogeneous tumor patterns can be included provided different 'clones' of cells are accounted for.

In conclusion, by retaining the tumor biological complexity in the progressively changing values of the growth rate and carrying capacity of the tumor-host system, a easy-to-handle lumped-model can be worked out, which can prove useful to further stimulate and improve cooperations between theoreticians and clinicians.

Epidemiology, Eco-Epidemiology and Evolution; Saturday, July 2, 11:00

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Multi-scale modelling of human sleep

Sleep is a complex dynamic process, regulated both by "long time" circadian and homeostatic rhythms and the alternance between Rapid Eyes Movement (REM) and non REM (NREM) sleep and by the occurrence of peculiar "short-time" transient Electro Encephalo Graphics (EEG) events, namely Transient Synchronized EEG Patterns (TSEP), which are thought to be expression of synchronous cortical neuron discharges and are supposed to play the main role in the building-up of NREM sleep and flexible adaptation against perturbations. Our study aims at collecting, analyzing and modeling the time series of TSEP related to the achievement, maintenance and interruption of NREM sleep, in physiological conditions.

Semigroups of Operators in Mathematical Biology I; Wednesday, June 29, 08:30

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Split-up algorithm in the metric space for the equations of structured population dynamics

The talk is based on the joint research with Jose Carillo, Rinaldo Colombo, Anna Marciniak-Czochra and Agnieszka Ulikowska. As the example of the structured population equations we mean the equation of so-called age-structured model (transport equation in a half space with non-local boundary conditions) or size structured model (transport equation with an integral term in space on the right hand side), see for more details B. Perthame "Transport equations in mathematical biology" 2007. From the biological reason there is a need for using initial data in the space of Radon measures. Using the Lipschitz-bounded distance (flat metric) we prove Lipschitz dependence of the solutions to linear and nonlinear system w.r.t. initial data and coefficients of equations. Significant simplifications of the calculations is done by using the split-up algorithm, dealing separately with a semigroup of transport and a semigroup of an integral kernel operator.

Applications of nonnegative Radon measure spaces with metric structure to population dynamic models; Wednesday, June 29, 17:00

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Mertics on the space of the measures and transport equation

The talk will be a short introduction to the issue of abstract methods of Wasserstein and related metrics in the context of the their applications to solutions in the space of Radon measures for linear and nonlinear PDEs. However the topic was studied in many aspects of PDEs coming from mathematical physics, but in the context of mathematical biology it is not very well understood. As an introductory talk to the mini-symposium we will give some survey of the most important facts, to give some general feeling of the topic.

Game theoretical modelling and optimization in evolution and ecology II;
Tuesday, June 28, 14:30

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Evolutionary games on graphs

Evolutionary game dynamics models have been mainly studied on homogeneous infinite populations. However, real populations are neither homogeneously mixed nor infinite. This study investigates the stochastic evolutionary game dynamics in structured populations as represented by graphs. In this talk, we consider analytically the fixation probability and the speed of the evolutionary process (absorption time) when a single mutant individual invades into three simple graphs of finite number of vertices: the star, the circle and the complete graph. Applying the obtained results, it is then shown the significant impact that the structure of the population might have on the evolutionary process. As a specific example, we consider a Hawk-Dove type game. Finally, it is demonstrated that although the update rule (evolutionary dynamics) of the evolutionary process does not significantly affect the evolution of the invader mutants in homogeneous populations, it might cause significant changes in populations with a non-homogeneous structure.

References.

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[2] Broom, M., Hadjichrysanthou, C., Rychtar, J. (2011), *Evolutionary games on star graphs under various updating rules* Dynamic Games and Applications (submitted).

Stem cells and cancer; Wednesday, June 29, 14:30

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A progenitor cell origin of myeloid malignancies

All cancers rely on cells that have properties of long-term self-renewal or stemness to maintain and propagate the tumor, but the cell of origin of most cancers is still unknown. Here, we design a stochastic mathematical model of hematopoietic stem and progenitor cells to study the evolutionary dynamics of cancer initiation. We consider different evolutionary pathways leading to cancer-initiating cells in JAK2V617F-positive myeloproliferative neoplasms (MPN): (i) the JAK2V617F mutation may arise in a stem cell; (ii) a progenitor cell may first acquire a mutation conferring self-renewal, followed by acquisition of the JAK2V617F mutation; (iii) the JAK2V617F mutation may first emerge in a progenitor cell, followed by a mutation conferring self-renewal; and (iv) a mutation conferring self-renewal to progenitors may arise in the stem cell population without causing a change in the stem cell's phenotype, followed by the JAK2V617F mutation emerging in a progenitor cell. We find mathematical evidence that a progenitor is the most likely cell of origin of JAK2V617F-mutant MPN. These results may also have relevance to other tumor types arising in tissues that are organized as a differentiation hierarchy.

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Invariant Measure for the Stochastic Models of the Population Dynamics with Spatial Diffusion

We consider a stochastic equations system modeling population dynamics of competition and prey-predator type with diffusion in a territorial domain. We prove the existence of an invariant measure for the competition and the prey-predator stochastic models. To demonstrate these results, we apply the Krylov-Bogoliubov's theorem, who requires an estimation of the solution of the stochastic equations system.
To obtain the appropriate estimates we apply the Itô's formula in infinite dimension space to an adequate function.

References.

[1] S. Hamdous, H. Fujita Yashima: *Mesure invariante pour le système d'équations stochastiques du modèle de compétition avec diffusion spatiale*. Rend. Sem. Mat. Padova, vol 122 (2009) p.p. 85-98.
[2] S. Hamdous, L. Manca, H. Fujita Yashima: *Mesure invariante pour le système d'équations stochastiques du modèle de proie-prédateur avec diffusion spatiale*. Rend. Sem. Mat. Padova, vol 124 (2010) p.p. 57-75.
[3] R. Rudnicki: *Long-time behaviour of a stochastic prey-predator model*. Stoch. Proc. Appl., vol. 108 (2003), pp. 93-107.
[4] E. Tornatore: *Stochastic equation of population dynamic with diffusion on a domain*. Rend. Circ. Mat. Palermo, Serie II, Tomo 52 (2003), pp. 15-29.

Fluid-structure interaction problems in biomechanics; Saturday, July 2, 08:30

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Excitable tissues in fluids

A wide range of numerical, analytical, and experimental work in recent years has focused on understanding the interaction between fluids and elastic structures in the context of cardiovascular flows, animal swimming and flying, cellular flows, and other biological problems. While great progress has been made in understanding such systems, less is known about how these excitable tissues modulate their mechanical properties in response to fluid forces and other environmental cues. The broad goal of this work is to develop a framework to integrate the conduction of action potentials with the contraction of muscles, to the movement of organs and organisms, to the motion of the fluid, and back to the nervous system through environmental cues. Such coupled models can then be used to understand how small changes in tissue physics can result in large changes in performance at the organ and organism level. Two examples will be discussed in this presentation. The first example considers how active contractions generated by the cardiac conduction system can enhance flows in tubular hearts, particularly at low Reynolds numbers. The second example considers how the interactions between pacemakers in the upside down jellyfish can alter feeding currents generated by the bell pulsations. In both cases, the ultimate goal is to simulate the electropotentials in the nervous system that trigger mechanical changes in 1D fibers representing the muscular bands. The muscular contractions then apply forces to the boundaries that interacts with the fluid modeled by the Navier-Stokes equations. The computational framework used to solve these problems is the immersed boundary method originally developed by Charles Peskin.

Bioinformatics and System Biology; Wednesday, June 29, 14:30

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GENPHEN: Genotype/Phenotype Association with Reference to Phylogeny

When genome sequences are obtained from organisms with different associated phenotypes, it should be possible to identify those sequence properties which confer a given phenotype. However, the evolutionary relationships between organisms lead to non-independence between the sequence properties. For example, the HIV-1 virus has a population structure reflecting both transmission between individuals and evolution of the HIV-1 quasispecies within each patient. This non-independence can introduce interdependence between unrelated mutations giving a false appearance of causation. These evolutionary relationships are an issue even in HIV-1 where recombination is rapid, and are pervasive in humans, where linkage disequilibrium is extensive. In human disease studies, this can sometimes be overcome by comparing siblings: alleles common only in sick siblings are likely true causative alleles. GENPHEN identifies, in a phylogenetic reconstruction, sibling lineages where the phenotype varies. Then, GENPHEN uses modified proportional hazard models to identify causal polymorphisms. GENPHENs advantages include: speed practical for high-throughput sequence data, estimates of relative strength or speed of different effects, and improved precision even vs. other tree-based methods: 50%-300% improvement in precision at same recall, either to predict experimental correlations (obtained from STRING: http://string-db.org/) or in simulations under biologically reasonable parameters on HIV quasispecies sequence trees.

Analysis of mathematical models for cancer growth and treatment, Part IV; Wednesday, June 29, 08:30

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The End of Linear-Quadratic Era in Radiation Biology

We review mathematical and biological grounds for the linear-quadratic (LQ) model of irradiated cell survival. The LQ model was a tool of choice in quantitative radiation biology for more than 60 years. We show that some of the premises of the LQ model are unrealistic, especially for intermediate and high doses of radiation. Furthermore, we develop a more realistic cell survival model based on rigorous accounting for microdosimetric effects [1]. The new model is applicable to low, intermediate, and high acute doses of radiation, and unlike the LQ model, it does not assume that the distribution of the number of primary lesions is Poisson. For small doses, the new model can be approximated by the LQ model. However, for high doses, the best fitting LQ model grossly underestimates cell survival. The same is also true for the conventional LQ model, only more so. It is shown that for high doses, the microdosimetric distribution can be approximated by a Gaussian distribution, and the corresponding cell survival probabilities are compared.

This is a joint work with Dr. Marco Zaider from the Memorial Sloan-Kettering Cancer Center, New York.

References.

[1] L.G. Hanin and M. Zaider (2010), Cell-survival probability at large doses: an alternative to the linear-quadratic model, Physics in Medicine and Biology, v. 55, pp. 4687-4702.

Developmental Biology; Wednesday, June 29, 17:00

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Dorsal-ventral patterning in sea urchin and *Drosophila* embryos

The dorsal-ventral axis in *Drosophila* is specified by gradients of bone morphogenetic proteins (BMPs). While initially secreted in a broad region, later concentrate into a narrow band, designating the dorsal-most 10% of the embryo. Modeling papers have focused on the dynamics seen in *Drosophila*, but the same mechanism specifies the sea urchin axis. Yet in urchins, the BMP secretion and expression domains are complementary. Reaction-diffusion models are considered for the patterning seen in both organisms, but are limited in their capabilities to reproduce the sharp curvature seen in the biological data. While positive feedback is likely responsible for the further concentrating the BMP gradient, we consider alternative types that could account for the patterning seen in both organisms.

Modeling mass spectrometry proteomics data using nonparametric regression methods

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The amount and complexity of the data collected from the mass spectrometry instruments has outpaced the methodological developments in their processing. We propose a number of approaches to address the issues arising in modeling such data. The methods used include local polynomial kernel regression with adaptive bandwidth selection and wavelet methods. We address the issues of non-stationarity in the variance process and correlated errors. In this talk, we provide the results of preliminary simulation studies and apply the methods to a lung cancer SELDI-TOF MS data set.

Mechanics of the cytoskeleton and cortical actin at the cellular level;
Saturday, July 2, 08:30

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Measuring the mechanical properties of cell monolayers

Cell monolayers are continuously exposed to mechanical stresses in development and normal physiological function. Mutations in cytoskeletal and cell-cell adhesion proteins lead to patient symptoms associated with increased tissue fragility, however a method for characterizing monolayer mechanics is lacking. We have developed a novel system for tensile testing of monolayers which are suspended between two test rods. One of the rods is rigid acting as a reference whilst the other is flexible to allow for force measurement. Analysis of stress-strain curves during monolayer extension enables the determination of a monolayer in plane elastic modulus. The contribution of different cytoskeletal filaments to monolayer elasticity is ascertained by treatment with inhibitors. By depolymerising the actin cytoskeleton with Latrunculin B a substantial decrease in the elastic modulus can be observed.

Epidemics; Tuesday, June 28, 11:00

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Epidemic Models for Leishmaniasis: Elucidation of Key Processes and Parameters

Leishmaniasis is a vector-borne Neglected Tropical Disease. It is caused by Leishmania protozoa transmitted between humans by infected female sandflies. Previously associated with the impoverished in Africa, Leishmaniasis is now considered to be an emerging disease as it spreads across a range of locations from South America to the Mediterranean Basin. We present a mathematical model for the epidemiology of Leishmaniasis. We use a range of techniques including elasticity analysis to make a comprehensive assessment of the importance of various processes and parameters in both the ignition and maintenance of disease spread. We show that the vector population is the critical link when determining whether an infection can become established in a naive population, but that the host population is key in the perpetuation of endemic infection. We conclude by discussing the implications of our analysis for the control of Leishmaniasis in different parts of the world.

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"Modeling Control Strategies for Influenza Epidemic with the Emergence and Evolution of Drug Resistance"

One of the most important problems in preventing influenza outbreak is the spread of drug resistance during disease infection. In this study, we model an influenza epidemic considering emergence and evolution of drug resistance. Since antiviral treatment is not effective on resistant infecteds, we implement the quarantine control strategy to mitigate the final size of the epidemic. In addition, prophylaxis and treatment strategies are considered in our model. A system of ordinary differential equation is formulated for a SIQR influenza epidemic model. The influences of these three main control strategies are investigated on the final size of the epidemic. Numerical simulations show that implementation of optimal quarantine and treatment together leads to outbreak containment. The basic reproduction numbers and control reproduction numbers are calculated for sensitive and resistant strains.

Crowd Dynamics: Modeling, Analysis and Simulation (Part 1); Wednesday, June 29, 11:00

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Particle systems and kinetic equations modelling interacting agents in high dimension

We explore how concepts of high-dimensional data compression via random projections onto lower-dimensional spaces can be applied for tractable simulation of certain dynamical systems modeling complex interactions. In such systems, one has to deal with a large number of agents (typically millions) in spaces of parameters describing each agent of high-dimension (thousands or more). Even with todays powerful computers, numerical simulations of such systems are prohibitively expensive. We propose an approach for the simulation of dynamical systems governed by functions of adjacency matrices in high-dimension, by random projections via Johnson-Lindenstrauss embeddings, and recovery by compressed sensing techniques.

Moving Organisms: From Individuals to Populations; Wednesday, June 29, 17:00

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From individual to collective behaviour of coupled velocity jump processes: a locust example

A class of stochastic individual-based models, written in terms of coupled velocity jump processes, is presented and analysed. This modelling approach incorporates recent experimental findings on behaviour of locusts. It exhibits nontrivial dynamics with a phase change behaviour and recovers the observed group directional switching. Estimates of the expected switching times, in terms of number of individuals and values of the model coefficients, are obtained using the corresponding Fokker-Planck equation. In the limit of large populations, a system of two kinetic equations with nonlocal and nonlinear right hand side is derived and analyzed. The existence of its solutions is proven and the systems long-time behaviour is investigated. Finally, a first step towards the mean field limit of topological interactions is made by studying the effect of shrinking the interaction radius in the individual-based model in the large population limit.

Modeling of immune responses and calcium signaling III; Wednesday, June 29, 17:00

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B cell activation triggered by the formation of the small receptor cluster: a computational study

B cells are activated in response to the binding of polyvalent ligands, which induces the aggregation of B cell receptors. The formation of even small clusters containing less than 1% of all the receptors is sufficient for activation. This observation led us to the model in which the receptor cluster serves only as a switch that turns on the activation process, involving also the remaining receptors. We have proposed that the system is bistable, and thus its local activation may start the propagation of a traveling wave, which spreads activation over the entire mebrane. We found that the minimal size of the activatory cluster decreases with the thickness of the cytoplasm and kinase diffusion coefficient. It is particularly small when kinases are restricted to the membrane. These findings are consistent with the properties of B cells, which have extremely thin cytoplasmic layer and in which the receptor interacting Src family kinases are tethered to the membrane.

Modeling and analysis of tumor invasion I; Tuesday, June 28, 11:00

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Mechanisms of glioma tumor invasion

Invasion of malignant glioma tumors is typically very aggressive and a highly complex phenomenon involving molecular and cellular processes at various spatiotemporal scales, whose precise interplay is still not fully understood. By means of a mathematical modeling, we compare theoretical results to the experimental data and deduce microscopic interactions (cellular mechanisms) from microscopic and macroscopic observables (experimental data). In particular, using multicellular spheroid data, we exhibit the key role of migration/proliferation in tumor invasion dynamics. Finally, we study the influence of vascularization on tumor growth with the help of a combination of in vivo data from implanted xenografts of U87 MG in nude mice brain and a mathematical model.

Delay Differential Equations and Applications II; Saturday, July 2, 08:30

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Delay in Structured Population Models.

The aim of this work is to put in evidence the onset of delays, distributed delays and state-dependent delays in models, especialy in threshold models for structured population dynamics. A unified approach to these models is provided, based on solving the corresponding balance law (hyperbolic P.D.E.) along the characteristic lines and showing the common underlying ideas. Size and age-structured models in different fields are presented: fish populations, insect populations, cell proliferation and epidemics. Existence and uniqueness results related to such models will be discussed as well as some results of semigroup's properties , of stability, and bifurcation results.

Turing !! Turing?? on morphogenesis via experimental and theoretical approaches; Wednesday, June 29, 17:00

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Periodic patterning across heterogeneous fields: insights from embryonic feather development

Vertebrate skin is characterized by its patterned array of pigments and structural appendages such as feathers, hairs and scales. A number of lines of evidence point to the action of a Turing type mechanism in laying out the periodic pattern of feathers and hairs in the developing skin. Several candidate Activator and Inhibitor pathways which act during this process have been identified, though the full set of interactions between them remains to be defined. Bone morphogenetic proteins (BMPs) act as key Inhibitors during feather formation, and we have uncovered different sensitivities to this Inhibitor in different regions of the skin. We then focused on combining mathematical modeling and experimental approaches to explore the pattern outcomes and propensity for pattern change arising from the operation of a Turing type system across a field with unequal Inhibitor sensitivities.

Cellular Systems Biology; Tuesday, June 28, 14:30

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Extensions to Kinetic Flux Profiling to determine the distribution of fluxes in the central carbon metabolism of Arabidopsis thaliana

Determining the stationary and transient behaviors of metabolic networks is tightly coupled with quantitative descriptions of metabolic states, characterized by the distribution of reaction fluxes and metabolite concentrations. Despite recent progress in methods for estimating the flux distributions in a metabolic network based on ^{13}C labeled metabolomics data, the existing approaches ultimately rely on precise stoichiometry, atomic mappings, and availability of data for all metabolites participating the analyzed biochemical reactions. Kinetic Flux Profiling (KPF) is a recently proposed method for determining reaction fluxes based on the washout of the unlabeled fraction of a metabolite pool and is described mass-action-like differential equation model [1,2]. However, without substantial assumptions, KPF is applicable only to linear pathways.

Here we propose an extension of KPF based on simulated annealing that allows analysis of branched and circular pathways. Our approach does not rely on atomic maps, and can efficiently utilize the time-resolved distribution of isotopomers to determine the fluxes in an experimentally studied metabolic network. With the proposed approach, we quantify the flux distribution of the central carbon metabolism of Arabidopsis thaliana based on the time-resolved isotopomoer data over 60 minutes for 16 metabolites together with information about their subcellular localization. We investigate the robustness of the findings due to partial data inclusion with respect to both metabolites and different time scales. In addition, we demonstrate that our method together with the employed data can be used to discriminate between different models of the underlying metabolic network.

References.

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[2] J. Yuan, B.D. Bennett, J.D. Rabinowitz (2008) *Kinetic flux profiling for quantification of cellular metabolic fluxes* Nat. Prot. **1** 1328–1340.

Mathematical modeling of biomechanical regulation in bone tissue (Session I); Wednesday, June 29, 08:30

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Bone fibrillogenesis and mineralization: Quantitative analysis and implications for tissue elasticity

Data from bone drying, demineralization, and deorganification tests, collected over a time span of more than eighty years, evidence a myriad of different chemical compositions of different bone materials. However, careful analysis of the data, as to extract the chemical concentrations of hydroxyapatite, of water, and of organic material (mainly collagen) in the extracellular bone matrix, reveals an astonishing fact: it appears that there exists a unique bilinear relationship between organic concentration and mineral concentration, across different species, organs, and age groups, from early childhood to senility: During organ growth, the mineral concentration increases linearly with the organic concentration (which increases during fibrillogenesis), while from adulthood on, further increase of the mineral concentration is accompanied by a decrease in organic concentration. These relationships imply unique mass density-concentration laws for fibrillogenesis and mineralization, which - in combination with micromechanical models - deliver 'universal' mass density-elasticity relationships in extracellular bone matrix - valid across different species, organs, and ages. They turn out as quantitative reflections of the well-instrumented interplay of osteoblasts, osteoclasts, osteocytes, and their precursors, controlling, in a fine-tuned fashion, the chemical genesis and continuous transformation of the extracellular bone matrix. Considerations of the aformentioned rules may strongly affect the potential success of tissue engineering strategies, in particular when translating, via micromechanics, the aformentioned growth and mineralization characteristics into tissue-specific elastic properties.

Poster Session; Friday, July 1, 20:00

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Evolutionary optimization of negative and co-operative autoregulation in RK2 plasmids

The central control operon of the RK2 plasmid is negatively and co-operatively autoregulated by dimers of two global plasmid regulators, KorA and KorB. Several roles for negative feedbacks in biosystems have been proposed by many researchers, and these roles include reduction of noise, increased robustness, speeding of response time and reducing burden on host. In this work, we seek to explain the evolutionary adaptation of the RK2 central control operon in terms of these proposed roles, using comparative analyses of the wild type system with a progression of simpler systems. We used a stochastic, multi-scale model that includes negative and co-operative gene autoregulation of the central control operon of the plasmid, plasmid replication and host cell growth and division. Keeping track of an RK2 plasmid line, we can observe the dynamics of protein abundance from entry of the plasmid into a naive host through to steady state. The comparative analyses between the regulation in models of the wild type central control operon and models with simpler, adequate architectures show a speed up of response time and a decrease in burden for the host, indicated by a decrease in the number of produced mRNAs. In comparison, minimal increased robustness and reduction of internal noise in steady state of bacterial growth phase were observed in these anayses. We conclude that possible reasons for evolution of the complex negative feedback regulation of the RK2 central control operon are the optimization of fast response times and reduced burden to host, and that it is unlikely that this regulatory system has evolved to reduced noise or increase robustness.

Speciation; Wednesday, June 29, 08:30

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Dobshansky-Muller incompatibilities in parapatry

The accumulation of Dobshansky-Muller incompatibilities is a widely accepted mechanism for speciation in allopatric populations. In this presentation, we analyze the scope and limits of this mechanism if the populations are not fully separated. We use classical migration-selection models to determine the limiting rates of gene-flow that allow i) for the origin and ii) for the maintenance of a single Dobshansky-Muller incompatibility in parapatry. We use our results to discuss the importance of ecological and genetic factors (such as recombination rate, strength of the incompatibility, level of local adaptation) for the speciation process in the presence of gene-flow.

Poster Session; Friday, July 1, 20:00

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Body mass variation in a two-dimensional regular network

In this work we study the mass variation of the human body using the model of Chow and Hall[1]. We implement the equations that provide a framework to consider a model for the single person mass dynamics, as well as a network in which agents can interact among them. We use as a components of the model the total energy expenditure per day (E) and the daily energy intake (I). We feed our model with data obtained from the FAO and other references[2]. We compare our results with data from mexican tables for persons with different ages. In the case of the network we took a two-dimensional regular lattice with 400 agents, each agent have a initial mass (Mo), initial intake (Io), and an initial total energy expenditure (Eo).In order to fit our model we proposed that the intake equation changes like I(t)=Io(deltaM)gamma, where deltaM=M(t)/Mo. We consider ages for the agents between 19 and 65 years.We could see how the change of the initial energy conditions produced large changes in the average mass of the network and in some cases the agent's mass can big very large and also can have low values, ie, there is a large spread in the mass values. Also we studied how the average mass changes when the agents have different numbers of links. We have implemnted the model to cover ages between 0 and 18 years old, as well.

Analysis of mathematical models for cancer growth and treatment, Part I;
Tuesday, June 28, 11:00

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Wave propagation and tumour growth

Travelling waves (TWs), a particular type of solutions of Reaction-Diffusion systems which move with constant speed, have been widely employed to model various aspects of tumour invasion. In this lecture, I shall deal with some TWs that have been recently used to describe particular types of tumour growth. More precisely, their capability to reproduce some observed morphological features will be addressed, and the relation between their dynamical properties and the underlying biological processes will be discussed.

Modeling and analysis of tumor invasion II; Tuesday, June 28, 14:30

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On the determination of the optimal radiation dose on a target tissue volume

A key problem in radiotherapy consists in determining the appropriate dose to be delivered to a clinical target in order to achieve maximum efficiency over malignant tissue on the one hand, while at the same time sparing healthy tissue and organs at risk as much as possible. In this lecture a model problem will be presented and discussed to address that issue , and a number of consequences of the behaviour of the corresponding solutions will be discussed

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents I; Tuesday, June 28, 17:00

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PK-PD Models for viral kinetics of combination treatments in viral hepatitis

Even in the era of direct anti-viral agents, interferon-based combination treatments are very important. It is well known that serum levels of long-acting interferons can vary considerably and that PK of interferon has an observable influence on viral kinetics also in combination treatment. Therefore, reliable viral kinetic modeling of interferon-based treatments should deal with non-constant treatment efficacies based on PK-PD models.

The first topic of the talk will focus on modeling results which analyze the effect of different PK and treatment schedules of long-acting interferons on the treatment efficacy and the development of resistance. Overall, high or low peak-to-trough levels of the PK of interferon has only minor influence on the development of resistance as long as the overall interferon efficacy is not changed.

Secondly, we will illustrate that modeling PK of direct antivirals can be quite challenging and simple open one-compartment models may be too simplistic to obtain reliable modeling results which fit with observed PK profiles.

Besides some theoretical background and illustration of simulation results, we will also show some clinical data analysis where a full PK-PD approach can give some indications how to optimize treatments.

Neurosciences; Thursday, June 30, 11:30

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Network reconstruction from nonstationary spike trains

Existing approaches to the problem of extracting neuronal connectivity from spike data [1,2] assume that the network is in a stationary state, which it is not in many experiments. Here we describe a method for inferring both the network connectivity and the time-dependent external drive that causes the nonstationarity.

Consider an experiment in which the neurons recorded are subjected repeatedly to a potentially unknown external input (such as would arise from sensory stimulation). The spikes are assumed to be binned in time and represented by a binary array: $S_i(t,r) = 1$ indicates a spike and $S_i(t,r) = -1$ indicates no spike by neuron i in time bin t of repetition r of the measurement. We fit these data to the simplest kind of binary stochastic model: At time step t of repetition r, each formal neuron receives a net input, $H_i(t,r) = h_i(t) + \sum_j J_{ij} S_j(t,r)$, and it takes the value $+1$ at the next step with a probability given by a logistic sigmoidal function $1/[1+\exp(-H_i(t,r))]$ of $H_i(t,r)$. Maximizing the likelihood of the data leads to learning rules

$$\delta h_i(t) = \eta_h \{\langle S_i(t+1,r)\rangle_r - \langle \tanh[H_i(t,r))]\rangle_r]\} \quad (1)$$

$$\delta J_{ij} = \eta_J \{\langle S_i(t+1,r) S_j(t,r)\rangle_{rt} - \langle \tanh[H_i(t,r)] S_j(t,r)\rangle_{rt}\} \quad (2)$$

for the model parameters – the couplings J_{ij} and external inputs $h_i(t)$. For weak coupling or densely connected networks, faster alternative algorithms are possible [3], based on expanding (1) and (2) around mean-field and TAP [4] equations for $m_i(t) = \langle S_i(r,t)\rangle_r$.

Here we present results of applying both this and methods assuming stationarity to (1) data generated by the stochastic model itself (the realizable case), (2) data from a realistic computational model of a small cortical network, and (3) data recorded from salamander retina under visual stimulation. We show that, in all three cases, performing the reconstruction assuming stationarity systematically overestimates the couplings in the network: the algorithms effectively invent fictitious couplings to explain stimulus-induced correlations. The nonstationary treatment outlined above enables us to find, for sufficient data, the correct (weaker) couplings and to extract the time-dependence of the external input.

References.

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Epidemics; Tuesday, June 28, 17:00

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Evaluating control strategies for TB in the Torres Strait Island region

There is a high prevalence of tuberculosis (TB) in Papua New Guinea (PNG), which is exacerbated by the presence of drug-resistant TB strains and HIV infection. This is an important public health issue not only locally within PNG, but also in Australia due to the high cross-border traffic in the Torres Strait Island–Western Province (PNG) treaty region. We use a metapopulation model to evaluate the effect of varying control strategies in the region, and perform a sensitivity analysis to determine the most important parameters.

Moving Organisms: From Individuals to Populations; Wednesday, June 29, 17:00

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A nonlinear parabolic-hyperbolic PDE model for contact inhibition of cell-growth

We consider a parabolic-hyperbolic system of nonlinear partial differential equations which describes a simplified model for contact inhibition of growth of two cell populations. In one space dimension it is known that global solutions exist and that they satisfy the segregation property which reflects the inhibition mechanism: if the two populations are initially segregated - in mathematical terms this is translated into disjoint spatial supports of their densities - this property remains valid for all later times. In this talk, we use recent results on transport equations and Lagrangian flows to obtain similar results in the case of arbitrary space dimensions.

Reports from US - African BioMathematics Initiative: Conservation Biology; Saturday, July 2, 14:30

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Using individual-based movement models to investigate mechanism of emergent herding behavior in African buffalo

Ungulate species worldwide have been observed to aggregate into variable-sized temporary or permanent herds. One important thread of research in ecology has been to try to understand why such aggregations occur, and what mechanisms control the dynamics of herding. Most research to date has focused on population-level herding dynamics, and evidence exists for both bottom-up control, wherein herds form as a result of patchy resource distribution, and top-down control, in which predator avoidance controls aggregation dynamics. In this study we used an individual-based model (IBM) to test whether population-level herding patterns emerge from individual-level movement decisions, and to examine the influence of bottom-up mechanisms on this emergent phenomenon. We used African buffalo (Syncerus caffer) in Kruger National Park, South Africa as our focal population, and simulated individual movement based on rules in which each buffalo attempts to meet its daily resource requirements. Our model did not incorporate birth or death processes but focused solely on spatial dynamics. To validate our model we compared herd size distribution observed in our IBM to herd size distributions observed in Kruger National Park between 1985 and 2001. Using IBM we found that herding behavior was an emergent property. We were able to emulate empirical herd size distributions when resources were available at low levels in large parts of the study area but abundant in small scattered areas. Our study demonstrates that empirically-based patterns of herding behavior can emerge from bottom-up mechanisms alone. Our continued research will attempt to elucidate whether predator avoidance behavior can produce similar empirically-validated herding patterns and how a combination of top-down and bottom-up mechanisms might change population-level herding dynamics.

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An on-pathway step explains the kinetic of prion amyloid formation

The pathogenic process of the transmissible spongiform encephalopathies diseases, is typically associated with the conformational conversion of the so-called prion protein (PrP). The protein-only model asserts that the misfolded isoform represents the infectious prion agent, self-propagating by binding to the normal PrP and inducing its conversion to the abnormal form [6]. This scenario was quantitatively described as a nucleation-dependent amyloid polymerization [4]. However, we obtained experimental results inconsistent with this theory. Indeed although the dynamics of polymerization resemble a simple nucleus-dependent fibrillogenesis, neither the initial concentration dependence nor off-pathway hypothesis fit completely with experimental results when submitted to theoretical models [1], comparable discrepancies were obtained by other [2,3,4,5]. We thus hypothesise the existence of an on-pathway before nucleation associated with a conformational change that generates intermediate conformations compatible with nucleation and polymerization. Using electron microscopy analysis, we observed odd-structures that behaved as precursor of the amyloid formation. We have developed a quantitative model with an explicit description of microscopic processes that takes into account our observations. Then, we confronted, under several conditions, the model predictions with the experimental data. It appears that they are in a good agreement. Several conclusions can be drawn from this model that better explain the nucleation kinetic barrier and prion misfolding. We discuss the consequences of the model in the light of the *in vivo* phenomenon.

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Semigroups of Operators in Mathematical Biology II; Saturday, July 2, 11:00

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Structured and unstructured continuous models for *Wolbachia* infections

Wolbachia is a maternally transmitted bacterium that lives in symbiosis with many arthropod species. We introduce and investigate a series of models for an infection of a diplodiploid host species by Wolbachia. The continuous models are characterized by partial vertical transmission, cytoplasmic incompatibility and fitness costs associated with the infection. A particular aspect of interest is competitions between mutually incompatible strains. We further introduce an age-structured model that takes into account different fertility and mortality rates at different stages of the life cycle of the individuals. With only a few parameters, the ordinary differential equation models exhibit already interesting dynamics and can be used to predict criteria under which a strain of bacteria is able to invade a population. Interestingly, but not surprisingly, the age-structured model shows significant differences concerning the existence and stability of equilibrium solutions compared to the unstructured model.

Keywords: *Wolbachia*, endosymbiosis, cytoplasmic incompatibility

Medical Physiology; Tuesday, June 28, 11:00

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A biomechanical model of the asthmatic airway

When asthmatics come in contact with agonists (e.g. cold air, chemicals or dust), the smooth muscle in the walls of their lung airways contracts, causing wheezing and other breathing difficulties. Over long periods there is also substantial thickening of the muscular airway wall. Mathematical modelling has significant potential to offer insights into the interactions between the signalling pathways that initiate smooth muscle contraction, the mechanical action of cross-bridges within smooth muscle that leads to contraction of the airway and surrounding tissue, and the longer-term impact of wall remodelling on airway function. Here we address some of the mechanical aspects of this problem by modelling an airway as a two-layer annulus in plane strain. The inner layer, representing the airway wall, is modelled as a nonlinear incompressible fibre-reinforced material. The outer layer, representing the surrounding parenchyma, is modelled as a linear compressible viscoelastic material. Airway deformations are induced either by imposing external stresses or via active forces generated in the inner muscular layer. When passively inflated, the airway wall exhibits strain-stiffening and creep. The model reveals differences in patterns of deformation depending on whether inflation is driven by stresses on the inner or outer boundary (reflecting differences between artificial and natural ventilation). The model also shows significant stress gradients across thickened airway walls. Initial results coupling wall and muscle mechanics will also be discussed.

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Mathematical investigation into the effects of the anti-cancer compound RHPS4 on cell-cycle dynamics

The pentacyclic acridinium salt RHPS4 displays anti-tumour properties *in vitro* as well as *in vivo* and is potentially cell-cycle specific. We have collected experimental data and formulated a compartmental model using ordinary differential equations to investigate how the compound affects cells in each stage of the cell cycle. The eukaryotic cell cycle primarily consists of five phases, namely a resting state, G_0, and four cycling phases: G_1, S, G_2 and M phase with cells progressing in this order and then dividing into two cells back in G_1. Understanding how a drug affects the cell cycle could give insight into the drug's mechanism of action and may assist research into potential treatment strategies.

We treated colorectal cancer cells with three different concentrations of the drug and fitted simulations from our models to experimental observations. We found that RHPS4 caused a concentration-dependent, marked cell death in treated cells, which is best modelled by allowing rate parameters in the cell cycle to be time-dependent functions. Our compartmental models fit data from control cells and cells treated with lower concentrations of RHPS4 particularly well. We have also shown that the model is "identifiable", meaning that, at least in principle, the parameter values can be determined from observable quantities. Our fitting procedure generates information on the sensitivity of parameters in the model.

We find that at low concentrations RHPS4 primarily affects the cells' behaviour in the G_2/M phase, and that the drug has a delayed effect with the delay decreasing at larger doses. Since the drug diffuses into the nucleus, the observed delayed effect of the compound is unexpected and is a novel finding of our research into this compound. We propose that secondary effects lead to the induction of observed cell death and that changes in the molecular structure of the non-coding DNA sequences at chromosome ends, called telomeres, might be a precursor of delayed cell death.

Multiscale mathematics of liver: bridging molecular systems biology to virtual physiological human scale; Wednesday, June 29, 11:00

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Regeneration after partial hepatectomy: from cell to organ scale

The liver is a vital organ with a wide range of functions. It plays a key role in detoxification of the blood and is essential for most metabolic functions of the body. One of the outstanding features of the liver is its capacity to regenerate a loss of large parts of its mass within days. This rapid regeneration is of utmost importance for patient survival for example after partial hepatectomy, a process where parts of the liver are surgically removed for example during liver transplantation or the treatment of liver cancer. In liver, function and architecture are tightly coupled. Therefore, a deep understanding of liver regeneration requires an understanding of how functional components like hepatocytes or blood vessels and their spatial organization together affect the regeneration process. In order to study regeneration after partial hepatectomy, we advanced the single-cell based spatial-temporal model in 3D established in [1]. The model is constructed based on experimental data, in particular confocal laser scans and whole slide scans, that were quantified by a novel image processing and analysis chain. It now spans from cellular scale up to organ scale.

The talk introduces the model along with the methods developed to construct it and presents first results obtained by model simulations.

References.

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Poster Session; Friday, July 1, 20:00

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Mechanisms for liver size regulation

The liver is a multi-functional organ that participates in major physiological processes and that possesses a remarkable regeneration capacity. After loss of functional liver mass the liver regrows to its original, individual-dependent size. A transplanted liver adjusts its size to the host organism by increasing in size when small-for-size or decreasing in size when large-for-size. Yet, how does the liver "know" when it has achieved its correct size?

The mechanisms of organ size control are still not well understood. Intracellular signaling pathways that control cell size regulation, cell proliferation and apoptosis have already been studied in the literature. However, organ size control is the collective result of decentralized, individual cell decisions. It is proposed in several works that this collective behavior might be guided by nonlocal interactions mediated through morphogen gradients. Here, we pose the question, whether organ size control can also be accomplished by a mechanism solely based on local intercellular interactions.

Based on a careful review of currently debated mechanisms and recent experiments for organ size regulation we will develop and analyze several model prototypes. We will focus on an Interacting Cell System Model to study especially the implications of local intercellular interactions as well as the regulatory role of organ-intrinsic growth factors and organ-extrinsic growth regulators. The study is part of the Virtual Liver project funded by the German BMBF.

Poster Session; Friday, July 1, 20:00

Symmetry Breaking and Cellular Polarization in Motile Cells

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Chemotaxis is the process by which cells undergo directed motion toward an external signal. In Eukaryotic cells, a precurser to such motion is a symmetry breaking event where proteins responsible for cytoskeletal remodelling and motility self organize to form a front and back. A model developed in collaboration with an experimental group of these regulatory proteins and their associated kinetics is presented. It is shown that this model accounts for observed characteristics not found in other models and provides new insights into the physiologically responsible processes. Novel psuedo-analytic methods for analysing such models will be briefly discussed and connections with experimental observations will be highlighted.

Statistical methods in computational neuroscience II; Wednesday, June 29, 17:00

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A Latent Variable Model for brain serotonin levels as measured by cerebral serotonin transporter and 5-HT_{2A} receptor binding *in vivo*

Today, it is not possible to non-invasively measure the extracellular levels of serotonin (5-HT) *in vivo*. However, indirect measurements can be obtained by positron emission tomography (PET) techniques. A non-linear structural equation model is proposed for describing the association between 5-HT_{2A} receptor binding and serotonin (5-HT) transporter binding as measured by PET imaging. The approach is based on a biological model where the 5-HT_{2A} receptor and serotonin transporter measurements are expressed non-linearly by a common regulator, e.g. the raphe serotonergic output. The proposed model makes it possible to study the association between latent brain 5-HT levels and other end-points, for instance development of mood disorders.

Methods for obtaining approximate maximum likelihood estimates are discussed and new model diagnostic methods based on cumulative residuals are presented.

Biofluids, Solute Transport, and Hemodynamics; Wednesday, June 29, 11:00

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Synchronization of nephrons in vascular networks

Tubuloglomerular feedback (TGF) has an important role in autoregulation of renal blood flow and glomerular filtration rate (GFR). Because of the characteristics of signal transmission in the feedback loop, the TGF undergoes self sustained oscillations in single nephron blood flow, GFR and tubular pressure and flow. Nephrons interact by exchanging electrical signals conducted electrotonically through cells of the vascular wall, leading to synchronization of the TGF mediated oscillations. To study the extent of synchronization we have used laser speckle contrast imaging to measure the blood flow dynamics of 50 – 100 nephrons simultaneously on the renal surface of anesthetized rats. Synchronized TGF oscillations were detected in pairs or triplets of nephrons. The amplitude and the frequency of the oscillations changed with time, as did the patterns of synchronization. Synchronization may take place among nephrons not immediately adjacent on the surface of the kidney. Nephrons are organized in a vascular network, and the interaction between them takes place across the network. To investigate the significance of the network structure, we modeled two alternative network configurations: a linear serial network, and a branching fractal structure. Although synchronization among nephrons was observed in both configurations, the tendency was for in phase synchronization among nephrons in the linear, serial network; whereas more complex in- and out of phase patterns of synchronization was observed in the branching model of the vascular network.

Multiscale mathematics of liver: bridging molecular systems biology to virtual physiological human scale; Wednesday, June 29, 11:00

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Mathematical modelling of liver metabolism — do we need a multi-scale approach?

The liver is the central metabolic organ of the human organism authoritatively involved in the detoxification of xenobiotics (drugs), the homeostasis of numerous blood compounds and production of anti-inflammatory agents. Most of these metabolic functions are accomplished by hepatocytes comprising about two thirds of liver cells. Therefore, mathematical modelling of liver metabolism hitherto has widely focused on the single hepatocytes. However, hepatocytes arranged along the same supporting vessel have different access to oxygen, nutrients and hormones in the blood and therefore differ in their functional capacities. Irregularities of the vascular tree and regional partial occlusions of blood vessels (e.g. caused by swollen cells due to lipid accumulation) may entail that within the organ normoxic and partly ischemic regions coexist. Furthermore, the molecular processes underlying complex physiological liver functions proceed at different time scales: Seconds for the hormonal initiation of glycogen degradation, some weeks for liver regeneration after partial hepatectomy and several months or even years for the development of a non-alcoholic fatty liver. Finally, the metabolic state of hepatocytes is affected by cellular contacts with each other and signals received from other hepatic cells, e.g. endothelial cells or macrophages. These are aspects that necessitate to study the metabolism of the liver on the basis of a multi-scale model that covers different spatial and temporal scales. This talk outlines the basic structure of such a liver model and presents some first results.

Analysis of mathematical models for cancer growth and treatment, Part I;
Tuesday, June 28, 11:00

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Using mathematical modeling to understanding the role of diacylglycerol (DAG) as a second messenger

Diacylgylcerol (DAG) plays a key role in cellular signaling as a second messenger. In particular, it regulates a variety of cellular processes and the breakdown of the signaling pathway that involves DAG contributes to the development of a variety of diseases, including cancer. We present a mathematical model of the G-protein signaling pathway in RAW 264.7 macrophages downstream of P2Y6 activation by the ubiquitous signaling nucleotide uridine 5'-diphosphate. Our primary goal is to better understand the role of diacylglycerol in the signaling pathway and the underlying biological dynamics that cannot always be easily measured experimentally. The model is based on time-course measurements of P2Y6 surface receptors, inositol trisphosphate, cytosolic calcium, and with a particular focus on differential dynamics of multiple species of diacylglycerol. When using the canonical representation, the model predicted that key interactions were missing from the current pathway structure. Indeed, the model suggested that to accurately depict experimental observations, an additional branch to the signaling pathway was needed, whereby an intracellular pool of diacylglycerol is immediately phosphorylated upon stimulation of an extracellular receptor for uridine 5'-diphosphate and subsequently used to aid replenishment of phosphatidylinositol. As a result of sensitivity analysis of the model parameters, key predictions can be made regarding which of these parameters are the most sensitive to perturbations and are therefore most responsible for output uncertainty.

Recent developments in the study of Lotka-Volterra and Kolmogorov systems; Saturday, July 2, 14:30

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Heteroclinic limit cycles in Lotka-Volterra systems

In this talk, we are concerned with the global, rather than local, attraction (repulsion) of a heteroclinic limit cycle in competitive Lotka-Volterra systems. Conditions will be explored for omiga (alpha) limit sets to be a single heteroclinic cycle for almost all interior initial points in the nonnegative cone.

Epidemic models: Networks and stochasticity I; Wednesday, June 29, 14:30

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Overview of Networks and Stochasticity in Epidemic Models

Two areas of much recent work in modelling epidemics are contact networks and population stochasticity. These concepts are closely related, since the existence of a small, finite neighbourhood of contacts around each individual (or simple demographic stochasticity) make chance events important at the local level, which can then scale up to significant population-level effects.

This talk will introduce the concepts of network structure and stochasticity, and by focusing on network models, will provide an overview of different mathematical, computational and empirical tools used to address these issues. In particular, the relationship between exact models, approximations based on heuristic arguments, and the results of Monte Carlo simulation will be discussed.

Mathematical modeling and simulations of angiogenesis II; Wednesday, June 29, 11:00

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A model for anti-angiogenic therapy

Since the proposal by J. Folkman in the 70's to use tumoral neo-angiogenesis as a therapeutic target, important efforts lead to the development of various anti-angiogenic drugs now used in the clinic. Though, the practical results obtained by these so-called "targeted therapies" are quite poor up to now and anti-angiogenic drugs are far from replacing the classical, very toxic, chemotherapies. In some cases, angiogenic drugs can even exhibit paroxystic effects such as metastatic acceleration [**3**]. It seems that the way of administering the drug, its *scheduling* is of fundamental importance and determining the best schedules for anti-angiogenic drugs alone or in combination with cytotoxic drugs is a clinical open question.

In order to give insights on these questions, we developed the model of [**2**] and included a module to incorporate the metastases [**1**]. We will present interesting simulations studying and optimizing efficient temporal administration protocols, and describing the paradoxal effect observed in [**3**].

In particular, we can give answers in an emerging area of clinical oncology named metronomic chemotherapy (or anti-angiogenic therapy) [**4**]. It consists in delivering the chemotherapy at doses below the maximum tolerated doses, with a frequent schedule and is based on the assumption that such a schedule would have an anti-angiogenic effect.

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From one to many: Cell-based modeling of collective, emergent behaviors in biology -I; Tuesday, June 28, 11:00

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Emergent patterns of hepatic zonation of xenobiotic clearance and hepatotoxicity: a plausible role for cell learning

Hepatic zonation is conspicuous periportal (afferent) to perivenous (efferent) attribute gradients within lobules. Zonal differences occur in the clearance of a variety of endogenous compounds and xenobiotics, and are evident for a number of normal hepatic functions. However, no concrete, causal, mechanistic theory is available to explain how, for example, different hepatic zonation patterns of P450 isozyme levels and hepatotoxicity emerge following dosing with different compounds. We used the synthetic method of modeling and simulation to discover, explore, and experimentally challenge concrete mechanisms that show how and why biomimetic zonation patterns emerge and change within agent-based analogues. Synthetic methods enable teasing apart complex systems in contrast to inductive methods, which target prediction. Following an iterative Refinement Protocol enabled construction of real (not conceptual), strictly defined, biomimetic mechanisms while also accounting for considerable uncertainty. Even though abstract, the mechanisms and their spatial context are flexible and sufficiently concrete to instantiate mechanistic hypotheses and test their plausibility experimentally. Our working hypothesis was that those mechanisms have counterparts in rats. Mobile objects map to compounds. One analogue is comprised of 460 identical, quasi-autonomous functional units called sinusoidal segments (SSs). SSs detect and respond to compound-generated response signals and the local level of an endogenous gradient. Each SS used a learning algorithm to adapt to new information with the objective of improving efficiency. Upon compound exposure, analogues developed a variety of patterns that were strikingly similar to those reported in the literature. A degree of quantitative validation was achieved against data on hepatic zonation of CYP1A2 mRNA expression caused by three different doses of TCDD (2,3,7,8-tetracholorodibenzo-p-dioxone).

Multiscale mathematics of liver: bridging molecular systems biology to virtual physiological human scale; Wednesday, June 29, 11:00

Peter Hunter
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Modelling infrastructure for the VPH/Physiome project

This talk will describe the model and data encoding standards and their associated databases and tools that are being developed as part of the VPH/Physiome project.

Modeling Dynamics of Complex Biological Systems; Tuesday, June 28, 17:00

Paul Hurtado
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In-Host Dynamics of Mycoplasma Infections: Conjunctivitis in Wild Passerine Birds

The host-pathogen interaction is at the core of every infectious disease system, and provides an important foundation from which to study infectious disease at the individual, population and community levels. This work uses tools from applied dynamical systems and bifurcation theory to investigate how different aspects of the host immune response affect the progression of a localized bacterial infection caused by small, persistent bacteria known as mycoplasmas. The goal is to better understand observed variation within and between host species in the motivating biological system: infectious conjunctivitis in the house finch (*Carpodacus mexicanus*) and other passerine birds caused by the novel pathogen *Mycoplasma gallisepticum*.

Population Genetics; Wednesday, June 29, 14:30

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Moment closure in a Moran model with recombination

The dynamics of processes of population genetics is often well understood in the limit of infinite population size where a law of large numbers leads to a deterministic description. Great challenges arise in models with finite populations and interacting individuals. In these nonlinear models even the analysis of the expectation is difficult. Its dynamics does, usually, not only depend on the current expectation but on higher moments, and there is no moment closure.

In my talk, I will present an exception to this rule. I will consider a continuous-time Moran model with arbitrary recombination and mutation, but without resampling (i.e., genetic drift). In this case the expectations of products of marginal processes defined via partitions of sites form a closed hierarchy, which is exhaustively described by a finite system of differential equations. One thus has the exceptional situation of moment closure in a nonlinear system. Surprisingly, this property is lost when resampling is included.

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From Gene Networks to Tissue Engineering: Computational Models of Pattern Formation

Limb bud development has long served as a paradigm of organogenesis and pattern formation. Decades of genetic and biochemical studies provide us with a wealth of information about the molecular circuits that control cell expansion and position-dependent cell differentiation in the developing limb bud. In spite of much detailed biological knowledge and much theoretical work a detailed mechanistic understanding of how the genes and regulatory circuits interact to control limb organogenesis is still lacking. In collaboration with the Zeller group at the Department of Biomedicine of the University of Basel we are developing detailed computational models for limb development in mice. By combining mathematical modeling with experimentation we seek to understand how key processes at the microscopic level interact to give rise to patterning at the macroscopic level.

The signaling pathways (Fgf, Shh, Bmp, Gremlin) that regulate limb bud development are strikingly similar to those that regulate lung morphogenesis. Based on the model for limb development we have also developed a mechanistic model for the regulatory network that governs lung branching. The branching of the bronchi in the lungs is highly stereotyped and results from a highly regulated process that restricts the types and sequence of branching modes.

In the long run we seek to use our mechanistic insights in the engineering of tissue and bone.

Poster Session; Friday, July 1, 20:00

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Model of coexistence of fish by mating territory

The feeding territories of three species (*P. polyodon, P. trewavasae, P. famula*) of genus *Petrochromis* in Lake Tanganyika in Africa are distributed in a mosaic pattern. The feeding territories rarely overlap with each other. Both conspecific and congeneric individuals invading in the feeding territory are driven out as they competes food resource. Males of *P. polyodon, P. trewavasae, P. famula* have feeding territory that is 1 m apart from those of conspecific males. Their distances are caused by mating territory where conspecific males are driven out.

To examine if the mating territory promote the species coexistence we construted total length dependent rank model. In the model, the territory arranged in continuous space and feeding territory radius is decided from its species and total length. If territory overlap, smaller individual shift its territory for once, so that its territory does not overlap. Dependence of the number of individuals of each species and the number of species mating territory to the radius of the male of *P. polyodon, P. trewavasae, P. famula* are examined. Moreover, one fictitious species is added, to examined whether coexistence species number is limited. For the total length dependent rank model, the mating territory does not promote the coexistence of species.

We constructed another model where the time concept is introduced. It deals with growth, the death, and breeding. When two territories overlap, the overlapped region is divided by the line of equal influemce. We caluculate the influence by the difference between the feeding territory radius and the distance from the center. For this model, the mating territory of intermediate radius promotes the coexistence of species.

Mathematical Modelling of Macromolecules and Molecular Aggregates;
Saturday, July 2, 14:30

Giuliana Indelicato
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The dynamic behaviour of viral capsids under structural transitions important for infection

We present a general method for the investigation and prediction of likely transition mechanisms for capsids of icosahedral viruses. Concepts from the theory of three-dimensional (3D) quasicrystals, and from the theory of structural phase transformations in 3D crystalline solids, are combined to give a framework for the study of these structural transformations. Applications to a number of viruses will be discussed.

Population Dynamics; Tuesday, June 28, 14:30

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Tempo and mode of inhibitor-mutagen therapies: a multidisciplinary approach

The continuous emergence of drug-resistant viruses is a major obstacle for the successful treatment of viral infections, and is steadily spurring the design of new therapeutic strategies [1]. Correspondingly, there is a pressing need to understand the dynamical effect of antiviral therapies on complex, diverse and fast mutating viral populations. Indeed, the evolutionary dynamics of viral populations is at the basis of some recently suggested therapeutic strategies, such as lethal mutagenesis and lethal defection, that use mutagenic agents to induce viral extinction [2,3]. Despite both procedures have proved to be effective *in vitro*, the use of high doses of mutagen *in vivo* could involve severe side effects. On the other hand, low doses allow the virus to get adapted through the rapid appearance of resistance mutants. Hence, research on combination therapies arises as a step towards reducing doses while keeping low the probability that the virus becomes resistant to the drug cocktail.

Here we discuss combination therapies involving two dissimilar drugs: the mutagen ribavirin, and an inhibitor of the viral replication, guanidine. These drugs were used *in vitro* to analyse the performance of their sequential versus simultaneous administration in the control of infections by foot-and-mouth disease virus [4]. Contrary to the well known case when two inhibitors are used, it was found that sequential administration of the inhibitor followed by the mutagen is more effective than simultaneous treatment. In order to explore the reasons for this behavior we designed a simple computational model representing the dynamical response of the viral population to the two drugs. It shows that the two-edged role of the mutagen, reducing the viable offspring of the virus but also favouring the appearance of resistant mutants, causes an interaction between inhibitor and mutagen that determines the efficience of this therapy. In agreement with the theoretical predictions, laboratory experiments confirm in particular cases that the suitability of simultaneous or sequential administration depends on the administered dose. The model predicts the dynamic response of the viral population for any dose combination and, in particular, determines the amount of inhibitor and mutagen required

to minimise the probability of appearance of resistant mutants. Knowledge of the relevant model parameters is obtainable by means of few, simple experiments, such that our predictions could be extended to other viral systems.

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Immunology; Wednesday, June 29, 14:30

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Quantification system of viral dynamics in vitro - the dynamics of SHIV on HSC-F -

What we want to obtain and analyze are quantitative time-course experimental data but not qualitative snap-shot experimental data for the purpose of getting dynamical information of viral infection such as half-life of infected cells, one of virions, burst-size of virus, basic reproductive number of infected cell and so on. Today, I am going to show our recent studies about "Quantification system of viral dynamics in vitro", in which we can quantify the above dynamics of SHIV on HSC-F cell line.

Modeling of immune responses and calcium signaling I; Tuesday, June 28, 17:00

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The dependence of expression of NF-B dependent genes: Statistics and evolutionary conservation of control sequences in the promoter and in the 3 UTR

Background: NF-B family plays a prominent role in innate (early) immune response and has impact on other processes such as cell cycle activation or cell apoptosis. Upon stimulation by pathogens such as viral RNA a kinase cascade is activated, which eventually strips the NF-B of its inhibitor IB molecule and allows it to translocate into the nucleus. Once in the nucleus, it activates transcription of approximately 90 genes, some of which trigger further stages of the immune response. NF-B-dependent genes can be categorized, based on the timing of their activation counted from NF-B translocation into the nucleus, as Early, Middle and Late genes. It is not obvious what mechanism is responsible for segregation of the genes timing of transcriptional response. Results: It is likely that the differences in timing are reflected in differences in the structure of promoter regions of genes in different categories. Specifically, this might concern differences in number and type of transcription factor binding motifs, required for NF-B itself as well as for the putative cofactors. Using this approach we analyzed if genes assignment to the Early, Middle or Late group based on expression pattern, is connected with special features in promoter structure. This connection may be one of the mechanisms underlying the different patterns of gene expression control. This issue is best considered in the evolutionary framework, first, since functional binding sites are likely to be conserved in evolution and second, since the patterns of evolutionary change of promoter regions are not very well-known and are of serious interest. Another control sequences are AU - rich elements (ARE) located in 3UTR. AREs target mRNA for rapid degradation and inflict mRNA instability. Latest studies show that genes transcribed with unstable mRNA have different transcription dynamic. We have found that there are significant differences between the Early and the Late genes promoter and 3UTR regions and many similarities are observed among the Early genes even between distant species, while the Late genes promoter regions are much more diversified. Conclusions: Wider phylogenetic analysis of NF-B dependent genes provides insight into the degree of cross species similarity found in the Early genes, opposed to many differences in promoter structure that can be found among the Late genes. This suggest that activation and expression of the Late genes is much more species specific than in the Early genes. Based on the promoter structure and ARE content Middle genes can be divided into two subgroups: Early like and Late like.

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Systems biology of *Clostridium acetobutylicum*

A renewed interest in the development of biofuels has emerged in recent years, principally due to dwindling crude oil reserves and concerns over the environmental impact of fossil fuels. Bacterial fermentation is a possible solution to questions over the source of future biofuels.

Clostridium acetobutylicum is an anaerobic, non-pathogenic, Gram-positive bacterium capable of producing the solvents acetone, butanol and ethanol. Though each of these can be used as a biofuel, the properties of butanol make it the most promising energy source of the three. For butanol production by *C. acetobutylicum* to be exploited on an industrial scale, however, genetically-engineered strains must be designed which can produce butanol at much higher levels than those achieved by wild-type strains.

The SysMO and SysMO2 programmes COSMIC (*Clostridium acetobutylicum* Systems Microbiology) were established to apply a systems approach to understanding the complex mechanisms behind solvent production by *C. acetobutylicum* and to establish this bacterium as the paradigm for clostridial systems biology. An iterative approach is adopted whereby experimental work is designed to complement mathematical models of solventogenesis which in turn generate experimentally-testable hypotheses. Notably, the gene regulation networks governing solvent production and the connected process of sporulation are modelled and parametrised according to experimental data. Systematic *in silico* alteration of gene expression for each component of the networks enables identification of those genes most crucial for butanol production and will elucidate the optimal genetic engineering strategies for maximising butanol yield.

Poster Session; Friday, July 1, 20:00

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Size-structured population model with discontinuous growth rate

Modelling size-structured population of copepods demands allowing growth rate to be discontinuous. This is the consequence of the moulting process, which ocures rapidly after a long period of stagnation. Introducing size structure simplifies modelling predator-dependent mortality. This leads to McKendrick equation system with nonlocal birth rate and mortality and discontinuous growth rate. It can be shown that there exists a solution to this problem and continuity of it (in weak* topology with respect to time) can be proven. Moreover a stable numerical scheme which is weakly convergent is presented.

Systems Biology of Development; Saturday, July 2, 14:30

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Reverse-Engineering the Evolutionary and Developmental Dynamics of the Gap Gene Network

Evolutionary developmental biology tries to close the gap between molecular evolution and phenotypic change. This requires a quantitative systems-level understanding of the gene networks underlying development across multiple levels from the molecular to the organismic. Obtaining such an understanding is challenging due to the large number of factors involved. We depend on computational models for this task. I present a reverse-engineering approach, where gene regulatory interactions are inferred from quantitative expression data, using data-driven mathematical models (called gene circuits). Gene circuit models of the gap gene network of Drosophila reproduce observed gene expression with high precision and temporal resolution and reveal a dynamic mechanism for the control of positional information through shifts of gap gene expression domains. We are extending this approach to a comparative study of the gap gene network between different species of dipterans (flies, midges and mosquitoes). I present preliminary results on data quantification and modeling for gap genes in the scuttle fly Megaselia abdita, and the moth midge Clogmia albipunctata. Our approach yields predictions of how changes of gene regulatory feedback affect the timing and positioning of expression domains. These predictions will be tested experimentally using RNA interference in all three species. No such quantitative systems-level analysis of an evolving gene regulatory network has been achieved to date.

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Employing Statistics in Systems Microscopy

As the role of metastasis is fundamental in the progression of breast cancer, it is of paramount significance to study cell adhesion and cell migration, mechanisms tightly related to the machinery of metastasis, in closer details. Yet, cell adhesion and cell migration result from a series of dynamic procedures in space on a sub-cellular level, namely the organization of cell-matrix adhesion complexes (CMACs) [1].

Using techniques of high-throughput microscopy and post-acquisition image quantification, large sets of data representing cell and CMAC properties are made available for statistical analysis. Such analysis is an essential component of what is now termed as Systems Microscopy: systems biology analysis of living cells using a coalition of automated microscopy, image quantification, data mining and statistical analysis [2].

The nature of the statistical analysis in Systems Microscopy includes unsupervised as well as supervised statistical learning. The unsupervised learning approaches are employed for purposes such as visualization using dimension reduction, and detection of sub-popultions using mixture models. The focus of the supervised learning methodologies is on between-population tests, spatial point pattern analysis, and predictive modeling using various techniques of classification. Naturally, given that the self-organization of living cells is a spatio-temporal process, all of the aforementioned statistical procedures are intended to interrogate static as well as dynamic (time-series) data.

Thus, by employing the necessary data and various statistical methodologies, the processes of cell adhesion and cell migration may receive further eluciation and potentially advance our understanding of the underlying causes as well as the progression of metastasis.

The aim of this talk is to give a brief description of some of the employed methods in the statistical analysis.

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Population Dynamics; Tuesday, June 28, 17:00

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Finite Populations Regulated by a Carrying Capacity

A population of independently reproducing individuals in a stable environment will die out, if reproduction is critical or subcritical. If it is supercritical, the population may escape extinction. But then it must grow exponentially beyond all limits, which is of course a mathematical artifact, unrealisabkle in a finite world. But what happens in reality, where there is a bound to growth? A carrying capacity such that individuals reproduce in a supercritical manner while population size is below it, reproduction however turning subcritical as soon as the population is larger than the habitat carrying capacity?

These questions are answered in terms of general branching processes, i.e. populations where individuals have arbitrarily distributed life-spans and may give birth according to an arbitrary pattern, and individual reproductive behaviour is influenced by population size in the manner described.

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From Data Analysis to Model Parameterization & Prediction of Tumor Growth and Therapy

In order to establish a predictive model for in-vivo tumor growth and therapy a multi-scale model has to be set-up and calibrated individually in a stepwise process to a targeted cell type. As a proof of principle we will present the process chain of model construction and parameterization from different data sources for the EMT6/Ro and the SK-MES-1 cell line.

In a first step the model has been built up and validated with EMT6/Ro mouse mammary carcinoma multi-cellular cell spheroid data from literature. For this cell line it predicted the growth kinetics to be controlled by spatial restrains over a wide range of oxygen and glucose medium concentrations. Only if both, oxygen and glucose are very limiting saturation was observed which the model could explain by cells switching from aerobic to anaerobic glycolysis.

In a seconde step the model was adapted to the SK-MES-1 cell line. The growth kinetics was calibrated quantitatively in comparison with growth curves and qualitatively by image analysis of spheroid cryosections stained for apoptosis and proliferation.

Poster Session; Friday, July 1, 20:00

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Mathematical Validation of a Novel Implantable Oxygen Sensor

Non-vascularized tissue engineering constructs and other solid implants with biomedical applications, such as encapsulated live cells or glucose sensors, need oxygen (O2) for proper functioning. To better understand the availability of O2 to implants, a novel sensor has been developed by researchers at the Ohio State University, that can non-invasively record, after implantation in mice, the signal provided by local pO2. This has subsequently been used to study the process of neovascularization and foreign body reaction in response to an implanted device. Briefly, bone marrow progenitor cells embedded in a Matrigel plug were implanted next to the sensor, or gel alone used as control, and weekly O2 readings noted. In order to explain these readings, we have developed a partial differential equation model of the experimental system. The model anticipates that pO2 in implant follows a parabolic pattern, the descending side of the curve being indicative of the response to normalization of metabolic demands of tissue which requires a lower pO2. The model is sensitive to angiogenic stimulation, predicting a rapid raise in pO2 and a slower reduction of the signal. These results can thus be used to predict the various stages of foreign body reaction that occurs in response to the implants, and the effect stem-cell therapy has on this. A 2D illustration of this is also simulated.

Bridging the Divide: Cancer Models in Clinical Practice; Thursday, June 30, 11:30

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The Impact of Androgen Ablation on Mutation Acquisition in Prostate Cancer

Prostate cancer (CaP) is the second most common cancer in American men. Although the majority of patients diagnosed with CaP are cured with primary treatment, it remains the second lead cause behind only lung cancer, of male cancer-related deaths in the western world. A few features set it apart from other cancers; it develops slowly over a period of years; CaP cells are dependent on male sex hormones for growth; treatment in the form of continuous androgen ablation fails due to the emergence of castrate-resistant CaP cells. Therefore, it has been proposed that intermittent androgen ablation therapy might be a better strategy for treating CaP. I present a model of prostate growth in humans, which can simulate the onset of CaP, as well as explain the emergence of resistance in response to therapy. Our model shall incorporate a variety of cell types such as healthy and CaP cells, as well as detailed biochemical pathways crucial to the growth of these cells. Fits to individual patient data will also be presented. By being able to distinguish between various drug actions, and being fitted to individual patient data, we hope to develop a truly prescriptive tool to aid physicians in treatment choices for CaP patients.

Poster Session; Friday, July 1, 20:00

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MicroImage as a tool for microarray image artifacts correction

Oligonucleotide single color microarrays are one of the most popular platforms used to characterize transcription profile changes induced by various chemical or physical factors. This method is based on hundreds of thousands unique 25-mer oligonucleotide probes grouped into gene specific sets. Single probes attach labeled transcripts of specific genes which quantity is proportional to the fluorescence intensity of the probe, accessed with a laser scanner. Microarray surface images obtained in such experiment often contain artifacts of various shape and size caused by either defects of the manufacturing process or impurities within target genomic material. Data processing methods often fail to exclude outlying signal values resulting from such defects which leads to artificially increased variation between replicate experiments, decreasing statistical significance of inter sample studies, or to reduced accuracy of sample classification if the experiment aims to search for factor induced genetic response signature.

In this work we present different kinds of artifacts and propose a novel detection and correction method based on signal intensities of other, unaffected replicate probes. The method was implemented as a standalone windows application with a very easy to use graphical interface allowing to process hundreds of microarray images within few minutes and visualize the analysis on various complexity steps. The usefulness of this method was evaluated by the analysis of breast cancer microarray dataset, with marked patients radiosensitivity and technical replicate data with simulated artificial noise objects.

Using common statistical methods inter-group correlation, inter-gene variance and discriminative gene analysis were performed. The overall impact of artifacts processing on sample classification accuracy was also evaluated. The results show that image artifacts correction increases dataset integrity, proving that it is possible to separate image defects from inter sample variations of biological origin and specific features of the microarray chip achieving higher quality of the analyzed data.

ACKNOWLEDGMENT:

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Applications of nonnegative Radon measure spaces with metric structure to population dynamic models; Wednesday, June 29, 17:00

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Measure-transmission conditions - a powerful tool in modeling bimodal dynamics

Differentiation of cells may be subject to two paradigms. Either a cell is in a state of inevitable alteration of its characteristics or the state is quasi-stationary, meaning that for a certain period of time the biochemical characteristics remain the same. A cell in the former, transient state usually originated in and heads towards the latter, reaching it in a finite time. On the other hand, a cell in a quasi-stationary state may stay there arbitrarily long and is typically capable of both self-renewal (by division) and differentiation (with or without division). Incidentally, all these scenarios may coincide in a single system, as e.g. in the case of neurogenesis, and lead to interesting bimodal dynamics. These two types of dynamics can be modeled by transport equations or (a system of) ordinary differential equations, respectively. Nonetheless, the two approaches can be unified in a purely continuous setting of measure-valued solutions of the transport equation with additional transmission conditions. In the simplest case, this leads to the following problem ([1]):

$$\begin{aligned}
\partial_t \mu(t) + \partial_x (g(v(t)\mathbf{1}_{x\neq x_i}(x)\mu(t)) &= p(v(t),x)\mu(t),\\
g(v(t))\frac{d\mu(t)}{d\mathcal{L}^1}(x_i^+) &= c_i(v(t))\int_{\{x_i\}} d\mu(t), \quad i=0,\dots,N,\\
\mu(0) &= \mu_0,\\
v(t) &= \int_{\{x_N\}} d\mu(t).
\end{aligned}$$

In the talk, we present this new setting and discuss how it allows to capture in an elegant way a wealth of effects, promising interesting applications well beyond its original motivation.

References.

[1] Piotr Gwiazda, Grzegorz Jamróz, Anna Marciniak-Czochra, *Models of discrete and continuous cell differentiation in the framework of transport equation.* Submitted.

Population Dynamics; Saturday, July 2, 14:30

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Chaotic properties of some partial differential equation with a random delay describing cellular replication

We study some model of a cell population, which is based on a model proposed by Mackey and Rudnicki in [1]. Our model is described by a partial differential equation of a transport-type with a random delay. We consider a random dynamical system generated by this equation and describe its chaotic behaviour.

References.

[1] M. C. Mackey and R. Rudnicki, *Global stability in a delayed partial differential equation describing cellular replication*, J. Math. Biol., **33**, 89–109.

Modeling of immune responses and calcium signaling II; Wednesday, June 29, 14:30

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Type of noise defines the most stable attractor in bistable gene expression model

We consider simplified stochastic model of gene expression with the nonlinear positive feedback. It is assumed that the gene may be in one of the two states: active or inactive. Protein molecules are produced directly from the active gene. We focus on the case in which in the deterministic approximation the system has two stable steady state solutions. Two types of noise are considered; transcriptional (characteristic for bacteria) - due to the limited number of protein molecules, and gene switching noise (important in Eukaryotes) - due to gene activation and inactivation transitions. We explore the correspondence between the stochastic system and its deterministic approximation in the limit of low noise. Analytical analysis of two approximations of the stochastic system, each with only one type of noise included, showed that when noise decreases to zero (I) the stationary probability density (SPD) converges to Dirac delta in one of two stable steady states, (II) in a broad range of parameters the SPD of the system with transcriptional noise converges to Dirac delta in a different steady state than the SPD of the system with gene switching noise. This suggest that the ratio of the transcriptional to the gene-switching noise dictates in which state the SPD concentrates. We verified this hypothesis by Monte Carlo simulations of the exact model. This finding has the following thermodynamic interpretation. The non interacting molecules diffusing in the uniform temperature field settle in the lowest potential well as temperature tends to zero. However when the temperature field is not uniform temperature profile dictates in which well molecules concentrate. Apparently, the two types of noise specific for gene expression are connected with two different temperature fields and thus favors the different attractors.

Our study demonstrates that in systems with the underlying bistability, like genetic switches, the noise characteristic controls in which of the epigenetic attractors cell population will settle.

Fractals and Complexity I; Wednesday, June 29, 14:30

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Lacunarity analysis and classification of microglia in neuroscience

Fractal analysis in the neurosciences has advanced over the last twenty years to include measures such as lacunarity. Lacunarity assesses heterogeneity or translational and rotational invariance in an image. In general, measures of lacunarity correspond to visual impressions of uniformity, where low lacunarity conventionally implies homogeneity and high lacunarity heterogeneity. It is now necessary to review some of the new permutations of this analysis technique and what it can tell the neuroscientist. This paper outlines methodological considerations associated with three different types of lacunarity analysis applied to the classification of microglial cells.

Ecosystems Dynamics; Tuesday, June 28, 11:00

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Exploring Algal Blooms through Planktons Interactions Using Trophic Model

We developed two-level trophic model to systematically understand the algal blooming in aquatic systems. The model combined two ecological processes: one is the predator (zooplankton)-prey (phytoplankton) interaction and the other is the advection and diffusion of the fluid. By using the model, we computationally revealed how the combination of biological and environmental factors causes the algal bloom in relation to the turbulent mixing of the planktons. We showed that the turbulent mixing is likely to strongly affect the occurrence of the blooming of the surface plankton. In addition, we briefly discussed the competition strategy between the planktons to increase the probability of their survival in connection with the blooming.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -II; Tuesday, June 28, 14:30

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Bacterial behavioral principles: Learning from Myxobacteria

Many bacteria are able to spread rapidly over surfaces by the process of swarming. Bacterial swarms are model systems for the study of multicellularity and biological self-organization. Swarming bacteria have rod-shaped cells, and are observed to move smoothly even when they are packed together at high density. Why dont swarming cells interfere with each others movements? Using a cell-based biomechanical model, we show that periodic reversals of moving direction in populations of rod-shaped bacteria can lead to extensive ordering of cells, thus enabling them to effectively resolve traffic jams formed during swarming. We also show that an optimal reversal period and an optimal cell length exist for producing such order. The optimal reversal period and the optimal cell length are connected by a simple relation. We suggest that basic behavioral principles exist for bacterial swarming that are independent of detailed motility mechanisms.

Mechanics of the cytoskeleton and cortical actin at the cellular level;
Saturday, July 2, 08:30

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Cortical actin and cell instabilities

Cortical actin and cell instabilities. JF Joanny, J. Prost, G. Salbreux

We present a review of our work on cortical actin and of the instabilities of cells induced by cortical actin. We first show how we can apply our active gel theory to describe the properties of the acti-myosin cortex in a cell. We then discuss the stability of the cortical actin layer. The results are applied to three problems: the formation of belbs to discuss the experimetns of the group of E. Paluch in Dresden where the blebs are induced by photoablation; oscillations of non adhering cells to discuss the experiments of the group of P. Pullarkat in Bangalore; and the formation of contractile rings. In this last case, we discuss both wound healing formation in a xenopus embryo and the formation of a contractile ring during cytokinesis

Epidemics; Saturday, July 2, 08:30

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Novel ABC - Bayesian Emulation Hybrid Algorithm For Complex Model Calibration: The First Waves

Introduction. The complexity of the dynamical systems underlying epidemics has led to the use of large-scale stochastic models for prediction purposes. However, methods for robustly calibrating and analysing these simulators can be prohibitively inefficient. We propose an algorithm for fitting complex models that incorporates elements of both Approximate Bayesian Computation (ABC) and Bayesian Emulation. ABC enables inference about model parameters without the need for calculating a likelihood function, by generating approximations from repeated model runs. However, each complex model run might take hours. Emulation methods are being developed in the fields of cosmology, oceanography and meteorological modelling. The complex model function is summarised as an 'emulator': a stochastic function that represents the global behaviour of the complex model function as a linear regression model and local deviations from this behaviour as Gaussian processes. The emulator then becomes a cheap proxy for the complex model, allowing both calibration and probabilistic sensitivity analysis to be conducted in a fraction of the computational time.

Methods. We report the initial application of an emulation-based calibration algorithm to an individual-based stochastic model of STI transmission in Uganda. Starting with uninformative priors for 19 behavioural and biological input parameters, we 'trained' an emulator with 200 sampled parameter sets and their corresponding complex model output (point estimates of HIV prevalence). Sampling a further 10,000 parameter sets from the priors, we used the emulator to make output predictions over a large area of input parameter space. Weighting each parameter set according to goodness of fit to observed data, we identified promising areas of parameter space to evaluate using the complex model. A more accurate emulator was then trained, incorporating this additional complex model output. This process was repeated in 'waves' as per sequential ABC methods.

Results. The use of emulators allowed an evaluation of large areas of parameter space due to increased computational efficiency. Processing time for one prevalence point estimate was reduced from over 15 minutes on an HPC cluster to less than 0.1 second on a PC. Even the first two waves of such an algorithm provided helpful insight into the most influential parameters and identified promising regions of parameter space.

Conclusions. The development of an ABC - Bayesian Emulation hybrid approach to complex model calibration is promising, with emulators offering large advantages in computational efficiency. However, further research is needed regarding weighting, tolerance levels and covariance.

Cell and Tissue Biophysics; Saturday, July 2, 11:00

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Helfrich Energy Model of the Phagocytosis of a Fibre

CNTs are a form of High Aspect Ratio Nanoparticles (HARN). Their radius is typically of only a few nanometres (10^{-9}) while their length can be on the micron scale (10^{-6}). Their shape has been found to make their removal from the lung surface on inhalation by macrophages especially difficult. This is widely regarded as a key mechanism of toxicity [**1**] [**2**]. Frustrated phagocytosis leads to scarring and granuloma formation which impairs the function of the lung.

Following the precendent set by Helfrich and Deuling [**3**] [**4**], the free energy of a cell membrane is taken to be given by

$$\mathrm{F} = \underbrace{\int_V \Delta_p}_{\text{Volume Energy}} + \underbrace{\int_S \lambda}_{\text{Surface Energy}} + \underbrace{\int_S (\text{mean curvature} - c_0)^2}_{\text{Helfrich Energy}}$$

The Helfrich energy was introduced in [**3**] to quantify the energy associated with a cell membrane of a particular shape. It is often referred to as the bending energy. The spontaneous curvature c_0 takes into account the natural curvature of a cell membrane due to proteins in the lipid bilayer and the cytoskeleton.

For a given set of boundary conditions, the shape of a the cell membrane is found by solving the associated Euler-Lagrange equations. The topology of the surface is restricted to that of a surface of rotation around an axis which is taken to be the axis of a fibre. Due to singularities in these Euler-Lagrange equations, the problem is a boundary value problem rather than an initial value problem.

The solutions of this energy minimisation problem in [**4**] correspond to solutions in the limit of a vanishing radius of the cell on a fibre problem. Boundary conditions specific to the cell on a fibre problem are introduced. These boundary conditions can be chosen to ensure that the boundary terms of the first variation in the free energy are set to zero. They can also be chosen to fix the contact angle of the cell membrane with the fibre surface.

It is assumed that the shape of a lipid membrane which has successfully engulfed a particle will be energetically stable, in order to conserve the limited resources of a macrophage. This does not take into account the energy required to remodel the cytoskeleton for the cell to reach this shape. However, the bending energy associated with cell membranes of increasing length can be used to suggest the amount of energy required in this dynamical process.

References.

[1] G. Oberdörster, V. Stone and K. Donaldson, *Toxicology of nanoparticles: A historical perspective* Nanotoxicology **1** 2–25, 2007.

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[3] W. Helfrich, *Elastic properties of lipid bilayers: Theory and possible experiments*, **28** Z. Naturforsch 693–703, 1973.

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Undergraduate Biomathematics Education Beyond BIO 2010 (Part I);
Wednesday, June 29, 14:30

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Discrete *vs.* indiscrete models of network dynamics

A key step in modeling biological network dynamics is the decision whether to use a stochastic process, a system of differential equations, or a discrete dynamical system. This step in the modeling process poses both special challenges and special opportunities for undergraduate teaching. The challenge is that performing this step requires familiarity with a number of different areas of mathematics, which cannot be taken for granted in undergraduate teaching. Moreover, undergraduates tend to view mathematics as neatly compartmentalized into subdisciplines, each with their own set of standard word problems. The opportunity is for leading students beyond this view and giving them a taste of *bona fide* mathematical modeling where the tools need to be chosen depending on the system and available computational resources. Moreover, one can introduce quite sophisticated mathematical concepts from a variety of areas of mathematics along the way.

This presentation will illustrate the potential of this approach based on ODE and discrete models with finite state spaces for certain networks. We will investigate conditions under which the coarse-graining via discrete models is a valid modeling approach and give examples of open problems that can be explored as undergraduate research projects.

Poster Session; Friday, July 1, 20:00

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Boolean dynamics vs. ODE dynamics

The correspondence between systems of piecewise linear ODE's and their Boolean idealizations has been extensively studied by Leon Glass and his collaborators. These types of dynamical systems have been proposed as frameworks for studying biological processes such as gene regulation.

We consider a different class of ODE systems that naturally admit Boolean idealizations. The ODEs in this class have Lipschitz-continuous right-hand sides, and our class is rather broad. We assume that the variables can be grouped into agents of sorts, with individual agents having a certain bifurcation structure and inputs from other agents acting as changing bifurcation parameters.

This talk will present both simulations and analytical results that show how structural properties of the systems influence the degree of consistency between the ODE dynamics and its Boolean idealizations with synchronous or asynchronous updating. In particular, we explore to what extent features of chaotic dynamics in the Boolean idealization correspond to the presence of chaos in the underlying ODE system.

Heart rate dynamics: models and measures of complexity (part I);
Wednesday, June 29, 14:30

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Entropy-based measures of complexity in the assessment of heart rate variability: a theoretical approach

Recently, in a study of heart rate variability and other physiological data, growing attention has been paid to entropy-based complexity measures, among which are Approximate Entropy, Sample Entropy, Fuzzy Entropy, local entropies and some others. Mathematical components of their definitions will be presented with the stress on the problems of vulnerability to noise, loss of data, relative consistency, dependence on sample length and sensitivity to the input parameters. The usefulness of the above methods to distinguish time series with respect to their irregularity and unpredictability will be discussed and tested on various kinds of stochastic, nonlinear and physiological data.

Cellular Systems Biology; Tuesday, June 28, 14:30

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Actuators of yeast potassium homeostasis

Potassium is the most abundant cation in living cells and is involved in a variety of essential cellular processes including translation, endocytosis and even cell cycle regulation. Changes of external and internal K^+ concentrations change the membrane potential required for the transport of molecules across the plasma membrane, affect the pH and osmolarity of the cytosol and induce changes of the cell volume [1]. Metabolic decarboxylation processes release CO_2, which affects the pH, the bicarbonate concentration, the proton buffer capacity and the potassium transport [2].

To gain a deeper understanding of the complex interplay between these variables we developed an ordinary differential equation model of potassium control in the yeast *Saccharomyces cerevisiae*. The basic model covers the thermodynamic constraints on the operation of the major potassium transport systems and the proton ATPase Pma1. Regulation mechanisms where only partly included as many of them are either unknown or not sufficiently characterized. This basic model qualitatively reproduces known aspects such as the hyperpolarisation in *trk1,2*Δ mutants and potassium starved cells, as well as the potassium uptake energized by the Pma1 driven proton extrusion.

To make quantitative predictions we calibrated the model to potassium starvation experiments given in [3]. For cells grown in a medium with high K^+ and shifted to K^+ free medium, a decrease of the intracellular K^+ content and cell volume was measured. While the external potassium drop occurs in minutes, the internal K^+ is slowly reduced during several hours.

The regulatory control of the various transport systems under potassium starvation conditions is not well understood. To identify potential control mechanisms and points of applications we regarded the experimental time course $K^+_{data}(t)$ as a signal which has to be tracked by the model $K^+_{sim}(t)$. More precisely, we determined a time dependent input function $p(t)$ that solves the minimization problem

$$|| K^+_{sim}(p(t), \theta, t) - K^+_{data}(t) || = \mathrm{Min}\,. \tag{1}$$

Each transport protein or any other component of the model for which such an input function exists was regarded as a potential actuator for potassium control. We found that the (i) the proton pump Pma1 and the (ii) the CO_2 system are the most likely actuators of potassium homeostasis. In addition, we found evidence that yeast cells sense external potassium rather than internal potassium, what is also supported experimentally. To demonstrate the consistency of our predictions we successfully designed a modified PI-controller which reproduces the experimental time courses of internal potassium. This PI controller mimics the unknown details of signalling and gene expression changes required for the maintenance of homeostasis.

In summary, we present a mathematical model which provides testable predictions about unknown regulatory mechanisms necessary for homeostatic control of potassium in *S. cerevisiae*. We also believe that our tracking approach to mathematical modeling has general applicability. It is a versatile strategy to detect unmodeled dynamics and their points of application.

References.

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Quantitative Multiparametric Image Analysis for Estimation of siRNA Induced Off-target Effect

Small Interfering RNA (siRNA) and automated high-throughput high-resolution microscopy provides technological platform for systematic genome-wide survey of individual gene knockdown phenotype. Quantitative multi-parametric description of knockdown phenotype can be used for gene functions elucidation and establishing mechanistic models of cellular processes in which genes participate. However, the large degree of morphological variation between cells in repetitions of biological experiment as well as variation between phenotypes of different siRNAs, which are targeting the same gene, represents a major challenge to the reliable identification of gene silencing phenotypes. We have developed a system for the high content analysis of automatically acquired high-resolution images, which describes the endosomal organelles in quantitative terms (gene silencing profile) (Collinet et al, Nature 2010). The stability of individual parameters of phenotypic profiles between different imaging sessions and experimental replicates were tested. The analysis showed that different parameters reveal a wide variation of stabilities which dependent on biological variability, typical automatic imaging problems and parameter calculation details. Analysis of multi-parametric phenotype profiles produced by independent siRNAs, which are targeting the same gene, reveals the mean level of off-target effect, its dependence on siRNA concentration and chemical modification. The estimation of the minimum number of independent siRNAs which are required to infer the gene knockdown phenotype with given confidence was done. Quantitative estimation of off-target effect gives an objective feedback for no off-target siRNA selection, for the new generation siRNA development and could provide insight for deeper understanding of siRNA-mediated gene silencing mechanism.

Structure and Dynamics of Biochemical Reaction Networks II; Tuesday, June 28, 17:00

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Classification of networks for their synchronous dynamics

Small subnetworks, such as network motifs, and their modularity have been considered to play an important role in large complex networks. In this context, a major topic is the interplay between network structures and their corresponding dynamics. We consider one form dynamics, synchrony-breaking in a network. This can be interpreted as speciation, differentiation of cells, or clustering of gene expression patterns. For any network we construct a mathematical structure, a lattice, which results from the eigenvalues and eigenvectors of the network's adjacency matrix. Many networks have the same lattice, allowing a large number of networks to be classified into a smaller number of lattice structures. Furthermore, by looking at the lattice structure we can identify networks with similar synchronous dynamics.

References.

[1] Construction of lattices of balanced equivalence relations for regular homogeneous networks using lattice generators and lattice indices, Internat. J. Bifur. Chaos Appl. Sci. Engrg., 19 (2009)

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Mathematical modeling of biomechanical regulation in bone tissue (Session II); Wednesday, June 29, 11:00

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Mathematical modeling of trabecular bone remodeling induced by osteocytic response to interstitial fluid flow

Bone is a load-bearing tissue that can adapt its internal structure and outer shape by remodeling to a changing mechanical environment. The morphological changes in the trabecular microstructure are realized by the coupling of osteoclastic bone resorption and osteoblastic bone formation. It is widely believed that the metabolic activities of these executive cells are regulated by a mechanosensory system of osteocytes buried in the extracellular bone matrix, forming a three-dimensional intercellular network through cellular processes in lacuno-canalicular porosity [1]. The small space surrounding the osteocytes in the porosity is filled with interstitial fluid. When the bone is subjected to dynamic loading, bone matrix deformation induces an interstitial fluid flow [2]. The fluid flow in the lacuno-canalicular porosity seems to mechanically activate the osteocytes and serve as the prime mover for bone remodeling, as well as transport cell signaling molecules [3]. To understand the mechanism of bone functional adaptation, it will be useful to propose a theoretical framework of trabecular bone remodeling that interconnects the microscopic cellular activities to the macroscopic morphological changes through the mechanical hierarchy. In this study, first, we constructed a mathematical model for trabecular bone remodeling, taking cellular mechanosensing and intercellular communication into consideration [4]. This model assumes that osteocytes respond to fluid-induced shear stress and deliver their mechanical signals to the surface cells by intercellular communication. The mechanical behavior of a trabecula with lacuno-canalicular porosity is modeled as a poroelastic material to evaluate the interstitial fluid flow under mechanical loading. Second, on the basis of the proposed mathematical model, we simulated morphological changes in a single trabecula under cyclic uniaxial loading with various frequencies, which is thought to be a significant mechanical factor in bone remodeling. The results of the simulation show the trabecula reoriented to the loading direction with the progress of bone remodeling. As the imposed loading frequency increased, the diameter of the trabecula in the equilibrium state was enlarged by remodeling. Finally, we conducted a remodeling simulation for a cancellous bone cube under monotonously increasing compressive loading, where all the trabeculae are randomly-oriented in the initial geometry. As a result, the degree of trabecular connectivity was gradually decreased and the trabeculae in cancellous bone aligned along the loading direction. These results indicate that our remodeling simulation model can successfully express the macroscopic changes in trabecular morphology from the microscopic cellular activities.

References.

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Poster Session; Friday, July 1, 20:00

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Tradeoff of Information Transmission and Decoding with Intracellular Kinetics

A variety of cellular processes functions reliably by intracellular reactions even though substantial noise is inevitable. In particular, detection of relevant information from environment is crucial for the fate of cells.

From the viewpoint of information theory, such information processing is composed of three parts: encoding, transmission and decoding. Here, for a simple setup in the context of biochemical reactions, the roles of the three parts can be played by environment, receptors on membranes, and intracellular reactions, respectively. In engineering, much efforts have been generally made to reduce noise in encoding and transmission parts. By contrast, decoding may also play equally important role in biological systems, which is suggested by the substantial noise in microscopic cellular systems.

While decoding is to extract as much information as possible from the transmitted signals, such processing, in reality, should be implemented in the chemical reactions. For example, kinetics with dual positive feedback structure can implement a dynamic Bayesian inference, which gives the statistical limit for the decoding[1][2]. However, the efficiency of decoding would be limited by physical constraints such as amount of available energetic cost. We still lack a general framework to quantify how the transmission and decoding work.

Here, we consider this problem by calculating mutual information among encoding, transmission, and decoding parts of simple models with several intracellular reactions. By the quantification, we clarify the tradeoff of transmission and decoding. When the transmission part carries a large amount of information, decoding need not necessarily work effectively, since it is clear from the transmitted information to detect the state of environment. On the other hand, decoding by intracellular reactions becomes essential to obtain information when detecting from transmitted information is not straightforward.

References.

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Epidemic models: Networks and stochasticity II; Thursday, June 30, 11:30

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Following epidemic spread: how epidemics travel and trim their network of infectious contacts

Epidemics of infectious diseases are ubiquitous, however, their patterns vary depending on the course of disease and the transmission network established by infectious contacts. Therefore, strategies to maintain public health cannot be applied uniformly but have to be adjusted to the specific epidemic scenario. Network models have proven to be a helpful tool to infer time scales of epidemic expansion and prevalence from the structure and dynamics of the underlying transmission network. We extend the existing mathematical framework to also quantify the reverse effect: epidemics impact on the way contacts are made among susceptible and infected hosts. A set of partial differential equations links the structure and dynamics of the transmission network to the epidemic process. It allows to study epidemics on dynamic transmission networks with arbitrary degree distributions and under demographic change [1,2]. The framework will be used in epidemic case studies including multi-staged HIV epidemics. These studies show how epidemics do not only travel but also trim their transmission networks and allow for an exploration of intervention strategies.

References.

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Modeling physiological systems: model validation and experimental design issues; Wednesday, June 29, 11:00

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Parameter selection in multi-output systems

We present methods for a priori selection of parameters to be estimated in inverse problem formulations for models with multiple measurable outputs. Since in many modeling processes we have to deal with dynamical systems with numerous state variables and an even larger number of parameters, but with limited availability of data, we cannot expect to estimate all parameters with sufficient accuracy. Therefore methods of the type indicated above are becoming increasingly important. In situations with multiple measurable outputs we are also interested to know if the possibility to measure additional outputs would improve parameter estimates. Such questions become important if these additional measurements involve high costs, for instance. We illustrate the results for a model for insulin-glucose dynamics [2] and a model for the reaction of the cardiovascular system to an ergometric workload [1].

References.

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Game theoretical modelling and optimization in evolution and ecology II;
Tuesday, June 28, 14:30

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Mixed Strategies, Evolution and the Tragedy of the Commons in Heterogeneous Populations

The question of sustainability and prevention of the tragedy of the commons, also known as evolutionary suicide, which occurs when extremely efficient consumers exhaust the common resource and eventually harm themselves, is becoming of vital importance in the modern world. In order to investigate it we consider a situation, when consumers can choose different strategies for resource consumption in different proportion, investing primarily in consumption or in sustaining the resource. This is modeled by an infinitely-dimensional system of ODEs, which is then reduced to a finitely-dimensional system using parameter distribution. The population of consumers is then allowed to evolve over time, and the changes in the frequency of different strategies are tracked through changes in the expected value of the parameter that describes the choice of a strategy. We demonstrate that under different parameter values different strategies predominate, leading to either sustained interaction with the resources, or to population extinction, which occurs after a series of transitional regimes.

Evolutionary Ecology; Wednesday, June 29, 08:30

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Adaptive trade-off between reproduction and survival in Mediterranean fruit flies induced by changing dietary conditions

The conception of the cost of reproduction provides an important insight on connection between fertility and life span in living organisms. Despite substantial progress in understanding this connection many important features of fertility-longevity trade-off are masked by confounding factors, and remain poorly understood. We performed reanalysis of data from experimental study of fertility and longevity response to different diets in females of Mediterranean fruit fly *C. capitata* [1, 2]. A negative dependence between average fertility and longevity was observed in the long lived part of experimental cohorts as the protein content of the diet changed. In order to explain the observed phenomenon we suggest a mechanistic resource allocation model. The model is further development of the resource allocation model proposed in [3]. The presence of a fertility-longevity trade-off suggests a possibility of existence of some resource used both by reproduction and somatic maintenance in a fly. The trade-off may be a manifestation of metabolic machinery, processes and genetically determined laws of control which define balance between the processes of reproduction and regeneration. We propose and discuss a principle of dynamic resource allocation which explains fertility-longevity data for the long-, intermediate- and short-lived flies. Adaptive allocation of metabolic and other resources allows flies to tailor their life history parameters to the environment. Due to limitations of the physiological adaptation a significant share of the population may be genetically "preadapted" to different environmental conditions thus contributing to population stability and heterogeneity. This may be observed even in relatively homogeneous populations, such as experimental fly cohorts.

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Evolutionary Ecology; Wednesday, June 29, 11:00

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Evolution of polymorphism on a heterogeneous landscape

The effect of spatial heterogeneity and habitat boundaries on the coexistence of multiple competing strains has been of recent interest as a novel mechanism for maintaining diversity above the level predicted by the competitive exclusion principle. Given that limited dispersal in heterogeneous landscapes can indeed enable the stable coexistence of more competitors than there are resources, a natural next step is to investigate the emergence and stability of such diversity under evolution. I present some results from individual-based simulations of evolving populations on a heterogeneous lattice landscape, and contrast these with some semi-analytical approximations, showing that evolution in such systems can indeed lead to the emergence of polymorphism and stabilize it against local extinction due to demographic stochasticity.

Analysis of mathematical models for cancer growth and treatment, Part III; Tuesday, June 28, 17:00

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A control approach for ODE cancer models

In this talk, we investigate cancer by using a control approach based on set-valued analysis and viability theory, given a class of ODE tumor dynamics. We show how adequate selection procedures can lead to feedback protocols with which cancer cells are eradicated. In contrast to the optimal control approach, our set-valued framework allows of highlighting the well known connection between the initial cancer stage and its curability, as well as the minimality and smoothness of a protocol and their impact on the patient quality of life. Examples from the literature are studied in order to illustrate the approach.

References.

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Poster Session; Friday, July 1, 20:00

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Modeling of β-catenin signaling in Medulloblastoma

Medulloblastoma is a brain tumor that mainly affects children and is caused by several mutations. Our research is devoted to understanding of the role of monosomy and trisomy of the *6* chromosome. Each perturbation is characterized by extremely different prognosis. Trisomy is found to have a very bad prognosis and monosomy surprisingly good after medical treatment. *6q loss* and *6q gain* are related with difference in expression of cMyc, SGK1, which are target genes of β-catenin signaling in mutated cells. Our observations suggest that disruption in chromosome balance strongly affects the mentioned signaling pathway. However, the mechanism is still not explained. We can only see consequences which result in different mRNA levels of cMyc and SGK1. It is also not well understood how these differences influence the prognosis. Thus investigation of particular interactions between proteins is so interesting. We propose an ODE model describing complicated dynamics of chosen genes, concerning transcription, translation as well as transport between cytoplasm and nucleus. We calibrate models based on clinical data for both types of medulloblastoma. Simulations lead to a better understanding of the process. In particularly, the model indicates the important role of SGK1 gene in the process of oncogene cMyc production leading to cancer relapse.

Poster Session; Friday, July 1, 20:00

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A mathematical model for the mode transition of locomotion in *Amoeba proteus*

In amoeba locomotion, pseudopods extend toward the direction of motion [1]. Recently, we found that the pseudopod of *Amoeba proteus* shows the characteristic extension modes depending on the tail speed of amoeba. When the tail speed is high, the pseudopod extends at almost constant speed (Smooth mode.) On the other hand, when the tail speed is low, the pseudopod extends and stopps alternately (Oscillatory mode.) Namely, the extension of the pseudopod shows the mode transition from the smooth mode to the oscillatory mode as the tail speed decreases. In the conventional understanding, the tail contraction was considered to be the origin of motile force of the locomotion in *Amoeba proteus* [2]. Our finding suggests that the tail contraction also contributes the pseudopodial extension patterns which exhibit the mode transition.

To understand the mechanism, we construct a mathematical model. In our model, the amoeba is described as an elastic tube in which the protoplasmic sol is confined. The locomotion is driven by the tail contraction. The head is extended by the inner pressure, and the velocity of the head is controlled by the softness of the head. Our model successfully represented the mode transition from the smooth mode to the oscillatory mode as the tail speed decreases.

References.

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[2] Sonobe, S., and Nishihara, E. *Cell biology of Amoeba proteus.* Jpn J Protozool, **37** 159–167, 2003.

Modeling of immune responses and calcium signaling V; Saturday, July 2, 11:00

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Buffered calcium waves with mechano-chemical effects

We analyze the following system of equations:

$$\begin{aligned} \frac{\partial c}{\partial t} &= D\frac{\partial^2}{\partial x^2}c + g(c) + \sum_{i=1}^{n} G_i(c, v_i) \ + R(c, \theta, J_1, J_2) \\ \frac{\partial v_i}{\partial t} &= D_i\frac{\partial^2}{\partial x^2}v_i - G_i(c, v_i), \quad i = 1, \ldots, n, \end{aligned} \tag{1}$$

$$0 = \nabla \cdot \left\{ \frac{E}{1+\nu}\left[\varepsilon + \frac{\nu}{1-2\nu}\theta\mathbf{I}\right] + \mu_1\frac{\partial \varepsilon}{\partial t} + \mu_2\frac{\partial \theta}{\partial t}\mathbf{I} + \tau(c)\mathbf{I}\right\} - \vartheta\mathbf{u}. \tag{2}$$

where c denotes the concentration of free cytosolic calcium ions, v_i the concentration of the i-th buffer, ε the strain tensor, $\mathbf{u}$ displacement field, τ active concentration stress resulting from the actomyosin traction $\tau(c)$. We assume that the ratio $(\mu_1 + \mu_2)/E$ is sufficiently small. We prove the existence of travelling waves to the above system, analyze the influence of viscosity on the speed of the wave and give the explicit formulae for some specific solutions. We confine ourselves to three geometrical cases: bulk medium (large in every direction), infinite plane layer of sufficiently small width and long cylinder of sufficiently small radius.

This study was supported by the Polish Ministry of Science and Higher Education grant N N 201548738 and Foundation for Polish Science grant TEAM/2009-3/6.

Mathematical Modelling of Macromolecules and Molecular Aggregates;
Saturday, July 2, 14:30

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Penrose-like tilings as geometric constraints on the structures of protein assemblies.

Non-crystallographic symmetry is common in protein assemblies, from icosahedral symmetry in viral capsids to five-fold and seven-fold axial symmetry in C-reactive proteins and chaperonin molecules, respectively. We have shown that the overall organisation of such structures can be predicted using affine extensions of non-crystallographic symmetry. In particular, important insights can be gained not only into the outer surfaces of these clusters, but also in how symmetry is correlated at different radial levels. For example, in applications to viruses, this has led to the discovery of a molecular scaling principle between different viral components. Here I will show that Penrose-like non-crystallographic tilings derived from higher dimensional lattices can be used to provide bounding boxes for proteins in non-crystallographic assemblies.

Moving Organisms: From Individuals to Populations; Wednesday, June 29, 17:00

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Integrin mediated Cell Migration: Multiscale Models, Analysis and Numerics

Invasion is a key property of cancer cells, whereby the contact with the surrounding tissue both enables the cells to move along tissue fibers and stimulates the production of proteolytic enzymes that destroy the tissue network, thus enhancing cell migration. The product of the tissue degradation is seen as a chemotactic signal influencing the movement direction of the cells.

Existing models for the migration of tumor cells deal with the interactions of the cells with the environment but do not account for biochemical processes in the cell or on its surface. This processes are however very important, since the dynamics of receptors on the cell surface and the cytoskeleton structure are decisive in determining the speed of the cell as well as the secretion of proteolytic enzymes.

We present a model incorporating this subcellular mechanisms in a kinetic equation for cell movement, which is then supplemented by a reaction-diffusion equation for the chemoattractant along with an integro-differential equation for the tissue fibers. We then address the question of existence and uniqueness of solutions for this strongly coupled system of equations.

This strongly coupled and high dimensional model presents a real challenge for the design of a suitable simulation methodology. Selected simulation results illustrate important phenomena that arise in the model.

Poster Session; Friday, July 1, 20:00

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Methods to model (and quantify the complexity of) bio-molecular conformational dynamics

We present methods for inferring hidden Markov models from continuous data clustered around discrete values without the necessity of assuming a model architecture and as such are capable of inferring the existence of degenerate states (states with the same distribution for the observable variable but different transition probabilities). The models inferred in this way are provably optimal and minimal statistical predictors of the data. Additionally, information theoretic measures applied to the inferred model quantify the complexity of the data.

The methods have been demonstrated on the conformational dynamics of Holliday (4 way DNA) junctions (under review - http://arxiv.org/abs/1011.2969) as investigated by fluorescence resonance energy transfer spectroscopy. However, the methods are applicable to any data meeting certain criteria and as such may be applicable to many dynamical systems.

Poster Session; Friday, July 1, 20:00

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Optimising chemo- and radiotherapeutic treatment protocols using synergy and tumour synchronisation

We present an agent-based approach to the modelling of cellular dynamics within tumour spheroids under the effect of combined chemotherapy and radiation treatment. Within our agent-based approach cells are represented as instances of a C++ cell-class which advance through a realistic cell cycle in response to external and internal stimuli such as the concentration of nutrients and the pressure upon the cell by neighbouring cells. The model makes use of a dynamic Delaunay triangulation in order to derive the cell neighbourhood topology while its dual, a Voronoi tessellation, is employed in order to calculate the contact surfaces between adjacent cells. Our model employs the well-known linear quadratic model for irradiation damage in combination with a stochastic model for the cell's dynamic reaction to damage.

We can study the growth of tumour spheroids up to a volume of about $1mm^3$ which show a high degree of complexity and can thus be used as a model system for larger amounts of tumour tissue as they possess all properties which are present in large-scale tumours (hypoxic regions, necrosis, concentration gradients). As a results of irradiation treatment a dynamic reaction is triggered in the tumour system which can be studied in detail. Reoxygenation of the tumour volume and a decrease in pressure due to cell necrosis lead to excessive regrowth after irradiation as previously quiescent cells are reactivated. A distinct resynchronisation of the cell cycle is observed which can be exploited within fractionated irradiation treatment or the timed delivery of drugs.

Using measured survival curves for single cell cycle phases we can show that the amount of tumour killing will strongly depend on the activation status of the tumour. A radiation- or drug-induced synchronisation of the cell cycle can be exploited to target the tumour in an optimal state where the sensitivity to the planed treatment is maximal. Thus we can calculate treatment protocols which will result in a greatly enhanced amount of tumour killing for the same dose of radiation or drug.

Combining medication and radiation treatment in our simulation we can show that the tumour can be optimally prepared to increase the radiosensitivity during following treatments. Vice versa there are optimal points to employ chemotherapy after irradiation sessions.

References.

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Mathematical Modelling of Macromolecules and Molecular Aggregates;
Saturday, July 2, 14:30

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Discrete groups and internal symmetries of icosahedral capsids.

The Caspar-Klug classification of icosahedral capsids [**1**] takes into account only their size, given by the triangular number T = p + pq + q. It can also note the difference between chiral and non-chiral capsids. But it does not take into account more subtle differences resulting from the differentiation of coat proteins serving as elementary blocks from which capsids are assembled by agglomeration. [**2**], [**3**]. We develop further the classification of icosahedral capsids introduced a few years ago [**4**], [**5**], using the symmetry group action on the elementary triangles

We analyze the differentiation of coat proteins forming an icosahedral viral capsid with a given triangular number T. A typical icosahedral capsid can be subdivided into twelve pentagons and 10(T-1) hexagons, which can be realized either as genuine hexamers, or as a combination of dimers or trimers.We assume that the pentamers, which are found in twelve vertices of the capsid, display five identical sides. This is usually the case, except for the Papovaviridae family in which all pentamers are maximally differentiated, displaying five different sides (abcde) instead of five identical ones (aaaaa).

Hexamers can display various degrees of differentiation. The symmetry imposes that their sides can be either of two types, or three types, or six different types: (ababab), (abcabc) or (abcdef), respectively, because 6 is divisible by 2, 3 and 6. These cases have been discussed in our previous work, and enabled us to introduce four internal symmetry classes in capsid viruses, according to the presence or absence of the aforementioned hexamer types. The full information about a given icosahedral capsid structure can be read from one of the twenty identical triangular faces. The first hexamer type, (ababab) is fouund only in triangles's centers, because of its three-fold symmetry; the type (abcabc) can be found at the edges of the triangular face, and maximally differentiated hexamers (abcdef) can be found in any position.

However, a more subtle analysis can be made if other hexamer types are taken into account. The partition into 2, 3 or 6 different sides must be maintained, but the two (ab) and three (abc) proteins can be placed differently in a hexamer, e.g. like (aaabbb) instead of (ababab), or (aabbab); the three different proteins (abc) can be displayed as (abccba) instead of (abcabc), generating even instead of chiral symmetry around the edge. With these new configurations included, the classification of icosahedral capsids becomes more complete.

We also show how the capsids agglomerate in a way that always minimizes the number of different proteins needed for the construction. This is being illustrated on the examples provided by the herpesvirus (T=16) and human adenovirus (T=25). Our classification gives some extra hints concerning genetic proximity of viruses displaying similar classes of capsid symmetries.

References.

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Ecosystems Dynamics; Tuesday, June 28, 14:30

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Modelling the Emergent Dynamics of Microbial Communities in the Human Colon

Modelling microbial ecosystem dynamics in the human colon is challenging due to large variations between individuals and limited amounts of data. In an attempt to overcome these issues we take a complex adaptive systems (CAS) approach to the problem. Thus a model is developed in which the dominant bacterial strains are not defined a priori but are allowed to 'emerge' from a stochastically generated bacterial population. To do this we begin by assuming that every bacterial strain falls into one of ten bacterial functional groups (BFGs) which are distinguished by their metabolic pathways and their preferred pH ranges. The metabolic pathways form a network which determines the dietary substrates each BFG grows on and which metabolites it may consume or produce. The parameters controlling the exact rates of transfer along these pathways, and the preferred pH ranges are then generated stochastically, within appropriate limits, for a population of 300 bacterial strains. The rates of change of mass of each strain, resource and metabolite are computed by solving a system of ordinary differential equations. Due to competition for resources, and interactions within the metabolic network, some strains will flourish and some will disappear, such that over time a viable community for the given environment emerges. In this work, the equations governing the model are described and the model results are compared to data from a fermentor study which examines the effects of pH on the microbial community. We then demonstrate how this CAS modelling approach allows the system to adapt to its environment through species succession and investigate different mechanisms for avoiding competitive exclusion within the BFGs.

Population Dynamics; Wednesday, June 29, 08:30

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Role of fluctuations in front propagation the insect outbreak model

Propagating fronts arising from bistable reaction diffusion equations are a purely deterministic effect. Stochastic reaction diffusion processes also show front propagation which coincides with the deterministic effect in the limit of small fluctuations (usually, large populations). However, for larger fluctuations propagation can be affected. We give an example, based on the classic spruce-budworm model, where the direction of wave propagation, i.e., the relative stability of two phases, can be reversed by fluctuations.

Connecting microscale and macroscale models of cellular migration;
Tuesday, June 28, 17:00

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Fronts of cells invading a wound: from discrete stochastic approach to continuum description

We present a stochastic model that describes fronts of cells invading a wound. In the model, cells can migrate, proliferate, and experience cell-cell adhesion. We find several qualitatively different regimes of front motion and analyze the transitions between them. Above a critical value of adhesion and for small proliferation, large isolated clusters are formed ahead of the front. This is mapped onto the well-known ferromagnetic phase transition in the Ising model. The results are compared with experiments, and possible directions of future work are proposed. We also focus on a continuum description of this phenomenon by means of a generalized Cahn-Hilliard equation (GCH) with a proliferation term. As in the discrete model, there are two interesting regimes. For subcritical adhesion, there are propagating "pulled" fronts, similarly to those of Fisher-Kolmogorov equation. The problem of front velocity selection is examined, and our theoretical predictions are in a good agreement with a numerical solution of the GCH equation. For supercritical adhesion, there is a nontrivial transient behavior, where density profile exhibits a secondary peak. The results of continuum and discrete models are in a good agreement with each other for the different regimes we analyzed.

Poster Session; Friday, July 1, 20:00

Afifa Iftikhar, Mudassar Imran, Adnan Khan
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A Stochastic Model for Calcium Regulation in Spines

The study of calcium signals in dendritic spines is of great interest, as these by either action potential or by synaptic activity play a crucial role in the synaptic plasticity within an individual spine. Because of the small size of spine and the indicators commonly used to measure spine calcium activity, calcium function can be severely disrupted. Therefore, it is very difficult to explain the exact relationship between spine geometry and spine calcium dynamics. Recently, it has been suggested that the medium range of calcium which induces long term potentiation leads to the structural stability stage of spines, while very low or very high amount of calcium leads to the long term depression stage which results in shortening and eventually pruning of spines. We discuss a stochastic model to examine the role of calcium and the mechanisms that govern its regulation in the spine morphology.

Epidemics; Saturday, July 2, 08:30

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Homotopy perturbation method for traveling wave solutions of system of biological reaction-diffusion equations

In this paper, we apply a technique which is called homotopy perturbation method (HPM) for obtaining analytical approximate traveling wave solutions of system of biological reaction diffusion equations of the type

$$\begin{aligned} S_t &= \varepsilon S_{xx} - \nu S_x - f(S)P, \\ P_t &= P_{xx} - \nu P_x + [f(S) - K]P. \end{aligned} \tag{1}$$

Biological reaction diffusion equations are used as mathematical model for several problems in biology and chemistry. For example (1) was used as a mathematical model for microbial growth and competition in a flow reactor. The theory of reaction-diffusion waves started in the 1930s, initial works was carried out in population dynamics, combustion theory and chemical kinetics. Nowadays, it is a well developed area of research. This includes qualitative properties of traveling waves for the scalar reaction-diffusion equation and for system of equations, complex nonlinear dynamics, numerous applications in physics, chemistry, biology and medicine. Existence of traveling waves reflects the important phenomena of wave propagation and has extensively studied by many authors. The homotopy perturbation method (HPM) proposed by Ji-Huan He in 1998 is a method for finding approximate solutions of non-linear differential and integral equations. This method is popular amongst non-mathematician and engineers because HPM decomposes a complex problem under study to a series of simple problems that are easy to be solved. The results obtained reveal that the homotopy perturbation method is effective and simple. Some plots are presented to confirm the theoretical results.

Cancer; Wednesday, June 29, 08:30

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The non-linear mathematical model of growth of tumors of different forms

The mathematical model of tumor growth is constructed taking into the account the competition of normal and tumor cells for the nutrients supply and new vessels formation under oxygenal stress. The character of different geometry of tumor growth is considered (such as cylindrical and spherical). The system of non-linear differential equations is obtained

$$\frac{dx}{dt} = g_1 x^{\frac{2}{3}} - \nu_1 y,$$
$$\frac{dy}{dt} = g_2 y^{\alpha} - \nu_2 y,$$

with the initial conditions

$$x(0) = x_0, \;\; y(0) = y_0,$$

where $x(t)$ is the volume of normal cells, $y(t)$- is the volume of tumor cells, which depends on time t, a and b are the nutrients consumption rates, g_1, g_2 are the growth velocity of $x(t)$ and $y(t)$ consequently, ν_1 and ν_2 reflects a necrotic factors, α is a geometric characteristic of the tumor volume.

The system is investigated numerically, computer simulations are given.

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Mathematical modeling of biomechanical regulation in bone tissue (Session II); Wednesday, June 29, 11:00

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Evolutionary simulation of the emergence of the mechano-regulated endochondral healing process

The ability of tissues to adapt to the mechanical environment is a remarkable feature of the skeleton. Several mechano-regulation theories have been proposed for describing how the mechanical environment modulates mesenchymal stem cell differentiation into bone, cartilage and fibrous tissue. Despite the biological complexity of the process, these theories have often been able to predict osseous healing through both membraneous and chondral healing, with reasonable success [1,2].

It is intriguing to wonder about the emergence of these healing processes, in particular the endochondral ossification process, in evolution and whether the ability of mechano-regulation has been involved in the emergence of new healing processes through natural selection. Early vertebrates, like cartilaginous fishes, could modulate their tissues to the mechanical environment and it is likely that evolution worked with adapting the skeletal tissues to the local conditions rather than involving major changes in cells or tissue types [3].

This study shows how the mechano-regulated endochondral ossification process could have emerged in evolution by being favoured in natural selection. The combination of a mechano-regulated tissue differentiation model [4] and a genetic algorithm for simulating evolutionary change [5], used in this investigation, was further able to capture inter-population variability in the mechano-regulated response and arrived at results that are in agreement with experimental studies of mechano-regulated differentiation and maintenance of bone [6,7].

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Getting old and misbehaving: Can stromal aging drive melanoma initiation?

We have implemented a hybrid cellular automata model of skin that focuses on key variables implicated in the regulation of normal homeostatic skin function and its disruption in melanoma initiation and progression. The model consists of both discrete cellular species such as melanocytes, transformed melanocytes, keratinocytes, and fibroblasts, and continuous microenvironmental variables such as growth factors and extracellular matrix. The behavior of each of the discrete cell species is defined using life cycle flowcharts. Based on experimental observations, we know that when fibroblasts age they can become senescent and start producing factors that may disrupt the very homeostasis that they should maintain. We incorporate these phenotypic changes as fibroblasts age and use our model to examine how these changes affect skin function.

Specifically, we examined the effects of disrupting interactions between melanocytes, keratinocytes, fibroblasts and their microenvironment and the role of aged fibroblasts in driving melanoma initiation. Model simulations provide a series of virtual skin pathologies that readily recapitulate a spectrum of true aberrant clinical pathologies. Direct comparison between these pathologies allowed us to find the critical perturbations that drive melanoma initiation and progression. We also utilize an *in vitro* 3D organotypic skin model to further investigate some of the model predictions.

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling I; Saturday, July 2, 08:30

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The role of the microenvironment in an early development of breast cancer: a hybrid (multiscale) model.

Mathematical modeling and computational analysis are essential for understanding the dynamics of the complex gene networks that control normal development and homeostasis, and can help to understand how circumvention of that control leads to abnormal outcomes such as cancer. Tumor microenvironment (TME) is comprised of various signaling molecules, cell types and the extracellular matrix. We investigate how the local biochemical and mechanical microenvironment can affect the progression of potentially-cancerous cells in an early development of breast cancer. The model deals with the effects of the mechanical properties of the microenvironment on tumor growth, and we report results from a multi-scale model of the signaling pathways and the TME. The results emphasize the complexities of the interactions within the TME and their effect on tumor growth, and show that tumor progression is not solely determined by the presence of a clone of mutated immortal cells, but rather that it is communitycontrolled.

Mechanical Models of Movement and Growth of Cells and Tissues I;
Wednesday, June 29, 14:30

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The role of the microenvironment in tumor invasion: a mathematical model

Glioma cells tend to migrate from the primary tumor into the surrounding tissue. We develop a mathematical model which includes the role of adhesion and mechanical interaction between glioma cells and collagen network. Simulation results show cell migration behavior through the extracellular matrix using information from the complex fibrous structure. We also take into account the intracellular signals at each cell site for this cell migration through the ECM. We consider the detailed mechanical interactions between cells and between a cell and the collagen fibers in addition to reaction-diffusion of molecules.

Modeling physiological systems: model validation and experimental design issues; Wednesday, June 29, 11:00

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Physiological modeling of trace gas exhalation kinetics: a non-invasive window to the body

Exhaled breath contains a plethora of volatile organic compounds (VOCs), resulting from normal metabolic activity as well as from specific pathological disorders. These trace gases can be detected and quantified at concentrations down to the parts-per-billion (ppb) level and hold great promise for medical diagnosis, therapeutic monitoring, and general assessments of physiological function. In particular, exhaled breath can nowadays be measured *on-line*, thus rendering VOC analysis as an optimal choice for gaining continuous and *non-invasive* information on the current metabolic and physiological state of an individual.

The success of using breath VOC concentration profiles for estimating endogenous processes will mainly hinge on the availability of valid mechanistic descriptions for the observable exhalation kinetics of the compound under scrutiny. Within this context, we focus on *real-time* measurements of VOCs during distinct physiological states, e.g., rest, exercise, and sleep [1,2].

An experimental setup for correlating breath-by-breath analyses using proton transfer reaction mass spectrometry (PTR-MS) with the behavior of major hemodynamic and respiratory variables will be presented. Building on the phenomenological findings from studies of normal volunteers, a novel compartmental modeling framework capturing the physiological flow of two prototypic VOCs, isoprene and acetone, is developed and validated [3,4].

Furthermore, several powerful concepts for system and parameter identification will be outlined, including qualitative system analysis, *a priori* identifiability, and numerical schemes based on multiple shooting.

The results discussed are intended as a first step towards employing breath gas analysis as a tool for examining exhalation, storage, transport, and biotransformation processes associated with volatile organic compounds *in vivo*.

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Ecology and evolution of infectious diseases; Friday, July 1, 14:30

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The curse of the pharaoh hypothesis revisited: Evolutionary coexistence of parasite strains

Several pathogens produce free-living stages that allow the infection to spread from one host to the next indirectly, via an outside environment. Since the reproductive success of pathogens with long-lived spores depends less on the host's survival, it has been hypothesized that such pathogens can afford to exploit their hosts more recklessly and thus evolve higher virulence. We revisit the so called 'curse of the pharaoh' hypothesis and study the evolution of virulence in pathogens that can transmit directly as well as indirectly, via free-living stages. We show that the two transmission routes introduce two environmental feedback variables, which allows for coexistence of two parasite strains one of the two specializes to some extent on direct transmission, while the other makes better use of indirect route of transmission. We give general conditions for coexistence in terms of incidence in host-to-host and host-propagule-host transmission, and discuss the conditions for evolutionary branching leading to coexisting strains in terms of the shape of trade-off functions.

Information, human behaviour and disease; Saturday, July 2, 11:00

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Multiple sources and routes of information transmission: implications for epidemic dynamics

In a recent paper [1], we proposed and analyzed a compartmental ODE-based model describing the dynamics of an infectious disease where the presence of the pathogen also triggers the diffusion of information about the disease. In this paper, we extend this previous work by presenting results based on pairwise and simulation models that are better suited for capturing the population contact structure at a local level. We use the pairwise model to examine the potential of different information generating mechanisms and routes of information transmission to stop disease spread or to minimize the impact of an epidemic. The individual-based simulation is used to better differentiate between the networks of disease and information transmission and to investigate the impact of different basic network topologies and network overlap on epidemic dynamics. The paper concludes with an individual-based semi-analytic calculation of R_0 at the non-trivial disease free equilibrium.

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Poster Session; Friday, July 1, 20:00

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Analysis of the uterine contractility: wavelet cross-correlation function and wavelet coherence measure

Evaluation of uterine contraction activity is an important element in physiological menstrual cycle and diagnostics of labor. Changes in synchronization of two simultaneously recorded uterine contractility signals accompany various kinds of gynecology disorders and obstetric pathologies, e.g. endometriosis, fibromyomas, preterm birth and tumors. The purpose of this study is to analyze these signals using wavelet cross-correlation function and wavelet coherence measure.

Spontaneous uterine contractions were recorded directly by a dual micro-tip catheter (Millar Instruments, Inc.). The device consisted of two ultra-miniature pressure sensors. The distance between the sensors was 30mm (one sensor was placed in the fundus and the other in the cervix). The sensors produced electrical signals, which varied in direct proportion to the magnitude of measured pressure. We have analyzed the signals obtained during examinations of women suffering from primary dysmenorrhea (28 examinations), endometriosis (11 examinations), uterine myomas (9 examinations), and 1 examination from healthy woman. The Bioethics Committee of Medical University of Białystok approved the study. This method is invasive thus there was no control group.

Wavelet cross-correlation function describes the dependency of correlation of two signals on the shift between them. Location of maximum or minimum of this function informs us about the relative time delay of these signals. Signals are considered similar if the maximum is close to 1 or minimum is close to -1 (inverted signal). We have used multiresolution analysis from wavelet analysis to create wavelet cross-correlation function. We have chosen suitable frequency level, where energy is transferred, as the base for computation of wavelet cross-correlation function. Wavelet coherence measure was calculated by multiresolution wavelet analysis of the uterine contraction signals and a coherence analysis by means of Welch method in selected frequency band containing the dominant frequency. By computation of wavelet coherence function we have obtained the information what are the common frequencies and when they appear. We were also able to estimate the similarity of two signals.

Negative shifts computed by means of wavelet cross-correlation function indicate improper propagation of contractions (wrong direction) in unhealthy women.

Using graphs of these functions one can distinguish visually the signals obtained from healthy woman from signals obtained from unhealthy women. Common frequency for signals from uterine fundus and uterine cervix computed by means of wavelet coherence function is about 0.05Hz. The lowest similarity (synchronization) between signals from uterine fundus and uterine cervix has been observed for signals from women suffering from primary dysmenorrhea.

We concluded that these methods may be useful tools in analyzing synchronization of two simultaneously recorded uterine contraction signals.

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Epidemic models: Networks and stochasticity II; Thursday, June 30, 11:30

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Controlling epidemic spread by responding to risk: Do it well or not at all

Disease outbreaks change people behaviour. This change can be used to control epidemics but it comes at a cost. We describe results from using simulation to study the costs and benefits of using social distancing as a form of control. Our model consists of a standard SIR model superimposed on a simple spatial network. Disease spread is controlled by allowing susceptible individuals to temporarily reduce their social contacts in response to the presence of infection within their local neighbourhood. We ascribe an economic cost to the loss of social contacts, and weigh this against the economic benefit gained by reducing the attack rate of the epidemic. Our first result is that, depending on the characteristics of the epidemic and on the relative economic importance of making contacts versus avoiding infection, the optimal control is one of two extremes: either to *panic*, that is, to adopt a highly cautious control, thereby suppressing the epidemic quickly by drastically reducing contacts as soon as disease is detected; or else to *relax* by forgoing control and allowing the epidemic to run its course. The worst outcome arises when control is attempted, but not cautiously enough to cause the epidemic to be suppressed. Our second result comes from comparing the size of the neighbourhood of which individuals are aware to that of the neighbourhood within which transmission can occur. We see that control works best when these sizes match, and that it is particularly ineffective when the awareness neighbourhood is smaller than the infection neighbourhood. These results have implications for the design of control strategies using social distancing. An important message is that a weak control, or one based upon inaccurate knowledge, may give a worse outcome than doing nothing.

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Dynamic regulatory on/off minimization infers key regulators of the Calvin cycle under internal temporal perturbations

Flux balance analysis (FBA) together with its dynamic extension, DFBA, have proven instrumental for analyzing the robustness of metabolic networks. Under the assumption of minimization of metabolic adjustment, DFBA has recently been employed to analyze the transition between metabolic states at systemic level. Here we propose a suite of novel methods for analyzing the dynamics of perturbed metabolic networks and quantifying their robustness without knowledge of kinetic parameters. Following the biochemically meaningful premise that metabolite concentrations exhibit smooth temporal changes, the proposed methods rely on minimizing the significant fluctuations of metabolic profiles to predict the time-resolved metabolic state characterized by both fluxes and concentrations. On a model of the Calvin cycle, we demonstrate that the principle of regulatory on/off minimization (ROOM) coupled with DFBA can accurately predict the changes in metabolic states. Our methods outperform the existing DFBA-based modeling alternatives, and help in revealing the mechanisms for maintaining robustness of dynamic processes in metabolic networks over time.

Mathematical modeling of biomechanical regulation in bone tissue (Session II); Wednesday, June 29, 11:00

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Tissue adaptation driven by chemo-mechanical coupling with application to bone

Based on the current knowledge of bone remodelling process, a biochemical model is proposed which describes the essential interactions that governs the whole bone remodelling process. Further, the influence of mechanical stimulation on bone tissue is well known. Considerations from non-equilibrium thermodynamics are used to quantify this effect and moreover to stress the importance of dynamic character of the loading. Particularly, the question of what constitutes a mechanical stimulation of biochemical reactions in general will be addressed and further to compare the importance of the two possible mechanical stimulations: shear rate and the rate of volume variation. Consequently, a modified form of the Law of Mass Action is derived which includes also the mechano-chemical coupling and not only the affinity of interaction based on the difference in chemical potentials. This rather different approach from the classical ones can predict bone density distribution as will be shown on some examples including the effect of stem insertion or osteoporosis.

Acknowledgement. This research has been supported by the Czech Science Foundation project no. 106/08/0557.

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Fractals and Complexity II; Wednesday, June 29, 17:00

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Applying Fractal Dimension in Analysis of Biosignals and of Medical Images

We present applications of fractal analysis of EEG and HRV signals, as well as of medical images, for supporting medical diagnosis and for assessment of influence of chemical and physical agents on living systems. We will show examples of stress assessment, sleep analysis, measuring the depth of anesthesia, classification of tumors based on Higuchis fractal dimension.

Population Genetics; Wednesday, June 29, 17:00

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The stationary distribution of the ancestral types in the Moran model with mutation and selection

We consider a stochastic model of population genetics, namely, the Moran model with mutation and selection. We use it to trace back the ancestral lines of single individuals, and are interested in the stationary distribution of the corresponding ancestral types. Two approaches to this problem are already available: The one by Fearnhead (2002), which is based on the ancestral selection graph (Krone/Neuhauser 1997), and the one by Taylor (2007), which relies on a description of the full population backward in time by means of a diffusion equation.
In both approaches, the resulting expression for the stationary distribution does not have an obvious interpretation in terms of the graphical representation of the model (i.e. the representation that makes individual lineages and their interactions explicit). In this contribution (which is joint work with Ellen Baake), we use the graphical representation to derive equations for the fixation probabilities of the offspring of all 'fit' individuals (regardless of the offspring's type). In the diffusion limit, this yields Taylor's differential equation - but now with a plausible interpretation attached to it. Furthermore, this also points the way towards a better understanding of the coefficients that define the stationary distribution.

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Dynamic Information and the Meaning of Biological Signs

The communication between cooperating and adversary organisms is central to the understanding of biological ecosystems. Commonly, this communication is formalized in terms of Claude E. Shannon's *Mathematical Theory of Communication* [4]. In this theory, information is represented as a measurable quantity arising from statistics on the underlying vocabulary. There have been several works addressing the application of Shannon information to biological systems [1,3,5].

Here, I argue that Shannon information encompasses significant shortcomings, which limit the applicability to communication in the life sciences. Since Shannon information is a purely statistical quantity, it treats only syntactic aspects of the communication process. In contrast, the levels of semantics, pragmatics, and dynamics [1] are not under consideration. Clearly, a message has always an impact on living systems, because it leads to a certain adaptive response. Yet this active response is part of the pragmatic-dynamic level and integral part of biological communication.

In this talk, I present an alternative concept of information [2]. The so-called *Dynamic Information* rates incoming signals with a relative importance depending on the internal state of an agent [1,2]. The bigger the induced change in the agent's behavior, the bigger are relative importance and the resulting dynamic information.

First, I introduce the mathematical framework modeling elementary biological communication by means of dynamical systems with input and output. In this approach, agents are represented by nonlinear coupled systems of ODEs with input terms. Next, the concept of dynamic information is developed as a bridge between the theory of dynamical systems and Shannons's theory of communication. Finally, I apply the developed framework to task allocation in ant colonies.

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Regulatory Networks; Friday, July 1, 14:30

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Mathematical Modeling of Phosphorelay Dynamics

Phosphorylation is one of the most prevalent forms of post-translational modifications by which signals are transmitted in living cells. A type of signaling pathway prevalent in bacteria is the two-component system (TCS), in which a signal is transferred through a series of phosphate group transfers moving the phosphate group from the sensor domain of one protein to the regulator domain of another protein. Similar pathways involving more than two proteins exist, and together with TCSs these are known as phosphorelays.

We present a rigorous mathematical analysis of phosphorelays assuming only mass-action kinetics. By combining an algebraic approach, previously applied to linear signaling cascades [1], with theory for monotone systems, we show that phosphorelays converge to unique stable steady states given initial total substrate concentrations. The proof relies on graph theoretical properties of the species-reaction Petri net (SR-net) and an analysis of the phosphorelay system in reaction coordinates. Using reaction coordinates, the system exhibits a special kind of monotonicity (the system is cooperative).

For the TCS, algebraic manipulations of the steady state equation lead to further insight into the system dynamics, for example in relation to stimulus-response curves. We obtain a polynomial equation relating stimulus and response, only depending on the rate constants and the total substrate concentrations. Using this relationship we are able to investigate, without restoring to simulation or further approximation, how the stimulus depends on the number phosphorylation sites of each protein.

Algebraic approaches to phosphorylation networks have been the topic of many recent publications, see [1,2] and references therein, and we believe that such approaches will be helpful for understanding many different types of systems.

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Statistical methods in computational neuroscience II; Wednesday, June 29, 17:00

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Made-to-Order spiking neuron model for a variety of cortical neurons

Information is transmitted within the brain through various types of neurons that respond differently to the same input. The Hodgkin−Huxley model has been revised by including ionic channels that account for typical neuronal firing phenomena. However, estimating parameters of the Hodgkin−Huxley models from experimental data is a notoriously difficult. Furthermore, the computational costs of these models are high, which hinders performing a simulation of massively interconnected neural networks.

Here we introduce a computationally fast spiking neuron model [1] that is capable of accurately predicting a rich variety of spike responses. We also developed a procedure for optimizing model parameters. The key features of the new model are a non-resetting leaky integrator and an adaptive threshold equipped with fast (10 ms) and slow (200 ms) time constants. The model can be easily tailored to various cortical neurons, including regular-spiking, intrinsic-bursting, and fast-spiking neurons, by simply adjusting three parameters. Both the high flexibility and low computational cost would help to model the real brain reliably and examine how network properties may be influenced by the distributed characteristics of component neurons.

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Cellular Systems Biology; Tuesday, June 28, 17:00

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Noise-Induced Symmetry-Breaking Underlies Reliable and Flexible Cellular Decision-Making

All-or-none decision-making by a cell such as differentiation and apoptosis is tightly linked to symmetry-breaking in intracellular networks. The underlying mechanism of such symmetry-breaking has been considered to be the deterministic bifurcation generated by positive feedback loops. By controlling the onset of the bifurcation and the stability of the bifurcated attractors by external inputs, it can also implement various cellular functions such as hysteresis, irreversibility, and history-dependent memory. Waddington expressed its importance for development in a metaphor of the famous epigenetic landscape, in which the fate of each cell is gradually determined in the the landscape of potential whose complexity increases during development. While the deterministic bifurcation has already been accepted as the primary mechanism of the experimentally observed symmetry-breaking, it has rarely been proven experimentally because the bistability is the deterministic concept and we cannot completely eliminate noise from biological systems. Furthermore, the bistable attractor lacks the property to flexibly produce the distinctive outputs according to the subtle external guidance signal. This indicates that the bistable attractor is not the best dynamical behavior to implement the flexible decision-making while it is better to reinforce and memorize the determined decision.

In this work, I reveal that a noise-induced symmetry-breaking, another mechanism of symmetry-breaking in a noisy system, can also produce the distinctive outputs required for cellular decision-making. Such noise-induced property is shown to have the function to flexibly respond to the external guidance signal even with substantial noise in the signal. The underlying logic of this flexibility is revealed to be the Bayesian information decoding that optimally extracts the information from the noisy signal. The biological validity of the noise-induced symmetry-breaking and Bayesian information decoding will be demonstrated by using various cellular phenomena such as signal transduction, immune-response and polarity formation. Furthermore, I propose an experimental procedure to discriminate the noise-induced symmetry-breaking from the deterministic bifurcation by using single-cell time-lapse measurement. This result will serve to experimentally investigate the noise-induced symmetry-breaking and the related Bayesian information processing by a cell.

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B and T cell immune responses; Wednesday, June 29, 11:00

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A spatially extended model of B cell receptor cluster signaling

The process of B cell activation is initiated by the clustering of B cell receptors (BCR) upon specific engagement and cross-linking with antigens (Ag). A BCR-Ag microcluster must comprise a minimum number of receptors ($\sim$ 10-20) in order to create an immunon – the smallest signaling unit capable of triggering intracellular signaling leading to the development of immunogenic response.

We have approached the kinetic simulation of early signaling events within a two-dimensional cellular automaton in which the plane representing a region of the B cell membrane is discretized using the hexagonal tiling. Transmembrane molecules of BCR and membrane-tethered Src-family kinases (represented in our study by single kinase Lyn) diffuse over the tiles while Ag ligands are placed in trigonal cells of a dual lattice. We assume that the Y-shaped extracellular part of the BCR (mIg) can bind up to two Ag, that may have higher valency. Movements of Ag-bound BCR are limited: singly linked BCR can move only to the cells that are adjacent to Ag, and BCR is immobilized when bound twice. Lyn may bind to the cytoplasmic part of BCR either by its unique domain (week binding) or by SH2 domain (strong binding to phosphorylated BCR), resulting in the creation of complexes that by convention occupy a single hexagonal cell of the plane. Associated Lyn can phosphorylate the neighboring BCR or Lyn. Every binding reaction is reversible and molecules undergo spontaneous dephosphorylation. The process is coded in software in the way that ensures the exact state-to-state dynamics: reaction and diffusion events are selected from the catalog of possible events and are fired at random with their propensities proportional to corresponding rate constants.

We found that when the receptors are freely moving over the surface (in the absence of ligands) the system exhibits only small basal activity – characteristic for unstimulated cells. In the presence of ligands BCR form clusters which enhance the effective interaction rate and triggers kinase activity. Trivalent ligands are much more effective than bivalent ones in building dense, signaling-efficient, BCR clusters. Due to the positive feedback in mutual receptor and kinase activation (phosphorylation of receptor stabilizes kinase binding and autophosphorylation) clusters exhibit switch-like activation. The cluster inactivation propensity decreases with the the size of the cluster, and clusters of ten or more receptors activate virtually persistently.

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936 and Foundation for Polish Science grant TEAM/2009-3/6.

Modeling of immune responses and calcium signaling II; Wednesday, June 29, 14:30

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Dimerization Effects in MAPK cascade

The MAPK (Mitogen-Activated Protein Kinase) cascades are among the most important signal transduction pathways in eukaryotic cells. The core of a MAPK pathway comprises a series of sequentially activated kinases, generically referred to as MAP3Ks, MAP2Ks, and MAPKs. Of particular importance are Raf/MEK/ERK and MEKK/MEK/JNK cascades due to their role in stress response, proliferation, differentiation, and the development of cancer. Consequently, these pathways have been extensively modeled. However, the models developed so far ignore homo- and heterodimerization events occurring between kinases within each tier of the cascade. The significance of dimerization of Raf and MEK proteins is especially well documented. In particular, the dimerization of RAF proteins appears critical for their activation - its dysregulation due to mutations or experimental chemotherapeutic inhibitors can lead to oncogenesis [1] or paradoxical activation [2], respectively. The dimerization of MEK1 and MEK2, on the other hand, introduces a novel regulatory mechanism of controlling the pathway's output via feedback phosphorylation by ERK [3]. Lastly, three-member scaffold proteins such as KSR, which assemble signalling complexes, have themselves been shown to dimerize [4], potentially providing a platform for dimerization of other MAPK components. We have incorporated these effects to produce more realistic models of the MAPK cascade as well as to explore their possible role in the pathway's regulation and dynamics.

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Regulatory Networks; Friday, July 1, 14:30

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Dynamic Optimization of Nitrogen Assimilation in *Chlamydomonas reinhardtii*

Optimization approaches are a useful tool to study principles behind dynamics observed in the regulation of metabolic pathways [**1**]. While earlier studies considered mostly steady-state systems [**1, 2**], the dynamic regulation, or just-in-time activation, of metabolic pathways has attracted increasing attention [**3, 4**] and was experimentally observed in the amino acid biosynthesis of *Escherichia coli* [**4**]. Using dynamic optimization by solving a nonlinear, dynamic optimal control problem with the quasi-sequential approach [**5**], we investigate the regulation of the nitrogen assimilation and the nitrogen metabolism [**6**] by the circadian clock [**7**] of the green algae *Chlamydomonas reinhardtii*. The aim of our analysis is to identify which enzymes within a drastically simplified model of the metabolism of *C. reinhardtii* need to be subjected to circadian control in order to adapt the organism to day-night rhythms. Moreover, the physiological and environmental constraints that imply the necessity of circadian regulation of different enzymes are investigated. Important components of such a model are appropriate kinetics of participating reactions as well as concentrations of enzymes and metabolites. We developed such a model focusing on nitrogen metabolism including assimilation, transport and processing in *C. reinhardtii*. This model was analyzed under different environmental conditions and provides first insights into the cause of the dynamics of metabolite and enzymes concentrations observed in the course of a day.

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Systems Biology of Development; Saturday, July 2, 14:30

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Paracrine vs Autocrine Regulation of Early Vascular Patterning

During embryonic vasculogenesis, the earliest mechanism of blood vessel morphogenesis, isolated vascular cell progenitors called angioblasts assemble into a characteristic network-like pattern. So far, however, the mechanisms underlying the coalescence and patterning of angioblasts remain unclear.

We consider a hybrid cell-based approach similar to that used for a similar *in vitro* process [1,2]. However, contrary to previous mathematical models that assume chemotaxis towards an autocrine signal [1,2,3,4], we favour an alternative mechanism based on matrix-binding of paracrine signals. Detailed morphometric analysis of simulated vascular networks and confocal microscopy images obtained from *in vivo* quail embryos reveals our model can reproduce the vascular patterns with high accuracy.

The work to be reported has been made in collaboration with W. de Back, J. Starruß and A. Deutsch (Center for High Performance Computing, Technische Universität Dresden), M. A. Herrero (Department of Applied Mathematics and IMI, Universidad Complutense de Madrid) and A. Mattiotti and J. M. Pérez-Pomares (Laboratory of Cardiovascular Development and Angiogenesis, Universidad de Málaga).

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Undergraduate Biomathematics Education Beyond BIO 2010 (Part II);
Saturday, July 2, 08:30

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Establishing an Undergraduate Program and Major in BioMathematics

To provide increased opportunity for students interested in the intersection of Biology, Mathematics and Computer Science, an interdisciplinary degree-granting program in BioMathematics was established at the Florida Institute of Technology (FIT). This new major encompasses a program that includes a significant undergraduate research component. The research students are supported by an NSF grant, UBM. Our emerging UBM program has already had a strong impact on the FIT campus, helping to create an atmosphere of excitement in undergraduates interested in exploring a new field and gaining novel research experience.

In this talk, the positive aspects as well as the difficulties in establishing this program at the departmental and institutional level will be discussed. Sample of projects and the newly established three biomath courses will be presented.

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Numerical analysis of a model of tumor invasion

We present a new algorithm for the numerical simulations of a mathematical model proposed by Chaplain and colleagues [1-3] describing tumor invasion and metastasis. The model takes into account the ability of cancer cells to produce and secrete matrix degradative enzymes, which allow the degradation of extracellular matrix, and the invasion of cancer cells due to diffusion and haptotactic migration.

For the numerical simulations of the interactions between the tumor cells and the surrounding tissue, we apply numerical approximations, which are spectrally accurate and based on small amounts of grid-points. Our numerical experiments illustrate the metastatic ability of tumor cells.

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Mathematical model of biophysical mechanisms of telomere length maintenance in mitochondrial DNA of C. parapsilosis

The terminal structures of linear mitochondrial DNA (mitochondrial telomeres) in C. parapsilosis consist of repetitive long tandem units. Besides these linear telomeres other cyclic configurations as telomeric circles and telomeric loops were experimentally observed and are suspected to play an important role in telomere length maintenance. We construct a mathematical model that captures biophysical interactions of various telomeric structures on a short time scale and that is able to reproduce experimental measurements in C. parapsilosis. Moreover, the model opens up a couple of interesting open mathematical problems in quasi-steady state approximation and discrete coagulation-fragmentation dynamical systems. This is a joint work with . Tomáška, J. Nosek and K. Boová.

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Speed selection in the model of infiltrative tumour growth with account of migration-proliferation dichotomy

A mathematical model of infiltrative tumour growth taking into account transitions between two possible states of malignant cells: proliferating and migrating, is developed. These transitions are considered to depend on oxygen level in a threshold manner: high oxygen concentration allows cell proliferation, while concentration below a certain critical value induces cell migration. Whenever a moving cell reaches the domain with high oxygen level it recruits into proliferation, otherwise it necrotizes.

It is demonstrated that model solution for localized initial tumour cell distribution tends to autowave solution. We investigate mechanism of autowave speed selection in the model with migration-proliferation dichotomy and compare results obtained with that for Kolmogorov-Petrovskii-Piskunov and Fisher (**KPP-F**) equations. It is known that in **KPP-F** equations speed is defined by asymptotics at leading edge of autowave (pulled regime). It is demonstrated that in the model considered autowave speed is determined by falling edge (pushed regime). The dependence of tumour spreading rate on model parameters is obtained. It is shown that the spreading rate depends on the oxygen level in tissue in a threshold manner.

This work was supported by grants No. 10-01-00289 and 11-01-00392 from the Russian Foundation of Basic Research.

Modeling of immune responses and calcium signaling IV; Saturday, July 2, 08:30

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Quantification of noise in signalling systems - importance of controlled signal degradation

The phenomena of stochasticity in biochemical processes has been intriguing life scientists for the last few decades. Studies revealed that living cells take advantage of stochasticity in some cases and counterbalance stochastic effects in others. The intrinsic source of stochasticity in biomolecular systems has been identified with random timings of individual reactions, which in a cumulative effect lead to the variability in outputs of such systems. In the presentation I will demonstrate how stochasticity of individual reactions contributes to the variability of system's output; and that some reactions have dramatically different effect on noise that others. Surprisingly, in the class of open conversion systems, that serve as an approximation model of signal transduction, degradation of an output contributes half of the total noise. We also demonstrate the importance of degradation in other relevant systems and propose a degradation feedback control mechanism that have capability of effective noise suppression. Our methodology constitutes novel, intuitive and simple framework to investigate stochastic effects in biochemical networks allowing for unprecedented insight into the origins of stochasticity.

Poster Session; Friday, July 1, 20:00

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Permanence induced by life-cycle resonances: the periodical cicada problem

Periodical cicadas (*Magicicada* spp.) are known for their unusually long life cycle for insects and their prime periodicity of either 13 or 17 years. One of the explanations for the prime periodicity is that the prime periods are selected to prevent cicadas from resonating with predators with submultiple periods (e.g., see [1,2]). Based on this idea, Webb [3] constructed mathematical models and gave a numerical example that periodically oscillating predators with 2- or 3-year period eliminate nonprime number periodical cicadas. However, in Webb's model, the interaction between well-timed cicada-cohorts and their predators is ignored. In our study, we construct an age-structured model for dynamically interacting predator and prey populations and consider the problem of the predator-resonance hypothesis. Our main result shows that preys are not necessarily eliminated by predators with submultiple periods since invasion of preys is always facilitated by their well-timed cohorts. It is also shown that synchronized life-cycles between predator and prey populations can produce a permanent system, in which no cohorts are missing in both populations. This contrasts with the result that systems with asynchronous life-cycles cannot be permanent. These results suggest that resonances with predators are not always deleterious to their preys.

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Turing !! Turing?? on morphogenesis via experimental and theoretical approaches; Wednesday, June 29, 17:00

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How experiment and mathematics can cooperate in the study of Turing patterns of real biological systems?

It was 60 years ago that Turing presented his outstanding idea about the biological pattern formation. Since then, many theoretical studies have been suggesting the RD mechanism could be one of the principles of biological morphogenesis. Such theoretical studies seem to be enough for the mathematicians to believe the biological relevance of the theory. However, majority of the developmental biologists still feel that the idea of RD is not so much related to their study in spite of the several empirical evidences.

We guess this problem comes from the gap of complexity between the simple differential equations and the complex real biological phenomena. Through the 15 years of experiment on the pigmentation stripe of fish skin, we recently found that many kinds of cellular events, migration, differentiation, dendrite elongation, and gap junctions, are involved in the pigment pattern formation. The whole system is not similar to any of simple model proposed before. After presenting our newest data, I would like to discuss the possible way for the cooperation between the theoretical and experimental sides.

Recent advances in infectious disease modelling II; Saturday, July 2, 14:30

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Stochastic model-based predictions on post-exposure prophylaxis strategies for prevention of HIV infection

Antiretroviral treatment (ART) leads to a much lower viral load in HIV patients and thus improves quality and length of life. When used as a post-exposure prophylaxis (PEP) shortly after exposure to HIV, ARTs are also known to reduce the risk of infection. However, many aspects of the very early stages of HIV infection remain poorly understood because the associated low viral loads are difficult to measure clinically. We present a continuous-time branching process model of early HIV infection in order to capture dynamics of the small number of virus particles. Using the related Chapman-Kolmogorov differential equation and the associated probability generating function we derive an expression for the virus extinction probability which we solve numerically. This allows us to predict the efficacy of different PEP strategies, considering initiation time, duration, and multi-drug regimens. We also evaluate the risk of emergent drug resistance in the event of PEP failure and then discuss how our results can be used to guide public health decisions on optimal PEP strategies.

Plants, growth and transport processes I; Tuesday, June 28, 11:00

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Dynamics of plant water transport derived from applying an optimisation scheme to Soil-Plant-Atmosphere-Continuum

In Central Europe, plant transpiration injects more than 40% of precipitation back into the atmosphere. Thus, plants play an important role in the exchange of water between soil and atmosphere.

Plants can actively open and close their leaf openings ("stomata"), gateways for incoming carbon dioxide molecules to be processed by photosynthesis as well as for outgoing water vapour. Since both gas species use the same pathways, the majority of terrestrial plants has to compromise between the conflicting tasks of (i) minimising transpiration (in order to avoid water stress and wilting) and (ii) maximising assimilation of carbohydrates (which constitute both building material and energy source of plants).

Plants deal with this conflict by regulating leaf gas exchange (via stomatal aperture) according to soil moisture and the diurnal cycles of temperature, insolation and relative humidity. The (physiological) details of this regulation mechanism are largely unknown. Nonetheless, it is possible, to emulate the actual plant gas exchange by a mathematical optimisation scheme ([1], [2], [3]): Optimum stomatal conductance as a function of time is determined by requiring that the assimilates assembled during one day accumulate to a maximum, being subject to the constraint that the quantity of water transpired during this time span equals a given amount. The diurnal variations of temperature, insolation and relative humidity have to be prescribed.

The calculus of variation subject to constraints introduces a Lagrangian multiplier whose value cannot be determined in the usual way, due to an intractable integral. Application of the continuity equation to the water current through soil, plant roots and xylem allows, however, to express the Lagrangian multiplier in terms of soil properties, tree anatomy and tree physiologic restrictions.

Applications of this model encompass the reconstruction of palaeo-environment from fossilised plant leaves and the predictions of the impact of changing atmospheric CO_2-level on climate ([4]). Redistribution of precipitation between soil (run-off and ground water) and atmosphere (transpiration) due to modified stomatal action caused by changing atmospheric CO_2-content can also be assessed.

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Poster Session; Friday, July 1, 20:00

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Entropy and Fisher information based measures of statistical dispersion

We propose and discuss two information-based measures of statistical dispersion of timing precision of neuronal firing: the entropy-based dispersion and Fisher information-based dispersion, and compare them with the standard deviation. Although the standard deviation is used routinely, we show, that it is not well suited to quantify some aspects of dispersion that are often expected intuitively, such as the degree of randomness. The proposed dispersion measures are not entirely independent, although each describes the firing regularity from a different point of view. We discuss relationships between the measures and describe their extremal values. We also apply the method to real experimental data from spontaneously active olfactory neurons of rats. Our results and conclusions are applicable to a wide range of situations where the distribution of a continuous positive random variable is of interest.

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Evolutionary Ecology; Wednesday, June 29, 08:30

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A model of intracellular virus replication with implications for virus evolution

Viruses are the simplest living organisms. In order to survive, a virus has to successfully invade a host cell, overcome cellular degradation mechanisms, produce progeny and export it to infect other cells; eventually evade immune response and jump to a new host to start the cycle again. The first challenge to virus survival is successful reproduction in the host cell. For RNA viruses, such reproduction includes a balance between several competing processes: production of RNA-derived RNA polymerase (RdRp), production of viral protein, RNA replication by the RdRp, formation of virions by combination of genomic RNA and structural viral protein and degradation of these products. Here we design a model representing these processes for positive-sense single stranded viruses (such as the family of Picorna or Flavi viruses) as a system of ODEs derived from stoichiometric enzyme-substrate reactions and explore the asymptotic dynamics of the model. The possible regimes are (1) virus extinction, (2) stable steady state and (3) a regime where RNA and RdRp are produced in excess (tend to infinity in the model) while the structural protein is fully utilized (converges to 0). If the net production of virions is a measure of virus fitness (such a claim is supported by the view that larger virus populations can maintain higher diversity and therefore be more adaptable), then we show that viruses that have evolved to utilize scenario (3) have higher fitness than viruses that establish equilibrium progeny production within the cell.

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Objective quality assessment of JPEG- and JPEG2000-compressed CT neuro images

We have employed various objective image fidelity measures to evaluate the quality of JPEG- and JPEG2000-compressed CT neuro images. Lossy compression degrades image quality. As the compression ratio is increased, JPEG produces blocking and ringing artifacts whereas JPEG2000 introduces blurring and ringing in the reconstructed images. Although subjective methods to evaluate quality of compressed medical images are complicated and difficult to conduct, they are the most accepted way for measuring diagnosis reliability. In order to overcome the problems with subjective quality assessment and to automate the process of assessing degradations, there is a need for reliable objective quality assessment of medical images. Although there is no generally accepted objective quality measure for medical images, Mean Squared Error (MSE) is widely used. It is, however, well known that MSE does not correspond well with the human visual system (HVS). We are therefore led to the question, "Which quality measures should be used that best correspond to visual and diagnostic quality?"

The HVS is highly sensitive to structural information and distortions (e.g. JPEG blockiness, "salt-and-pepper" noise, ringing effect, blurring). The structural similarity (SSIM) index, introduced by Wang and Bovik **[2]**, assumes that images are highly structured and that there exist strong neighbouring dependencies among pixels. On the other hand, these features are completely ignored by the MSE.

We also introduce another approach to measure the quality of compressed CT images, the so-called "Weberized L^2" method. It is a weighted version of the MSE that incorporates the Weber model of perception.

We analyze the quality maps of compressed images associated with the L^1, L^2, Weberized L^2 and SSIM measures. Our investigation supports the conclusions of an extensive subjective quality evaluation study conducted by radiologists in Koff

et al. [**1**] . The presence of edge artifacts introduced by JPEG2000 compression is revealed only by the SSIM quality map and may explain the results of Koff et al.. In conclusion, our study suggests that the SSIM measure and the SSIM quality map provide the most promising approach to predict subjective quality assessment of compressed brain CT images.

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Skew Laplace Distributions: Theory and Some Applications in Biology

Skew Laplace distributions, which naturally arise in connection with random summation and quantile regression settings, offer an attractive and flexible alternative to the normal (Gaussian) distribution in a variety of settings where the assumptions of symmetry and short tail are too restrictive. In particular, this model has been recently found useful for gene selection and classification methods in analysis of microarray data sets. In another application, it was observed that the Laplace distribution adequately represents the size distribution of microbial cells. We shall present fundamental properties of this model, which give insight into its applicability in these areas, and discuss its extensions to multivariate models, time series, and stochastic processes.

Models in Spatial Ecology; Tuesday, June 28, 17:00

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Diffusion in fragmented landscapes: habitat split

This talk gives an overview of some recent results concerning stage-structured species in fragmented habitats. It focus on amphibians, which need two distinct habitats in different life stages. We discuss the particular case where the habitat is split: the terrestrial habitat of the adults is separated from the aquatic habitat of the larvae. A central question is how the distance between the two required habitats affects population size and persistence in isolated fragment. We find a condition for persistence in a simple model based on diffusion equations supplemented with boundary conditions encompassing population regulation. The habitat split model improves our understanding about spatially structured populations and has relevant implications for landscape design for amphibian conservation.

Epidemics of Neglected Tropical Diseases; Wednesday, June 29, 11:00

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A model for malaria with ecological components

We present a model for malaria epidemics which takes into account, besides humans and anopheles mosquitoes, the existence of other mosquitoes species which are not vectors for plasmodium but which create a competition effect that can reduce the basic reproductive number. Further, we consider the occurrence of other species that can provide blood meals for mosquitoes but are immune to malaria, creating a dilution effect. These effects are meant to model observed situations in which almost no malaria cases are observed, although the anopheles mosquito is abundant.

Neurosciences; Wednesday, June 29, 08:30

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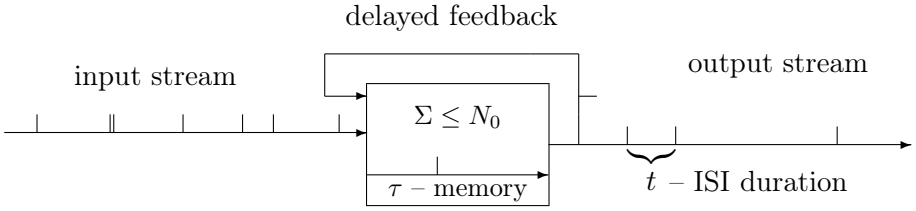
Delayed feedback results in non-markovian statistics of neuronal firing

The output inter-spike intervals (ISI) statistics of a single neuron with delayed feedback is considered. The construction is driven externally with Poisson stream of excitatory impulses. Via the feedback line, neuron's output impulses are fed back to its input with a fixed time delay. We consider cases of both excitatory and inhibitory neuron. Namely, in the first case, the neuron receives excitatory impulses both from the driving Poisson stream and from its own output stream through the feedback line. In the second case, apart from the external Poisson excitation, the delayed self-inhibition is present. For analytical derivation, we take binding neuron (BN) model [1].



We obtain exact analytical expressions for the single-ISI conditional probability density $P(t_2 \mid t_1)$, which gives the probability to obtain an output ISI of duration t_2 provided the previous ISI duration was t_1, and for the double-ISI conditional probability density $P(t_2 \mid t_1, t_0)$.

It turns out, that $P(t_2 \mid t_1)$ does not reduce to the output ISI probability density $P(t_2)$, found before. This means, that firing statistics is non-renewal one even in the simplest possible neuronal network. Moreover, we prove exactly, that $P(t_2 \mid t_1, t_0)$ cannot be reduced to $P(t_2 \mid t_1)$, the dependence on t_0 cannot be eliminated. This exactly means that ISIs stream does not possess Markov property.

Also, we introduce the conditional probability density $P(t_{n+1} \mid t_n, \ldots, t_1, t_0)$. It is proven exactly, that $P(t_{n+1} \mid t_n, \ldots, t_1, t_0)$ does not reduce to $P(t_{n+1} \mid t_n, \ldots, t_1)$ for any $n \geq 0$. This means that the output ISIs stream cannot be represented as Markov chain of any finite order.

We conclude, that the delayed feedback presence causes non-markovian behavior of neuronal firing statistics for both excitatory and inhibitory neurons. We suggest, that interpretation of experimental records of spiking activity should take this fact into account.

References.

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Computational toxicology and pharmacology - in silico drug activity and safety assessment; Saturday, July 2, 11:00

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Combining two model paradigms: How an agent-based hematopoietic stem cell model couples to an ordinary differential equations model of mature granulopoiesis and chemotherapy

To model the organization of hematopoietic stem cells Roeder *et al.* have introduced an agent-based model which succeeded well in explaining several experimental data of clonal competition and stem cell dynamics with clinically relevant applications in the field of chronic myeloid leukemia [**1**]. The model assumes two growth-environments and regulates stem cell activity by an intrinsic feedback that controls the transition between these environments.

In order to model the effects of chemotherapy and growth factor applications on the number of mature granulocytes, a compartment-based ordinary differential equations (ODE) model of granulopoiesis has been introduced by Scholz *et al.* [**2**]. Here the stem cell compartment is represented in a very simplified fashion.

To overcome this simplification and to take advantage of the established model of hematopoietic stem cells we replaced the ODE stem cell compartment with a difference equation formulation of the agent-based stem cell model [**3**]. Two feedback mechanisms for stem cell activation were introduced for replacing the regulation of self-renewal probability and proliferative fraction in the stem cell compartments of the ODE model. Stem cell activation was implemented firstly by increasing the probability of exiting quiescent states and secondly by a general acceleration in the stem cell compartment.

The resulting hybrid model was capable of reproducing the experimental data for the chemotherapy regime of Chop21. Interestingly, the comparison of feedback mechanisms for stem cell activation showed that the best agreement with the regeneration response in the clinical trials was achieved for the intrinsic regulation of the agent-based model without additional activation.

On the basis of the combined model, we aim to improve the modeling of chemotherapy effects on the hematopoietic system in the future. In particular we expect further insights into the role of role of hematopoietic stem cells with respect to the development of a toxicity induced leukopoenia with subsequent regeneration

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Cellular Systems Biology; Saturday, July 2, 11:00

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Modelling and elucidating design principles underlying attractive and repulsive gradient sensing

Many cells, both prokaryote and eukaryote exhibit the feature of chemotaxis, the directed motion in response to gradients of chemicals. Furthermore, many of these cells exhibit both attractive and repulsive gradient sensing to either the same or different chemicals. In this talk, I will discuss two aspects of this problem.

The first is the mechanistic modelling of a network postulated to describe chemorepulsion in the model system Dictyostelium. The signalling network is complex since it is strongly non-linear incorporating a combination of feedforward and feedback loops with spatial signalling. A systematic mechanistic modelling of this work describes whether and under which condition the network can exhibit the desired behaviour and makes clearcut predictions of the important features in this regard, resulting in very non-trivial conclusions.

The second aspect which I will discuss is how the cell signalling networks may be organized to give rise to both attractive and repulsive gradient sensing in a given cell, and how the resulting behaviour depends on the qualitative aspects of signal transduction (eg. adaptation, spontaneous polarization). Here a framework using qualitatively simplified models will be used to distill transparent insights. The relevance to individual systems will also be discussed.

Game theoretical modelling and optimization in evolution and ecology II;
Tuesday, June 28, 14:30

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On evolutionary stability in some population games

The classical models of population dynamics (e.g., the Lotka-Volterra predator-prey model) assume that interaction strength is fixed and independent of population densities. However, empirical evidence suggests that both prey and/or predators change their behavior with changes in population numbers. For example, an increase in predator numbers often decreases prey activity. Such plasticity in animal behavior leads to variable interaction strength that can strongly influence population dynamics. As predators and prey often play avoidance game (i.e., prey try to avoid predators while predators try to find prey), to solve this game methods of evolutionarily game theory are often used. In particular, it is assumed that the optimal solution to such a game corresponds to the evolutionarily stable strategy. By definition, such a strategy cannot be invaded by rare mutants, and from this respect it is the ultimate outcome of evolution. However, the classical theory does not consider changes in population numbers and in such a dynamic setting it is not a priori clear, if evolutionarily stable strategies can be invaded by rare behavioral mutants when population dynamics are considered. In this talk we will show that this can happen, although behavioral mutants cannot replace residents. However, a polymorphism can arise. Whether this happens or not, depends on particular dynamics and food web topology.

Poster Session; Friday, July 1, 20:00

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Interplay of mechanical and biochemical signals in plant morphogenesis

The Shoot Apical Meristems (SAM) initiate growth of new aerial plant organs like the leaves and flowers. Formation of the new primordia on the surface of the meristem involves complicated mechanical and biochemical interactions, yet meristem is able to achieve amazing regularity in repeating the patterns of outgrowth of the new leaves and flowers for the whole lifetime of the plant. From the mechanical point of view this requires a precise regulation of the amount and direction of the

cellular growth. The former is influenced by polarized transport of the plant hormone auxin, while the latter is related to the directionality of the microtubule array. By using the combination of experiments and modeling we have provided evidence that microtubules respond to mechanical stress and contribute to a feedback loop encompassing physical forces, microtubule orientation, mechanical anisotropy and morphogenesis [1]. We have shown also that auxin transport regulation by PIN1 can be explained by the mechanism which uses the mechanical stresses in the cell walls to convey information about auxin concentration in the neighboring cells. We presented a model of such interactions which is capable of creating phyllotactic patterns and is consistent with experimental results of cell ablations [2]. These results suggest that the mechanical signals are not only passively influenced by auxin patterning, but also actively direct transport of auxin using mechanical stress as a common regulator of PIN1 localization and mechanical anisotropy contributing to the emergence of the phyllotactic patterns.

References.

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Poster Session; Friday, July 1, 20:00

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Molecular and mechanical interactions in early mammalian embryo

Mammalian embryogenesis is a dynamic process involving gene expression and mechanical forces between proliferating cells. Despite a wealth of research and identification of the key genes contributing to the development of the early embryo, the precise nature of these interactions is still elusive. We have developed a computational modeling framework by which we can analyze the process of embryo development and differentiation to specific tissues during its first 4.5 days [1]. We combine mechanical and biochemical interactions between the cells to investigate how different mechanism contribute to the specification of the trophectoderm, primitive endoderm and alignment of the embryo axes. In the case of the trophectoderm formation we compare robustness of two models by which the characteristic pattern of Cdx2 and Oct4 transcription factors forms: gene expression is influenced by position of the cell or both expression and position are regulated by the pattern of symmetric/asymmetric divisions depending on the Cdx2 levels. During endoderm formation we examine influence of differential adhesion, geometrical constraints and stochastic active movement of cells on efficiency of endoderm layer specification. We demonstrate how purely mechanical factors can be responsible for alignment of the animal-vegetal and embryonic-abembryonic axes of the embryo. This work by combination of the cell-based spatial mechanical simulations with a genetic network approach hints that these two domains may be inseparably linked and that taking their interactions into account can be necessary for explaining mammalian embryogenesis.

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Analysis of mathematical models for cancer growth and treatment, Part IV; Wednesday, June 29, 08:30

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Markov model of cancer development – survival time prediction

We will present a newly developed [1] Markov model of cancer development. This is a compartmental model which allows one to separately consider different stages of the disease's progress. The model assumes that the distribution of waiting times between stages is exponential with the rate depending linearly on an arbitrary number of predictors. We apply this model to a breast cancer data set of women from the Pomerania region (1987–1992) [2]. We use the medical data in conjunction with a modified Bloom grading system to assign patients to different states of the Markov chain and explore what clinical predictors (which include amongst others age, tumour size, number of infected nodes, presence of estrogen and proestrogen receptors) best describe the state dependent transition probabilities and whether they have detrimental effects via a regression analysis. We also explore the possibility of survival time prediction under this Markov model of disease and consider extensions of the assumption of exponentially distributed waiting times.

References.

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Computational toxicology and pharmacology - in silico drug activity and safety assessment; Saturday, July 2, 11:00

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Hematopoietic cell populations as therapeutic targets

Pharmacodynamics is a rapidly growing field with a focus on mathematical modeling of drug effects. A very important class of therapeutic/toxic effects is hematological cell populations, dynamics of which have been a well investigated subject of physiologically structured population models. However, only recently such models have incorporated drug effects on cell populations.

This talk will introduce the pharmacodynamic models of drug effects on hematopoietic cell populations. It will also make a link to physiologically structured population models through such structures as cell age and fluorescent label. The roles of physiological structures in describing therapeutic effects of various drugs will be emphasized.

Analysis of mathematical models for cancer growth and treatment, Part V; Wednesday, June 29, 11:00

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Existence and Asymptotic Behaviour of Solutions to Nonlinear Evolution Equations Arising in Mathematical Models of Tumour growth

In this talk we investigate the global existence in time and asymptotic profile of the solution of nonlinear evolution equations with strong dissipation. Applying the above result to some models of mathematical biology and medicine, we discuss mathematical properties of them.

For this purpose we first show the solvability and the asymptotic profile of the solution to the intial boundary value problem of non linear evolution equations:

$$(\mathrm{NE})\begin{cases} u_{tt} = D\nabla^2 u_t + \nabla\cdot(\chi(u_t, e^{-u})e^{-u}\nabla u) & in\ \mathbf{\Omega}\times(0,T) \quad (1.1)\\ \dfrac{\partial}{\partial\nu}u\,|_{\partial\mathbf{\Omega}} = 0 & on\ \partial\mathbf{\Omega}\times(0,T) \quad (1.2)\\ u(x,0)=u_0(x),\quad u_t(x,0)=u_1(x) & in\ \mathbf{\Omega} \quad (1.3)\end{cases}$$

where Ω is a bounded domain in R^n and $\partial\Omega$ is a smooth boundary of Ω and ν is the outer unit normal vector and we denote

$$\frac{\partial}{\partial t}=\partial_t,\ \frac{\partial}{\partial x_i}=\partial_{x_i},\ i=1\cdot\cdot,n,\ \nabla u=\mathrm{grad}_x u=(\partial_{x_1}u,\cdots,\partial_{x_n}u)$$

$$\nabla^2 u=\nabla\cdot\nabla u=\Delta u=\partial_{x_1}^2 u+\cdots+\partial_{x_n}^2 u.$$

(1.1) includes the nonlinear evolution equations considered in **[4]**-**[6]** to show the global existence in time and the asymptotic profile of the solution of the corresponding mathematical models. We improve our mathematical approach and obtain the solution of (NE), which is in general form of one obtained in them. Next we apply our result to mathematical models of tumour growth, tumour induced angiogenesis and tumour invasion, proposed by Chaplain and Anderson(see **[1]**-**[3]**).

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Mathematical models of evolutionary dynamics of infectious agents;
Tuesday, June 28, 17:00

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Strain dynamics and influenza drift

One of the most exciting current areas in infectious disease modelling is in bringing together the epidemic and evolutionary dynamics. Influenza drift is perhaps the most striking example of where the two processes must be considered together: epidemics give rise to new strains, which in turn permit new epidemics.

We will begin with a general introduction to models of multiple strains, and some of their challenges, both technical and in terms of capturing observed biological phenomena. In most population-based models of strain dynamics, the number of variables grows exponentially with the number of strains. We present two items of our recent work, each of which avoids this problem in one way or another:

1) The impact of evolutionary constraints on influenza drift: standard drift models assume influenza is free to mutate to escape host immunity. In practice, there may be some functional cost associated with these mutations, and this can be incorporated into a mathematical model. In contrast to unconstrained drift models, this system is bistable, exhibiting both drift-like patterns and single strain dynamics for the same parameter values. This raises some important questions for vaccination strategies.

2) Age-structure and immune history: although relatively simple assumptions about the acquisition of immunity capture well the general dynamics of influenza drift, recent outbreaks have highlighted the importance of considering the details of precisely how immunity is acquired by an individual over their lifetime. In particular, strains that infect us when we are young may be disproportionately important (e.g. through original antigenic sin), and the immune response may be weakened in the elderly.

Developmental Biology; Wednesday, June 29, 17:00

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The role of mechanical stress and Merkel cells in the formation of fingerprints

In spite of the great importance of fingerpint patterns in forensics and biometrics there is still no generally accepted theory how fingerprint patterns are formed in utero. Substantial evidence exists that mechanical forces are decisive for determining the direction of the ridges [**1**]. Further, it is well-supported that a certain skin cell, the Merkel cell, is the primary pattern forming agent [**2**]. However, until now no connection has been established between these findings.

In my talk I will present a model that links stress distribution in the developing embryonal skin to the Merkel cell. This model is an agent-based model with the Merkel cells as agents that are interacting with each other. As an outcome of the model I will explain what factors in fingerprint formation are genetically controlled and why indeed every fingerprint — even the ones of identical twins — is unique.

References.

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Poster Session; Friday, July 1, 20:00

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Stochastic time-time interactions in biocatalytic and signalling systems

This contribution deals in general terms with the stochastic interplay of time points (P's, durationless events) and time intervals (I's, eventless or eventful durations). P's are visualized as the heads or feet of time arrows (hitting or leaving an I). I's are represented as simple linear segments on the time axis or as 1-dimensional parts of more sophisticated geometries (time loops, composite time strings, time nets, *zeitgestalten*). The lengths of I's and the placements of P's within I's are assumed to be describable by probability distributions (possessing positive, negative or no memory). Physical carriers of I's are macromolecules, metabolons, "signalons" or whole cells. Physical examples of P's are ligand arrivals at (or departures from) specific sites on macromolecules and - at the cellular level - nerve pulse arrivals at synapses. For the quantitative analysis of P-I interactions we apply matrix-analytic methods as used in Queueing Theory (cf. Kühl PW and Jobmann M (2006) J Rec Signal Transd 26, 1-34).

Analogously to light-matter interactions, we distinguish three major ways how a P may interact with an I: (i) reflection, (ii) absorption and (iii) emission. Depending on the degree of timing-sensitivity of the macromolecular or (sub)cellular structures and on the distributional shape of P's and I's, the overall performance of the system may be optimal, suboptimal or pessimal. Furthermore, the time patterns created by P's and I's may form - analogously to *zeitgestalten* in speech and music - a delicate mean of intra- and intercellular communication and information transfer.

The above-described P-I interactions belong to the theory of timing *sensu latissimo*, termed by us TIMETICS (Kühl PW (2007) FEBS J 274 (Suppl 1) 247); contrary to kinetics, not rates but times and time patterns are of primary concern. TIMETICS (which also includes temporal logic and memory-based phenomena) is a vast field with applications in biological as well as nonbiological sciences.

Cell migration during development: modelling and experiment; Saturday, July 2, 08:30

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Experimental analysis of neural crest migration during development

Experimental analysis of neural crest migration during development Cell migration and cell fate decisions are strongly influenced by microenvironmental signals during embryonic development and cancer. Yet, it is largely unclear how cells receive and interpret microenvironmental signals that influence their fate and choice of direction. To address these questions, we use the neural crest (NC) as our model system. NC cells are a highly invasive, multipotent embryonic cell population that are sculpted into discrete migratory streams and patterned into multiple derivatives by the microenvironments cells travel through. We have developed an in vivo imaging platform in chick that permits single cell resolution and behavior analysis of fluorescently labeled NC cells. By combining molecular intervention with time-lapse imaging, we have discovered a role for NC cell chemotaxis and how cells may respond to distinct microenvironmental signals and navigate to precise locations. We will show recent tissue transplantation and ablation experiments that alter the position of NC cells along a migratory route and discuss how cells respond to local microenvironmental signals. These data provide the basis for close collaboration with mathematical modellers and offer insights into the underlying mechanisms of embryonic pattern formation.

Epidemics; Thursday, June 30, 11:30

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Global stability analysis with a discretization approach for an age-structured SIR epidemic model

The global stability analysis for each equilibrium of an age-structured SIR epidemic model is carried out. After discretizing the model that is a system of PDE with respect to the age variable, we obtain a multigroup epidemic model that is a system of ODE and can apply the classical method of Lyapunov, a recently developed graph-theoretic approach and a monotone iterative method in order to show the global asymptotic stability of the disease-free equilibrium for $R_0 \leq 1$, and the global attractivity of an endemic equilibrium for $R_0 > 1$, where R_0 is the basic reproduction number. Although for the original PDE model the possibility of local instability of an endemic equilibrium was shown even for $R_0 > 1$, for the discretized version of it we can obtain the aforementioned global attractivity result, and this implies that the possibility of periodic solutions might be ruled out from the model, which has been discussed as an open question for more than two decades. Numerical simulation provides an example indicating that the numerical solutions of the two PDE and ODE systems become closer to each other as the step size of discretization decreases.

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Modelling biofilms: from gene regulation to large-scale structure and function; Wednesday, June 29, 17:00

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Modelling approaches for Quorum sensing in *Pseudomonas putida* and its observation in a biofilm compartment

More and more bacterial species are found to regulate gene expression via extracellular signals called autoinducers. By that mechanism, usually called Quorum sensing (QS), they check for the environmental conditions as population density and diffusion limitation. *Pseudomonas putida*, a rhizosphere bacterium, has one such QS regulation system. Expression of a fluorescence protein (GFP) allows for direct monitoring of induction behaviour on single cell level, but uses as second autoinducer receptor which perturbs the original system to some extent. An ODE model allows to estimate this perturbation and helps to interpret the observed behaviour.
In an experimental approach the dynamics of upregulation was observed under flow and non-flow conditions. A two compartment model was set up and fitted to the experimental data. By that, several hypotheses could be checked, giving a clear hint on a growing layer which is not directly accessible by the flow compartment, probably a biofilm.
A second interesting topic concerns an QS-induced (delayed) production of an autoinducer-degrading enzyme. We introduce a delay differential system, analyse its behaviour and compare it to simpler models. Transferred to a spatial model (as part of a reaction-diffusion equation) it allows to consider the ecological consequences for single bacteria in a biofilm.

Immunology; Wednesday, June 29, 14:30

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Perspectives of mathematical modelling for understanding of intracellular signalling and vesicular trafficking in macrophages

Perspectives of mathematical modelling for understanding of intracellular signalling and vesicular trafficking in macrophages

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Macrophages are essential elements of immune system that orchestrate activation and downregulation of inflammatory reactions, tissue remodelling, healing processes and tissue homeostasis. Macrophages have to respond to complex signals specific for homeostatic or pathologic conditions. To retain sufficient accuracy of reaction macrophages make use of cooperative action of multiple extracellular factors that may amplify required activities and suppress undesired ones. This cooperativity is based on complex branching signalling networks coupled to positive and negative feedback loops; ligand uptake by scavenger receptors; intracellular sorting and multiple secretory pathways. Deregulation of cooperativity leads to pathological situations such as chronic inflammation, allergy, tumour initiation and progression. The complexity of the system makes it impossible to assess the impact of every particular molecular event using classical molecular biological methodology. Mathematical modelling of signalling and membrane trafficking pathways using frameworks of differential equations will allow qualitative and quantitative description of macrophage behaviour in conditions simulating physiological situation. Although the model construction requires large amounts of quantitative experimental data, the analysis of the model using mathematical methods enables the identification of the elements critical for the system. Established models may be used to simulate behaviour of macrophages under different conditions and to predict their reactions in vivo. Identified critical elements of the system will facilitate the isolation of predictive/diagnostic markers as well as potential therapeutic targets.

Bioengineering; Tuesday, June 28, 14:30

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Accuracy indices for assessing performance of different versions of Gillespie Algorithm for stochastic molecular simulations

Dynamics in population models at the molecular level are commonly described using the deterministic approach based on systems of coupled first-order ordinary differential equations (ODEs). Deterministic approach although fast in calculation is not always accurate for systems containing low-rate reactions particularly for species occurring in small quantities. To account for random fluctuations in numbers of molecular species numerous variants of stochastic Gillespie Algorithm has been introduced. There are already several survey studies comparing and summarizing different approaches in stochastic modeling of molecular mechanisms. In these studies the problem of accuracy of modeling is addressed at the level of simplifying hypotheses and their verification [3], [4]. In our talk we critically discuss several possibilities of assessing accuracy of different strategies of stochastic molecular modeling. We also propose a new, direct and precise method of comparing different stochastic modeling strategies based on comparisons of probability distributions of observed time instants of molecular events. By using our methods we compare several variants of stochastic simulation methods, direct, approximate and hybrid (numerical integration of ODEs and stochastic simulation) [5], [6]. We grade accuracies of predictions of different algorithms in terms of differences betweeen conditional distributions of times of sequences of molecular events. In comparisons the basic version of the Gillespie algorithm is considered as an accurate one, predictions of other algorithms are analyzed based on its comparison to the basic version of the Gillespie Algorithm [1], [2]. Dedicated system written in C++ is used as a computational platform for calculation of models applying deferent approaches. Efficiency of system is also evaluated in comparison to common solutions.

Acknowledgment. This work was supported by the European Community from the European Social Fund.

Acknowledgment. This work was financially supported by The Fundation for Polish Science.

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Semigroups of Operators in Mathematical Biology II; Saturday, July 2, 11:00

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Some Markov Jump Processes in Mathematical Biology

The general approach that allows to construct the Markov processes describing various processes in mathematical biology (or in other applied sciences) is presented. The Markov processes are of a jump type and the starting point is the related linear equations. They describe at the micro–scale level the behavior of a large number N of interacting entities (particles, agents, cells, individuals,...). The large entity limit ("$N \to \infty$") is studied and the intermediate level (the meso–scale level) is given in terms of nonlinear kinetic–type equations. Finally the corresponding systems of nonlinear ODEs (or PDEs) at the macroscopic level (in terms of densities of the interacting subpopulations) are obtained. Mathematical relationships between these three possible descriptions are presented and explicit error estimates are given. The general framework is applied to propose the microscopic and mesoscopic models that correspond to well known systems of nonlinear equations in biomathematics.

Analysis of mathematical models for cancer growth and treatment, Part IV; Wednesday, June 29, 08:30

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Macroscopic limits of a model of alignment

The macroscopic limits of the kinetic model for interacting entities are studied. The kinetic model is one–dimensional and entities are characterized by their position and orientation (+/-) with swarming interaction controlled by the sensitivity parameter. The macroscopic limits of the model are considered for solutions close either to the diffusive (isotropic) or to the aligned (swarming) equilibrium states for various sensitivity parameters. In the former case the classical linear diffusion equation results whereas in the latter a traveling wave solution does both in the zeroth ("Euler") and first ("Navier–Stokes") order of approximation.

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Combined experimental and mathematical modeling of circular dorsal ruffles

Circular dorsal ruffles (CDRs) are transient actin-based structures that are observed on the dorsal plasma membrane upon stimulation by receptor-tyrosine-kinase growth factors such as the platelet-derived growth factor (PDGF). While the function of CDRs has not been elucidated, it has been suggested that they are involved in cell migration and macropinocytosis. Here, we combine experiments with mathematical modeling to attempt to understand the regulation of CDRs. Experimentally, we find that lifetime of CDRs can be modified by varying the substrate stiffness, whereas their sizes are independent of substrate stiffness. To understand these results, we construct a mathematical model of the signaling pathways that regulate CDRs. By coupling such reactions to protein diffusion, we find that our reaction-diffusion system of equations can reproduce the ring-like structure of CDRs, and how substrate stiffness modifies their lifetime via the focal adhesion kinase (FAK). We also show that the low diffusion coefficient of membrane bound proteins relative to the high diffusion coefficient of cytosolic proteins is key to the generation of CDRs. Finally, we reduce the model to a coupled two-species model involving the proteins Rac (which has been shown to result in the generation of actin filaments) and Rho (which has been shown to be involved in cell-substrate adhesion), and their antagonism, and was able to explain the formation of the CDRs as an excitable system. Using this reduced model, we study the conditions for this excitability to occur, and therefore make predictions on when and where CDRs will appear.

Poster Session; Friday, July 1, 20:00

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Modeling the dynamics of osteoblast-monocyte cocultures on calcium-modulating biomaterials

We adapt and extend an existing model of bone remodeling [1] and simulate the population dynamics of osteoblast-monocyte coculture on two different types of calcium-modulating biomaterials [2],[3], covered by monolayers of hMSC-derived osteoblasts. From experimental findings it is known that upon increased extracellular calcium concentrations, the activity of bone forming cells is greatly enhanced, while bone resorption is reduced significantly [4], [5]. We include these observations by inserting a forth state variable and response functions into the original model, describing the extracellular calcium concentration and the kinetics of calcium sorption to or from the biomaterial, respectively. Starting from different initial conditions, we simulate the population dynamics of active osteoblasts and monocytes, reacting to different levels of extracellular calcium and different sorption properties of the underlying scaffolds. As a result, we identify interesting parameter regimes for inducing transient changes in the osteoblast/osteoclast ratio, indicating possible new approaches for tissue engineering applications, e.g. in the context of bone healing approaches for systemically diseased patients. In ongoing experiments, we develop methods to compare our results to both monoculture and coculture experiments of osteoblasts and monocytes [6] on different resorbable biomaterials [2],[3] in vitro.

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Mathematical Models in Eco-epidemiology II; Wednesday, June 29, 11:00

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Prey abundance, fragmented spatial structures and predator persistence in a predator-prey mathematical model

In this talk we develop a complex fragmented spatial model in which both dispersing well-fed and starving domestic cat populations are sharing a common multi-patch range occupied by non dispersing prey. The overall dynamic is rather intricate to decipher for Lotka-Volterra functional responses to predation. It becomes even quite complex when Holling type II functional responses to predation are considered. Assuming dispersal occurs at a fast time scale while reproduction and predation are much slower processes it is possible to transform our complex model into a simpler one for which some (local) stability analysis is feasible. A toy model consists of a spatial range made of three patches with two resident predators in the first two patches, that can be either a well-fed or a starving resident predator, and no predator at all in the third one, predators traveling all over the spatial range. For the three resulting toy models more (local) stability analysis results are available and illustrated by numerical simulations.

Poster Session; Friday, July 1, 20:00

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Multiple neuronal spike trains observed in a short-time window

Information obtained in experiments in which the spikes are recorded, usually from a single neuron or from quite limited number of them, is fundamentally different from that which a neuron receives from the network of interconnected neurons. In the experiments, a spike train is recorded for a relatively long period of time and the properties of the firing are deduced. If the type of the investigated firing is transient, like in the stimulated activity, then the extensive length of the record is replaced by repetitions assuming that these are identical and independent copies of the same phenomenon. In natural conditions, neuron receives a large number of spike trains, up to several thousands, and the information has to be deduced in short-time intervals. This creates a discrepancy between what can be read from the experiments and how real neurons perform. To estimate the firing frequency in the parallel neuronal data is rather simple task even if the time window available for the observation is very short. In paper 1 we showed how to estimate the coefficient of variation of interspike intervals under the scenario with the short-time window. Several nonparametric methods for estimation of the cumulative distribution function of the interspike intervals under the same restriction posed on the observation appear in our recent paper 2. The aim of the present contribution is summarize the results and to show furter development in studying the problem.

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Poster Session; Friday, July 1, 20:00

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Stirred Bioreactor Heating: Temperature Experience of a Single Organism

Rapid heating of bioreactors is extensively used for the production of recombinant proteins. Such temperature-induced expression systems show high levels of recombinant protein productions and present important and convenient features for bioprocessing. The heating of a lab-scale stirred bioreactor is investigated, based on a two layer turbulence model. The wall temperature is assumed to be about 80 degree Centigrade.

We observed the occurrence of a narrow high temperature layer near the bioreactor wall. Bioorganisms entering the viscous hot layer usually stay there for a long time and this typically induces the their death. The simulation results show that a considerable part of the microorganism population is endangered by the high temperature near the bioreactor wall.

Neurosciences; Thursday, June 30, 11:30

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Dynamical switching between network states in the hippocampal circuit

It is known that hippocampus is a structure required for processes of learning and memory [**1**]. Gloveli et al. [**2**] reported that the dynamics of neuron network of CA3 region exhibits some types of oscillations, so called gamma (30-80 Hz) and theta(4-12 Hz) rhythms. These oscillations are responsible for information transmission, storage, and spatial encoding [**3**]. Also, it have been shown that gamma and theta rhythms are generated by different types of cells in CA3 region of hippocampus.

We have considered a minimal network scheme, which describes connections between different types of cells. We have developed model based on this scheme which reproduces important physical characteristics of the oscillations of all cells types: the period, amplitude and phase shift. The model allows us to analyze the influence of synaptic strengths on the network synchronization and dynamical switching between theta, gamma, and bursting regimes. In particular, we perform a thorough bifurcation analysis and identify parameters of synaptic connections that can efficiently induce switches in the network activity.

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Biofluids, Solute Transport, and Hemodynamics; Wednesday, June 29, 11:00

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Myogenic Response of the Afferent Arteriole

We have formulated a mathematical model of the rat afferent arteriole (AA). Our model consists of a series of arteriolar smooth muscle cells, each of which represents ion transport, cell membrane potential, cellular contraction, gap junction coupling, and wall mechanics. Blood flow through the AA lumen is described by Poiseuille flow. Model results suggest that interacting calcium and potassium fluxes, mediated by voltage-gated and voltage-calcium-gated channels, respectively, give rise to periodic oscillations in cytoplasmic calcium concentration, myosin light chain phosphorylation, and crossbridge formation with attending muscle stress mediating vasomotion. The AA model's representation of the myogenic response is based on the hypothesis that the voltage dependence of calcium channel openings responds to transmural pressure so that vessel diameter decreases with increasing pressure. With this configuration, the results of the AA model simulations agree well with findings in the experimental literature, notably those of Steinhausen et al. (J Physiol 505:493, 1997), which indicated that propagated vasoconstrictive response induced by local electrical stimulation decayed more rapidly in the upstream than in the downstream flow direction. The model can be incorporated into models of integrated renal hemodynamic regulation. This research was supported in part by NIH grants DK-42091 and DK-89066, and by NSF grant DMS-0715021.

Biofluids, Solute Transport, and Hemodynamics; Wednesday, June 29, 11:00

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Countercurrent Multiplication in the Kidney: Is it Real?

A fundamental function of the mammalian kidney, when blood plasma osmolality is too high, is to produce a urine that is more concentrated than blood plasma and thereby reduce blood plasma osmolality to a normal level. Urine is concentrated in the renal medulla by means of a concentration gradient that promotes osmotic water withdrawal from the kidney's collecting ducts. It has become widely accepted that the osmolality gradient along the cortico-medullary axis of the mammalian outer medulla is generated and sustained by a process of countercurrent multiplication: active NaCl absorption from thick ascending limbs is coupled with a counter-flow configuration of the descending and ascending limbs of the loops of Henle to generate the axial gradient. However, aspects of anatomic structure (e.g., the physical separation of the descending limbs of short loops of Henle from contiguous ascending limbs), recent physiologic experiments (e.g., those which suggest that the thin descending limbs of short loops of Henle have a low water permeability), and mathematical modeling studies (e.g., those which predict that water-permeable descending limbs of short loops are not required for the generation of an axial osmolality gradient) suggest that countercurrent multiplication may be an incomplete, or perhaps even erroneous, explanation. We propose an alternative explanation for the axial osmolality gradient: we regard the thick limbs as NaCl sources for the surrounding interstitium, and we hypothesize that the increasing axial osmolality gradient along the outer medulla is primarily sustained by an increasing ratio, as a function of medullary depth, of NaCl absorption from thick ascending limbs to water absorption from thin descending limbs of long loops of Henle and from collecting ducts.

Analysis of mathematical models for cancer growth and treatment, Part II; Tuesday, June 28, 14:30

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Optimal protocols for chemo- and immunotherapy in a mathematical model of tumor-immune interactions

In this talk, a classical model for the interactions between tumor and the immune system under treatment is considered as an optimal control problem with multiple controls representing actions of cytotoxic drugs as well as of agents that give a boost to the immune system. In the objective, a weighted average of several quantities that describe the effectiveness of treatment is minimized. These terms include (i) the number of cancer cells at the terminal time, (ii) a measure for the immunocompetent cell densities at the terminal point (included as a negative term), (iii) a measure for the side effects and cost of treatment in form of the overall amount of agents given and (iv) a small penalty on the terminal time that limits the overall therapy horizon which is assumed to be free. This last term is essential in obtaining a well-posed problem formulation. The form of the objective is motivated by the dynamics of the system without treatment and models the goal to move the state of the system from a region of malignant cancer growth into a benign region. Employing a Gompertzian growth model for the cancer cells, for various scenarios optimal controls and their corresponding system responses are calculated. Both the cases of mono- and combination therapies will be considered.

Poster Session; Friday, July 1, 20:00

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Recent Methods for Computations of Reaction Networks

We consider reaction networks where many biological or biochemical species interact through various reaction channels. We introduce the background for analysis and computation of the reaction networks and we present recent results on the computational methods for simulations of reaction networks. We also show numerical results obtained by simulating some motivating biological models.

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Poster Session; Friday, July 1, 20:00

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An Open Tank System of Valveless Pumping

We present a mathematical model of flows driven by periodic pumping without valves (valveless pumping) in an open tank system. The model consists of a cylindrical elastic closed tube with two open tanks under gravity. The two dimensional elastic tube is constructed based on the immersed boundary method and the tank model is governed by a system of ordinary differential equations based on the law of conservation of energy. We have observed the difference of fluid heights in the tanks by the periodic compress-and-release action that is applied to an asymmetric region of the elastic tube. As the previous research on the open systems of valveless pumping, we have also observed that the direction and magnitude of a net flow in our open tank system are determined sensitively by the driving frequency and the compression duration. We are able to explain the occurrence of local maximum or minimum mean flows (difference of tank heights) due to the resonances of the system.

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Poster Session; Friday, July 1, 20:00

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Relaxation of End-Grafted DNA Chains

By spreading front of a bioadhesive vesicle over stained end-grafted DNA molecules, DNA molecules are stapled into frozen confinement paths. As the conformational relaxation of topologically trapped chain is very slow, it has been shown that the stapled DNA gives access to the local stretching values of individual DNA molecules and provides evidence of self-entanglements. By means of two dimensional computer simulations and scaling arguments, we study the relaxation of single grafted semiflexible chains freely rotating around the grafting point. We provide the autocorrelation of the end-to-end vector for the whole chain and for terminal sections of various lengths.

Turing !! Turing?? on morphogenesis via experimental and theoretical approaches; Wednesday, June 29, 17:00

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Gene Expression Time Delays and Turing Pattern Formation

There are numerous examples of morphogen gradients controlling long range signalling in developmental and cellular systems. The prospect of two such interacting morphogens instigating long range self-organisation in biological systems via a Turing bifurcation has been explored, postulated or implicated in the context of numerous developmental processes. However, modelling investigations of cellular systems typically neglect the influence of gene expression on such dynamics, even though transcription and translation are observed to be important in morphogenetic systems.

The investigations of our study demonstrate that the behaviour of Turing models profoundly changes on the inclusion of gene expression dynamics and is sensitive to the sub-cellular details of gene expression. These results also indicate that the behaviour of Turing pattern formation systems on the inclusion of gene expression time delays may provide a means of distinguishing between possible forms of interaction kinetics, and also emphasises that sub-cellular and gene expression dynamics should not be simply neglected in models of long range biological pattern formation via morphogens. We present results mainly for Gierer-Meinhardt systems but our results are observed more universally in many Turing pattern formation systems. Exploring the dynamics of these systems suggests that the basic Turing mechanism should be reconsidered or would generally require a novel and extensive secondary mechanism to control reaction diffusion patterning.

***This work has already been extended in several papers. The works have been collaborated with E.A. Gaffney (University of Oxford), R.E. Baker (University of Oxford) and N.A.M. Monk (University of Nottingham).** Papers related with this work are given in the following References.

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Fluid-structure interaction problems in biomechanics; Saturday, July 2, 08:30

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A Mathematical Model of Thrombus Formation Under Flow

To explore how blood flow affects the growth of thrombi (blood clots) and how the growing masses, in turn, feed back and affect flow, we have developed a spatialtemporal mathematical model of platelet deposition and coagulation under flow. The model includes detailed descriptions of coagulation biochemistry, chemical activation and deposition of blood platelets, as well as the two-way interaction between the fluid dynamics and the growing platelet mass. In this talk, I will present the mathematical model and use it to explain what underlies the threshold behavior of the production of an important enzyme within the coagulation system. I will then show how the wall shear rate of flow and a near-wall enhanced platelet concentrations affect the development of growing thrombi. Since we account for the porous nature of thrombi, I am also able to demonstrate how advective and diffusive transport to and within thrombi affects their growth at different stages and spatial locations.

Poster Session; Friday, July 1, 20:00

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A structured growth model for hairy roots of beetroot (*Beta vulgaris*)

Secondary metabolites produced by plant in vitro cultures such as Betanin (red-dye in beetroot) are nowadays in the main focus within the branch of White Biotechnology. Cells genetically altered using *Agrobacterium rhizogenes* form hairy roots which can be cultivated in hormone free media in modern bioreactors.

In order to improve the cultivation process (higher yield, shorter cultivation time) and the bioreactor design (bubble column vs. stirred) a structured growth model with consequent simulations and visualization is necessary. While the growth of these tissue cultures on agar plates, in shaking flasks or bioreactors for industrial use has been heavily investigated experimentally only limited theoretical descriptions of the growth processes exist. The gained knowledge can be used by other scientists to improve their cultivation protocols and to simulate growth of their own cultures by amending the parameters of the model.

The hairy roots of beetroot (*Beta vulgaris*) have been chosen for modeling the growth morphology of hairy roots also with respect to the distribution of secondary metabolites such as the red dye Betanin. A matrix based approach is used for the proposed model which consists of a 2-dimensional model matrix for agar plates containing information about the condition of each cell forming the organ complex. Conditions are position, age, nutrient concentration inside the cell as well as concentration of secondary metabolites. A second matrix contains nutrient concentrations such as carbon source and oxygen in the media.

The simulation process begins with a given start state of a small organ complex which is recalculated recursively for a defined time step. The growth processes involved such as elongation and branching through cell division as well as secondary thickening of already existing cells are described using differential equations. After each growth step the organ matrix and the nutrient matrix with the involved diffusion processes are calculated using partial differential equations (PDE). The newly formed matrices are used for the next calculation step. Experimental results of cultivations of *B. vulgaris* are compared with the results of simulations.

Poster Session; Friday, July 1, 20:00

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A Computational Model of Vascular Tumour Growth as Observed by Intravital Microscopy through a Dorsal Skinfold Chamber on the Mouse

A computational model is potentially a powerful tool to apprehend complex phenomena like solid tumor growth, and to predict the outcome of therapies in order to find the best solution to fight the disease. To that end, the confrontation of the model with biological experiments is essential to validate this tool.

In this poster, we present a model specifically constructed to match and interpret biological results obtained in vivo on mice by the dorsal chamber method. We will focus especially on the vascular adaptation and alteration of the blood rheology. In order to reproduce the tumor evolution, interrelation between vascular development and tumor growth are established thanks to oxygen diffusion and the angiogenesis process. Indeed, oxygen is transported to the tumor by the vessels and hypoxia induces the growth of new blood vessels via the emission of vascular endothelial growth factors by the tumour cells. Vascular collapse in tumor is also taken into account as well as dilation or constriction of the vessels.

Simulations based on existing vascular network and measured rheological parameters reproduce the observed tumour evolution including the increased vascular density at the periphery and the formation of a necrotic core. Biological results obtained by the dorsal chamber method and numerical simulation results are further compared to calibrate the model so as to use it as a predictive tool in order to further test and design new therapy protocols.

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Resampling with Applications to Neurophysiological Time Series

Resampling with Applications to Neurophysiological Time Series

Jacek Leskow Department of Quantitative Methods in Management The Polish-American Graduate School of Business WSB-NLU Nowy Sacz

One of the fundamental tools in the analysis of biosignals including functional magnetic resonance imaging (fMRI) is a time series model and corresponding set of parameters. Such time series are known to exhibit temporal autocorrelation which is one of the fundamental characteristic for such fMRI observations (see e.g. Bullmore et al (2001)). In the presentation, a general survey of resampling methods for time series will be presented and consistency issues will be addressed. The focus of the presentation will be application-oriented toward fMRI signals that exhibit non-gaussian behavior and are non-stationary. The statistical results presented e.g in Leskow et al (2008) will be accompanied by applications to neurophysiological time series.

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Population Genetics; Wednesday, June 29, 17:00

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Sampling HIV intrahost genealogies based on a model of acute stage CTL response

Genealogy based methods have become a common tool in analyzing intrahost HIV evolution. These methods require a coalescent model which implicitly describes the role of evolutionary forces in shaping HIV genealogies. Currently, HIV genealogies are constructed assuming variants of the Kingman coalescent. The Kingman coalescent is a generic coalescent model that does not explicitly account for the special features of HIV evolution. For example, the Kingman coalescent does not account for the role of CTL attack.

In this talk we introduce a coalescent model of the acute stage that explicitly incorporates the role of early CTL attack. Using this coalescent model, we develop a computational method that allows us to sample HIV genealogies shaped by CTL attack. We show that such genealogies are different in form than Kingman coalescent genealogies. We use our genealogy sampler to explore the type of CTL attack that is best at controlling HIV diversity. Our work is a first step in developing computational tools that can use HIV genetic data to infer parameters describing CTL attack.

Cell and Tissue Biophysics; Saturday, July 2, 11:00

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Effects of Cell Compressibility, Motility and Contact Inhibition on the Growth of Tumor Cell Clusters

We analyze the effects of cell migration, compression, and contact inhibition on the growth of tumor cell clusters using the Cellular Potts Model (CPM) in a monolayer geometry. Cell proliferation, motility, cell-to-cell adhesion, contact inhibition, and cell compressibility are incorporated in the model. We find that increased motility has a direct effect on the growth rate of clusters. Cell lines with greater motility overcome the attractive forces of cell-to-cell adhesion and have more space to proliferate. We analyze the interplay between cell motility and compressibility within the CPM, and find that more motile cells are generally smaller than their more sedentary counterparts, which can lead to smaller clusters. We obtain an explicit inverse-relationship between the cell compressibility and motility parameters and use this relationship to compensate for motility-induced cell compression. Clusters of motile cells that do not experience significant compression grow faster than those composed of less motile cells. In addition, contact inhibition amplifies the effect of motility. Strict contact inhibition in the CPM penalizes clumped cells by halting their growth, giving motile cells a greater advantage. We have begun testing our model with *in vitro* data obtained from a collaborator and our model is reflective of the data.

Evolutionary Ecology; Thursday, June 30, 11:30

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Persistence of the Sickle Cell Genome in the Presence of Malaria

It is believed that the sickle cell gene has persisted in the human population due to the partial resistance it confers on victims of malaria. We use a system of six equations tracking populations of three genotypes and two age brackets to study what relative death rates for malaria and sickle cell are required in order for the gene to persist, and what resulting proportions of the population are expected to carry the gene under different assumptions about malarial death rates. The results can be compared with current data to infer historical death rates for malaria. The model also allows estimation of the length of time it takes such a gene to reach equilibrium in a population, and how this depends on assumed death rates.

Bridging Time Scales in Biological Sciences; Saturday, July 2, 14:30

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The Quasi-steady state hypothesis for stochastic models of enzyme kinetics

In a stochastic version of the Briggs-Haldane equations, we show that the classical quasi-steady state hypothesis corresponds to a averaging principle or local ergodic theorem for the fast enzymatic reaction. This way, we obtain a more natural explanation of the Michaelis Menten kinetics on the slow time scale. Some more detailed estimates are presented, too.

Game theoretical modelling and optimization in evolution and ecology I;
Tuesday, June 28, 11:00

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Evolution of tree architecture

The astounding biodiversity of the Earth's ecosystems is the outcome of competition, cooperation, and migration among species and within-species varieties. The potential for frequency-dependent selection to shape these biodiversity patterns is easily appreciated in plants, where height-asymmetric competition for light has not only driven the evolution of tall trees, but is also responsible for their coexistence with smaller plants. Less is known, however, of how frequency-dependent competition for light has affected other salient aspects of plant architecture. Here, we present a trait-, size-, and patch-structured model of vegetation dynamics to study the evolution of tree-crown architecture. Our study extends a related model by Falster et al. (2011), by incorporating self-shading within tree crowns and a more detailed representation of biomass-allocation to branches. Tree-crown architecture is described by two individual-level traits for crown shape and crown width. Three scenarios are investigated and contrasted for different combinations of sun angle, site productivity, and disturbance frequency. First, we consider optimal tree-crown architectures for solitary trees growing apart from competing trees. Second, we ask the same question for a monoculture of identical trees subject to density-dependent growth. Third, we investigate the coevolution of tree-crown shape and tree-crown width under competition and for potentially polymorphic traits, and determine the resultant evolutionarily stable state. Finally, we critically reassess the common belief that a low sun angle is a main force driving the conical tree-crown architectures observed in boreal forests.

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Modeling of collective phenomena in biological systems; Saturday, July 2, 08:30

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A combined process algebraic and a stochastic approaches to bone remodeling

In adult life the bone is being continuously resorbed and replaced by new bone. Here we present a stochastic model of the homeostatic nature of bone remodeling, where osteoclasts perform bone resorption which is equally balanced by bone formation performed by osteoblasts. The stochastic model is embedded in an algebraic process based on Shape calculus, which provides an effective multiscale description of the process. Our model considers increasing dimensionality from Rankl molecular signalling to osteoclast/osteoblast stochastic dynamics within a basic multicellular units (BMU) to a bone mass formation. We show that after a microfracture the simulated bone remodeling dynamics has timescale consistent with the biological process. Our combined methodology provides a first effective stochastic model of bone remodeling framework which could be used to test healthy and pathological conditions.

Modeling of immune responses and calcium signaling II; Wednesday, June 29, 14:30

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A rule-based model for early events in B cell antigen receptor signaling

B cell antigen receptor (BCR) signaling regulates the activities and fates of B cells. Here, we present a rule-based model for early events in BCR signaling that encompasses membrane-proximal interactions of BCR, two membrane-tethered Src-family protein tyrosine kinases, Lyn and Fyn, the adaptor protein PAG, and two cytosolic protein tyrosine kinases, Csk and Syk. The signaling is triggered by aggregation of the BCR by foreign antigens, which increase the rate of BCR-Src kinases interactions. The interactions involve two feedback loops: a positive feedback loop acting on a short time scale and a negative feedback loop acting on a longer time scale. The positive feedback loop arises because of the way that the two Src-family kinases, Lyn and Fyn, interact with the two signaling chains of the BCR complex, Igα (CD79A) and Igβ (CD79B). Lyn and Fyn constitutively associate with BCR via low-affinity interactions and trans-phosphorylate tyrosine residues in the immunoreceptor tyrosine-based activation motifs (ITAMs) of Igα and Igβ in neighboring receptors within antigen-induced clusters of BCR. These sites of phosphorylation then serve as high-affinity docking sites for the SH2 domains in Lyn and Fyn, which recruit more Lyn and Fyn to BCR clusters. Lyn and Fyn also undergo autophosphorylation within antigen-induced clusters of BCR, which upregulates their kinase activities. The negative feedback loop is mediated by PAG, which associates with Lyn and Fyn in a phosphorylation-dependent manner. PAG serves as a docking site for Csk, which mediates the phosphorylation of a C-terminal regulatory tyrosine residue found in both Lyn and Fyn. Phosphorylation of this residue enables an intramolecular interaction that downregulates Lyn/Fyn kinase activity. The model makes the distinction between the two Src kinases, Lyn and Fyn. Whereas Lyn is allowed to phosphorylate PAG at all tyrosine residues, Fyn may not phosphorylate its own binding sites on PAG due to allosteric constraints. This distinguishes Lyn as the only Src kinase capable to induce the negative feedback in the system. A dynamical stability analysis of the model reveals that the BCR circuit can display two interesting behaviors. Bistability can be expected in PAG -/-, Csk -/-, and Lyn -/- cells, whereas oscillatory pulse-like responses to BCR clustering can be expected in cells with the negative feedback loop intact (wild-type

cells and Fyn -/- cells) under some conditions. The qualitative behaviors predicted by the model are consistent with the known behaviors of Lyn and Fyn deficient cells.

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Poster Session; Friday, July 1, 20:00

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Molecular Motor-Cargo systems: Modeling energetics of the kinesin with different approaches

Motor proteins, sometimes referred to as mechanoenzymes, are a group of proteins that maintain a large part of intracellular motion. Being *enzymes*, they undergo chemical reactions leading to energy conversion and changes of their conformation. Being *mechano*, they use the (chemical) energy to perform mechanical work, leading to the phenomena of motion. Series of novel experiments, e.g. single molecule observations, were performed to gain the knowledge about the performance of chemical states of the molecular motors as well as their dynamics in presence or absence of an external force.

At the same time, many theoretical models were proposed, offering deeper insight into the small-world (nanoworld) dynamics. They can be divided into three main categories: chemical models, ratchet models and molecular dynamics models. Chemical models focus on the Markovchain, kinetic description of the reaction cycles responsible for the mechanical transitions. Ratchet models are mostly based on sets of Langevin equations and treat the kinesin dimer as two linked Brownian particles moving in a periodic potential. Molecular dynamics models approach the problem from the low level dynamics of single or grouped molecules, based on information obtained from crystallographical data.

We show that by combining those complementary approaches one can gain deeper understanding of the dynamics and chemistry of the motor proteins. As a working example, we choose kinesin and dynein — motor proteins responsible for bidirectional transport of organelles and vesicles using microtubular tracts.

References.

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Mathematical Modeling of Mosquito-Borne Diseases; Tuesday, June 28, 11:00

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Modeling Wolbachia-Based Strategies for Controlling Mosquito-Borne Diseases

Mosquito borne infections, most notably malaria and dengue, kill over a million people every year. Traditional control measures (such as insecticides) against these infections in developing countries have had mixed success. A novel avenue of attack involves the production and release of mosquitoes that have been manipulated or genetically engineered to be less able, or even unable, to transmit infection.

Mathematical modelling is playing an important role in several large-scale projects that are currently under way to assess the feasibility of these techniques. In this talk I shall discuss the biology of one approach that uses the bacterial symbiont Wolbachia and the accompanying modelling work, illustrating how a number of different models are being used as the projects move along the path from lab-based studies to field deployment.

Modeling and analysis of tumor invasion I; Tuesday, June 28, 11:00

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The Lymphatic Vascular System in Lymphangiogenesis, Invasion and Metastasis: A Mathematical Approach

There are two distinct categories of tumors: benign and malignant. Benign tumors remain confined to the tissue in which they arise and although they may continue to grow, they do not spread to other parts of the body. Unlike benign tumors, malignant tumors grow rapidly, invade and destroy the surrounding tissues and, by exploiting the blood or the lymphatic systems, establish new colonies, a process called metastasis. Metastasis is the predominant cause of cancer death. There are four major routes of neoplastic dissemination: (1) local invasion; (2) direct seeding to body cavities; (3) hematogenous spread; and (4) lymphatic spread, preferentially to regional lymph nodes and later to distant sites.

For a primary tumor to grow, it needs a supply of nutrients, delivered by the blood. The tumor therefore secrets growth factors which induce the formation of new blood vessels, sprouting them from preexisting vessels and directing them toward. the tumor. This is the process of tumor angiogenesis. Targeting angiogenesis, namely, cutting of blood supply, is one off the strategies for blocking tumor growth and dissemination.

A similar, although far less well studied process, also occurs in the lymphatic system and is referred to as lymphangiogenesis or lymphagenesis. Surprisingly, almost all of the published literature focuses on the correlations between angiogenesis, microvessel density, metastatic spread, and tumor prognosis, leaving a missed link between primary tumor and nodal metastases: the lymphatic system.The lymphatic system comprises a vascular network of one-way, open-ended, thin-walled complex network of capillaries and larger vessels, collecting vessels, lymph nodes, trunks, and ducts that transport lymph and cells from body tissues back to the circulatory system.

Various studies have shown that angiogenesis is important for solid tumour growth and, presumably, also in hematogenous metastasis. By contrast, the role of lymphatic vessels and the relevance of lymphangiogenesis to tumor pathology is less clear. Until recently only limited information concerning the molecular mechanisms and pathways involved in tumor lymphangiogenesis and tumor lymphatic invasion have been obtained

Although intensive research in tumor angiogenesis has been going on for the past four decades, experimental results in tumor lymphangiogenesis began to appear only in the last five years. In this paper we propose the first mathematical model of lymphangiogenesis, and obtain numerical results that qualitatively agree with experimental results. In conclusion, we propose the possibility to use the mathematical model presented as a possible lymphangiogenesis assay for better understandingand preventing tumor invasion and tumor lymphangiogenesis

Cancer; Tuesday, June 28, 11:00

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Some Mathematical Problems in Radiotherapy

Determining the optimal distribution of radiation over a target and selecting the best manner to deliver it are two key issues in radiotherapy. In this lecture, I shall describe recent results on optimizations methods aimed at addressing these goals, and some examples of application of these techniques will be presented.

Epidemics; Tuesday, June 28, 14:30

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The SIS and SIR stochastic epidemic models Length of an outbreak and time to infection

We deal with the SIS and SIR stochastic epidemic models. The aim of this talk is to present the study of some continuous characteristics of an epidemic. In this sense, we first extend the classical study of the length of an outbreak by investigating the whole probability distribution of the extinction time via Laplace transforms. Moreover, we also study the time until a non-infected individual becomes infected. The obtained results are illustrated by numerical examples including an application to head lice infections.

Population Dynamics; Thursday, June 30, 11:30

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Numerical analysis of a population model of marine invertebrates with different life stages

In this work, we consider an age-structured population model of marine invertebrates whose life stage is composed of sessile adults and pelagic larvae, such as barnacles contained in a local habitat. In the model, proposed by Roughgarden and Iwasa and mathematically analyzed by Kamioka, space is the principal limiting resource. The long time simulation of this kind of coupled systems is difficult. Here, we propose and analyze a numerical method in order to investigate the asymptotic behavior of the solutions.

References.

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Poster Session; Friday, July 1, 20:00

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The role of fluctuation theorems in biological adhesion

The catch-slip bond mechanism are bonds between ligands and receptors, that shows a counterintuitive effect. At low forces the bond lifetime increase until a maximum value, wich is called the catch bond; after the maximun the bond lifetime decrease as describe the Bell's theory of adhesion(Bell, 1978). In biology this effect can be observed in many ligand-receptor interactions such as Escherichia coli adhesion, FimH and P-L selectins expressed in leukocytes, actin-myosin interaction, or in integrins. But also this effect can be useful in order to develop new nanotechnological applications. From the development of the fluctuations theorems during the late 90's. These theorems had shown be very usefull in order to describe the behavior of small systems in biology, such as folding/unfolding cooperative effects. This systems operates away from equilibrium, where the fluctuations induce transitions between steady states. In this work we apply the Crook's fluctuation theorem in order to derive an expression for the bond lifetime, as a function of the applied elastic energy. The propossed model it is validated with other published works.

Multiscale modelling of reaction kinetics in biology; Tuesday, June 28, 14:30

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Stochastic simulation of reaction-diffusion processes in living cells on multiple scales

The number of molecules of each chemical species in biological cells is small and the molecules react with each other with a certain probability. A stochastic mesoscopic model of the diffusion and the chemical reactions is therefore more accurate than a deterministic, macroscopic model based on the reaction rate equations. In a computer simulation of a trajectory of the system, the diffusion is often the most computationally expensive part. The diffusion of different species are treated differently in [**1**] in order to reduce the computational cost. Depending on if the copy number is high, intermediate or low the diffusion events are simulated macroscopically, with the tau leap method or with the stochastic simulation algorithm (SSA) by Gillespie in an unstructured mesh covering the cell. The reactions are handled by SSA. Sometimes the mesoscopic model is not sufficiently accurate and a microscopic description is necessary. In such a model, single reacting and diffusing molecules are tracked [**2**]. The molecules move in the unstructured mesh by Brownian motion and are coupled to the mesoscopic model via the reactions [**3**]. Examples from molecular biology will be given.

References.

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Poster Session; Friday, July 1, 20:00

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Energy localization and shape changing solitons in microtubules

Microtubules are protein polymers made of / tubulin heterodimers that form an essential part of the cytoskeleton of all eukaryotic cells. Besides giving structural stability and rigidity to a cell, microtubules play key roles in many physiological processes such as intracellular vesicle transport and chromosome separation during mitosis. Nucleated MTs (e.g., as nucleated from the centrosome during the mitosis) are tightly attached to the nucleated site by their minus ends and MTs exchange tubulin dimers between the soluble and polymer pools at their free plus ends using the dynamic instability mechanism. Modulational instability (MI) is a universal process in which small phase and amplitude perturbations that are always present in a wide input beam grow exponentially during propagation under the interplay between dispersion and nonlinearity. The mechanism of depolymerization and repolymerization provides continual supply of energy into the microtubule structures in a cell. As the tubulin heterodimers are polar, the vibrations generate an oscillating electric field that can be excited by the energy released from the hydrolysis of the GTP. Also, we employ the symbolic computation and look for the dynamical equation that supports soliton excitations. It was assumed that the anti-kink formation is mainly due to the hydrolysis of GTP into GDP so that one can act as a hydrolyser which corresponds to the conformational change resulting in the formation of a solitary profile. The propagation will then distribute the energy of hydrolysis at a preferred end of MT. On the other hand, each solitary profile can be viewed as a bit of information whose propagation can be controlled by an external electric field.

Modelling dengue fever epidemiology; Saturday, July 2, 08:30

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Determinants of dengue virus phylodynamics.

Dengue fever (DF) and the more severe dengue haemorrhagic fever (DHF) are mosquito borne viral infections which have seen a major increase in terms of global distribution and total case numbers over the last few decades. There are currently four antigenically distinct and potentially co-circulating dengue virus (DENV) serotypes and each one shows substantial genetic diversity, organised into phylogenetically distinct lineages (genotypes). While there is some evidence for positive selection, the molecular evolution of DENV is supposed to be mostly dominated by purifying selection due to the constraints imposed by its two-host life-cycle. Results from our previous work demonstrated that although small differences in viral fitness can explain the rapid expansion and fixation of novel genotypes, their fate is ultimately determined by the epidemiological landscape in which they arise. Using a stochastic, spatially explicit model we revisit previous conclusions and address the impact of host and vector population structure on DENV molecular evolution and disease epidemiology.

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Viruses selectively mutate their CD8+ T cell epitopes an optimization framework, a novel machine learning methodology and a large scale genetic analysis.

The relation between organisms and proteins complexity and between the rate of evolution has been discussed in the context of multiple generic models. The main robust claim from most such models is the negative relation between the organism complexity and the rate of mutation accumulation.

We here validate this conclusion, through the relation between viral gene length and their CD8 T cell epitope density. Viruses mutate their epitopes to avoid detection by CD8 T cells and the following destruction of their host cell. We propose a theoretical model to show that in viruses the epitope density is negatively correlated with the length of each protein and the number of proteins.

In order to validate this conclusion, we developed a novel machine learning methodology to combine multiple modalities of peptide-protein docking measurement. We use this methodology and large amount of genomic data to compute the epitope repertoire presented by over 1,300 viruses in many HLA alleles. We show that such a negative correlation is indeed observed.This negative correlation is specific to human viruses.

The optimization framework also predicts a difference between human and non-human viruses, and an effect of the viral life cycle on the epitope density. Proteins expressed early in the viral life cycle are expected to have a lower epitope density than late proteins.

We define the "Size of Immune Repertoire (SIR) score," which represents the ratio between the epitope density within a protein and the expected density. This score is applied to all sequenced viruses to validate the prediction of the optimization model.

The removal of early epitopes and the targeting of the cellular immune response to late viral proteins, allow the virus a time interval to propagate before its host cells are destroyed by T cells. Interestingly, such a selection is also observed in some bacterial proteins. We specifically discuss the cases of Herpesviruses, HIV and HBV showing interesting selection biases.

Stem cells and cancer; Wednesday, June 29, 14:30

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Feedback, lineages and cancer

We have developed a multispecies continuum model to simulate the dynamics of cell lineages in solid tumors. The model accounts for spatiotemporally varying cell proliferation and death mediated by the heterogeneous distribution of oxygen and soluble proteins. Together, these regulate the rates of self-renewal and differentiation of the cells within the lineages. Terminally differentiated cells release feedback factors that promote differentiation (e.g., from the TGF superfamily of proteins) and decrease rates of proliferation (and self-renewal) of less differentiated cells. Stem cells release a short-range feedback factor that promotes self-renewal (e.g., representative of Wnt signaling factors), as well as a long-range inhibitor (e.g., representative of Wnt inhibitors such as Dkk) of this factor. We find that the progression of the tumors and their response to treatment is controlled by the spatiotemporal dynamics of the signaling processes. The model predicts the development of spatiotemporal heterogeneous distributions of the feedback factors (Wnt, Dkk and TGF) and tumor cell populations with clusters of stem cells appearing at the tumor margin, cyesonsistent with recent experiments. The nonlinear coupling between the heterogeneous expression of growth factors, the heterogeneous distribution of cell populations at different lineage stages and the tumor shape may sufficiently depress feedback control in parts of tumors to favor eventual escape from control. This is shown to lead to invasive fingering, and enhanced aggressiveness after standard therapeutic interventions. We find that using a combination therapy involving differentiation promoters and radiotherapy is very effective in eradicating the tumor.

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling II; Saturday, July 2, 11:00

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Physical oncology

Cancer models relating basic science to clinical care in oncology may fail to address the nuances of tumor behavior and therapy, as in the case, discussed herein, of the complex multiscale dynamics leading to the often-observed enhanced invasiveness, paradoxically induced by the very antiangiogenic therapy designed to destroy the tumor. Studies would benefit from approaches that quantitatively link the multiple physical and temporal scales from molecule to tissue in order to offer outcome predictions for individual patients. Physical oncology is an approach that applies fundamental principles from the physical and biological sciences to explain certain cancer behaviors as observable characteristics arising from the underlying physical and biochemical events. For example, the transport of oxygen molecules through tissue affects phenotypic characteristics such as cell proliferation, apoptosis, and adhesion, which in turn underlie the patient-scale tumor growth and invasiveness. Here, we illustrate how tumor behavior and treatment response may be a quantifiable function of marginally stable molecular and/or cellular conditions modulated by inhomogeneity. By incorporating patient-specific genomic, proteomic, metabolomic, and cellular data into multiscale physical models, physical oncology could complement current clinical practice through enhanced understanding of cancer behavior, thus potentially improving patient survival.

Developmental Biology; Thursday, June 30, 11:30

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Mechanical control of spheroid growth: distinct morphogenetic regimes

We develop a model of transport and growth in epithelio-mesenchymal interactions. Analysis of the growth of an avascular solid spheroid inside a passive mesenchyme or gel shows that sustained volumetric growth requires four generic mechanisms: (1) growth factor, (2) protease, (3) control of cellularity, and (4) swelling. The model reveals a bifurcation delineating two distinct morphogenetic regimes: (A) steady growth, (B) growth arrested by capsule formation in the mesenchyme. In both morphogenetic regimes, growth velocity is constant unless and until a complete capsule forms. Comprehensive exploration of the large parameter space reveals that the bifurcation is determined by just two ratios representing the relative strengths of growth and proteolytic activity. Growth velocity is determined only by the ratio governing growth, independent of proteolytic activity. There is a continuum of interior versus surface growth, with fastest growth at the surface. The model provides a theoretical basis for explaining observations of growth arrest despite proteolysis of surrounding tissue, and gives a quantitative framework for the design and interpretation of experiments involving spheroids, and tissues which are locally equivalent to spheroids.

Developmental Biology; Friday, July 1, 14:30

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Invariances of cross- and trippel-ratios of human limbs?

Recall that in the complex plain, four points, p, q, r, s, can be mapped to four other points, $\tilde{p}, \tilde{q}, \tilde{r}, \tilde{s}$, by a Möbius transformation, $z \mapsto \frac{az+b}{cz+d}$, if and only if the cross-ratio, $\frac{(p-r)(q-s)}{(p-s)(q-r)}$, equals the cross-ratio of $\tilde{p}, \tilde{q}, \tilde{r}, \tilde{s}$. In [**1**], a bold and highly inspiring statement was given that the cross-ratio of consecutive joints of human limbs, are invariant, not only over time, but also between different limbs, and even different persons! In order to investigate this intriguing statement, but also to develop new morphometric tools for development studies, we geometrically analyze the morphological development of the human body, and we examined the cross-ratio of three consecutive body parts that are segmented by four landmarks in their configuration. Moreover, we introduce an generalization of the cross-ratio: the triple-ratio of five landmarks that segments four consecutive parts (e.g. the shoulder, upper arm, forearm, and hand) and examined their growth patterns. The triple-ratio was defined for five arbitrary points, p, q, r, s, and t as:

$$\kappa(p, q, r, s, t) = \frac{|p-r||q-s||r-t|}{|q-r||r-s||p-t|}.$$

It is easy to show that also the trippel-ratio is invariant under Möbius transformations. The cross- and triple-ratios of the upper limb and shoulder girdle in fetuses were constant when biomechanical landmarks were used although the cross-ratio of the upper limb varied when the anatomical landmarks were used. The cross-ratios of the lower limbs, trunk, and pelvic girdles of fetuses differed from their corresponding cross-ratios in adults. These results suggest the Möbius growth in the fetal upper limb and shoulder girdle, but not in the other body parts we examined. However, the growth balance of the three contiguous body parts was represented by the developmental change in the cross-ratio. Therefore, the cross- and triple-ratios may be applicable for the assessment of growth balance or proportion of the body parts.

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Poster Session; Friday, July 1, 20:00

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Functionality and Speciation in Boolean Networks

Boolean Networks have been used to model Genetic Regulatory Networks since Stuart Kauffmann proposed them as a model in the 1960s. Early work focused on how the topology of a network influenced its dynamics. We investigate the inverse problem asking which network topologies satisfy a specified dynamic. In earlier work by A. Wagner a biological function or cell process was specified by an initial condition v(0) and an end point v1 in the expression state space. By so specifying a biological function one can then ask which networks perform this function. Our view is that in many cases a more appropriate means for defining a biological function would be by specifying the entire path v(0), v(1), ... , v(T). We will report on how these two contrasting definitions of biological functionality lead to divergent results for their respective functional topologies, particularly regarding the implications for neutral evolution, multi-functionality and speciation.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits I; Wednesday, June 29, 14:30

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Macroscopic model of self-propelled bacteria swarming with regular reversals

Periodic reversals of the direction of motion in systems of self-propelled rod shaped bacteria enable them to effectively resolve traffic jams formed during swarming and maximize their swarming rate. In this paper, a connection is found between a microscopic one dimensional cell-based stochastic model of reversing non-overlapping bacteria and a macroscopic non-linear diffusion equation describing dynamics of the cellular density. Boltzmann-Matano analysis is used to determine the nonlinear diffusion equation corresponding to the specific reversal frequency. Macroscopically (ensemble-vise) averaged stochastic dynamics is shown to be in a very good agreement with the numerical solutions of the nonlinear diffusion equation. Critical density p_0 is obtained such that nonlinear diffusion is strongly suppressed for $p < p_0$. An analytical approximation of the pairwise collision time and semi-analytical fit for the total jam time per reversal period are also obtained. It is shown that cell populations with high reversal frequencies are able to spread out effectively at high densities. If the cells rarely reverse then they are able to spread out at lower densities but are less efficient to spread out at higher densities.

Mathematical Modeling of Mosquito-Borne Diseases; Tuesday, June 28, 11:00

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Modelling mosquito dispersal in a heterogeneous environment

Mosquito foraging behaviour for hosts and oviposition sites/habitats is an important aspect for malaria control. Recent studies have highlighted the impact of the presence of habitats on mosquito search for oviposition sites. While others have highlighted the significance of habitat elimination within certain distances from human habitations to prevent mosquitoes using human hosts for blood meals. While minimizing or eliminating the impact of mosquitoes on the spread of malaria has been a concern of current malaria research, mosquito dynamics and mosquito spatial distribution remain a challenge. The goal of this work is to describe and understand mosquito population dynamics in relation to dispersal in spatial environments.

A simple mathematical model based on the mosquito life cycle is formulated to describe the population dynamics of mosquitoes. Dispersal of adult mosquitoes searching either for hosts or oviposition sites is also modelled and its effects incorporated in the population dynamics. The spatial aspect of mosquito dispersal is described by their movement between patches in a two-dimensional spatial environment. A hexagonal grid with each hexagon representing a patch is used where vital dynamics are allowed to occur. Numerical simulations are carried out to demonstrate the biological application of the model.

The modelled population dynamics of each stage of the mosquito life cycle in space are presented and the links between factors influencing the spatial dynamics are discussed.

Population Dynamics; Saturday, July 2, 11:00

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Resistance Distance and Relatedness on an Evolutionary Graph

When investigating evolution in structured populations, it is often convenient to consider the population as an evolutionary graph – individuals as nodes, and their relations as edges. There has, in recent years, been a surge of interest in evolutionary graphs, especially in the study of the evolution of social behaviors ([5],[6]). An inclusive fitness framework is best suited for this type of study [2]. An expression for the genetic similarity between individuals residing on the graph is required for inclusive fitness calculations. This has been a major hindrance for work in this area as highly technical mathematics are often required [1]. In this presentation, I will derive a recent result [4] that links genetic relatedness between haploid individuals on an evolutionary graph to the resistance between vertices on a corresponding electrical network. Specifically, if R_{ij} be the relatedness and γ_{ij} the resistance distance [3] both between individuals i and j on a transitive graph G with N vertices each of degree k. Then,

$$R_{ij} = 1 - \frac{\gamma_{ij}}{\gamma_{ave}}.$$

An example that demonstrates the potential advantage of this result over contemporary approaches will be provided. I will discuss some new insights into the relatedness concept brought about by this result and mention possible directions for future investigation.

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Using mathematical modeling to tailor the administration of chemotherapy and G-CSF

In this talk I will briefly describe recent work that we have carried out using a mathematical model for the regulation of human hematopoiesis to investigate optimal delivery strategies for granulocyte colony stimulating factor (G-CSF) in the treatment of patients with cyclical neutropenia, and to aid patients in the post-chemotherapy phase. Additionally I will discuss optimal ways to deliver chemotherapy.

Mathematical models of gene regulation; Tuesday, June 28, 11:00

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Molecular distributions in gene regulatory dynamics

Extending the work of Friedman et al.(2006), we study the stationary density of the distribution of molecular constituents in the presence of noise arising from either bursting transcription or translation, or noise in degradation rates. We examine both the global stability of the stationary density as well as its bifurcation structure. We have compared our results with an analysis of the same model systems (either inducible or repressible operons) in the absence of any stochastic effects, and shown the correspondence between behaviour in the deterministic system and the stochastic analogs. We have identified key dimensionless parameters that control the appearance of one of two stable steady states in the deterministic case, or unimodal and bimodal densities in the stochastic systems, and detailed the analytic requirements for the occurrence of different behaviours. This approach provides, in some situations, an alternative to computationally intensive stochastic simulations. Our results indicate that, within the context of the simple models we have examined, bursting and degradation noise cannot be distinguished analytically when present alone.

Poster Session; Friday, July 1, 20:00

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Distribution of recombination hotspots in human genome the comparison of computer simulations and real data

Analyses of meiotic recombination between homologous human chromosomes revealed the uneven distribution of recombination events along the chromosomes. This phenomenon has been observed in different genomic scales. At the megabase scale, the mean recombination rate is higher in the sub-telomeric regions than in the middle parts of chromosomes. On the other hand, at the finer scale, recombination events tend to cluster into narrow spans of a few kb in length, which are called recombination hotspots. These short regions with very high recombination frequency occur also more frequently at the ends than in the centre of chromosome. They were discovered based on high-resolution recombination maps which were inferred from high-density single-nucleotide polymorphism (SNP) data using linkage disequilibrium (LD) patterns. Recently, it has been reported a degenerate 13 bp long motif, CCNCCNTNNCCNC, which is overrepresented inside the human hotspots. Moreover, many experiments suggest that the zinc-finger protein PRDM9 binds to this motif, which can indicate the existence of a common mechanism of recombination regulation. Furthermore, hotspot locations are not shared between human and chimpanzee, which suggests their short lifespan. Understanding the function of recombination hotspots can provide insight into the linkage disequilibrium patterns and help create the accurate linkage map for disease association studies. We have found that many recombination properties, for example the uneven distribution of hotspots, can be predicted and explained by computer simulations of population evolution. Assuming spatial distribution of genes along the chromosomes and finite size of populations, simulations render a perfect picture of recombination observed in the human genome. The obtained results of simulations indicate that the distribution of crossing points are subjected to evolution. Therefore, it is expected that the distribution of the recombination motifs for the hotspot regulation should follow the uneven distribution of recombination events. In order to test our hypothesis, we check the location of the motif along the human chromosomes using both the physical and the genetic map. The analyses showed the correlation between the frequency of recombination and the location of motif. In addition, the examination

of the distances between motifs confirmed their non random distribution along the human chromosomes.

Poster Session; Friday, July 1, 20:00

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Clustering and genomic analysis of phages from Podoviridae family

Phage genomes evolve, according to the modular evolution, by the exchange of interchangeable genetic elements. This causes that the standard hierarchical branching phylogeny of phages and their classification are unsatisfied and even impossible. To show relationships between the phage genomes by an alternative approach, we applied CLANS software which uses a version of the Fruchterman–Reingold graph layout algorithm to visualize pairwise sequence similarities in either two-dimensional or three-dimensional space. The analyses were performed on the 92 Podoviridae complete genome sequences using all-against-all TBLASTX searches on the amino acid level. Additionally, we made the pairwise comparison on the nucleotide level in BLASTN for 36 genome sequences from Autographivirinae subfamily to study relationships between these phages in detail. In the studies we also included the newly sequenced genome from Klebsiella pneumoniae KP34 phage. The analyses made possible to group the phage genomes in clusters and proposed some modifications in their current taxonomic classification. The applied method is very sensitive and enabled to find a signal coming from horizontal gene transfer from some Picovirinae members to Lactococcus phage KSY1. Detailed comparison of genomes from phiKMV viruses revealed distinct gene content and arrangement at the 3'-end genomic region which may be responsible for differences in the host recognition and infection mechanisms.

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling I; Saturday, July 2, 08:30

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An illustration of patient-specific cancer modelling: from microscopic data to macroscopic, quantitative predictions

Ductal carcinoma in situ (DCIS)—a type of breast cancer whose growth is confined to the duct lumen—is a significant precursor to invasive breast carcinoma. DCIS is commonly detected as a subtle pattern of calcifications in mammograms. Mammograms are also used to plan surgical resection (lumpectomy) of the tumour, but multiple surgeries are often required to fully eliminate DCIS. This highlights deficiencies in current surgical planning. Immunohistochemical measurements have been proposed to assess DCIS and plan treatment, but no standard has emerged to quantitatively predict a patient's clinical progression (i.e., macroscopic measurements such as the growth rate) based upon such microscopic measurements.

We present a mechanistic, agent-based model of solid-type DCIS with comedonecrosis and calcification [1]. Each agent has a lattice-free position and phenotypic state. Cells move by exchanging biomechanical forces with other cells and the basement membrane. Each phenotypic state has a "submodel" of changes in cell volume and composition. Phenotypic transitions from the quiescent state are regulated by proteomic- and microenvironment-dependent stochastic processes. We combine a model analysis, a mathematically-oriented literature search, and a new patient-specific calibration protocol to fully constrain and calibrate the model to an individual patient's immunohistochemical and morphometric data [3].

The model predicts linear growth at approximately 7–10 mm per year, consistent with mammography [4]. It also predicts a linear correlation between the calcification size (as in a mammogram) and the tumour size (post-operative pathology measurement), in excellent quantitative agreement with 87 clinical data points [4]. These results suggest that hybrid multiscale models can be rigorously calibrated to molecular data by upscaling mechanistic cell-scale models. Such multiscale models can potentially bring mathematics to the clinic to improve patient care.

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Mechanical Models of Movement and Growth of Cells and Tissues II;
Wednesday, June 29, 17:00

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Mechanistic cell-scale modelling of ductal carcinoma in situ (DCIS): impact of biomechanics in comedonecrosis

Ductal carcinoma in situ (DCIS)—a type of breast cancer whose growth is confined to the duct lumen—is a significant precursor to invasive breast carcinoma. The presence of a central necrotic core in one or more affected ducts (comedonecrosis) indicates poorer patient prognosis. Microcalcifications—calcium phosphate deposits that gradually replace necrotic cytoplasmic debris—are critically important to detecting DCIS by mammography. Nonetheless, most models only include necrosis as a simplistic volume loss term, and none have examined necrotic cell calcification.

We present a mechanistic, agent-based model of solid-type DCIS with comedonecrosis and calcification [1]. Each agent has a lattice-free position and phenotypic state. Cells move under the balance of biomechanical forces that are exchanged with other cells and the basement membrane. Each phenotypic state has a "submodel" of changes in cell volume and composition. Necrotic cells swell, lyse, and leak cytoplasmic fluid. Their nuclei degrade (pyknosis), and microcalcifications form in their cytoplasm and deteriorate over long time scales [2]. Phenotypic transitions from the quiescent state are regulated by proteomic- and microenvironment-dependent stochastic processes. The model is fully calibrated to patient data [3].

The model predicts that fast necrotic cell swelling and lysis account for the mechanical separation of the viable rim and necrotic core seen in histopathology—a feature often assumed to be an artifact of tissue preparation. Necrotic cell lysis is a major source of mechanical relaxation, directing proliferative cell flux towards the duct centre, rather than along the duct. Due to this necrotic "flux absorbing" effect, DCIS growth is linear, and growth is slower in larger ducts, with a minimum growth rate of 7.5 mm/year—in excellent agreement with mammography [4]. These results illustrate that well-calibrated, mechanistic cell modelling can provide quantitative insight on the biophysical phenomena that drive cancer progression.

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Developmental Biology; Wednesday, June 29, 17:00

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The evolving surface finite element method (ESFEM) for pattern formation on evolving biological surfaces

In this talk we propose models and a numerical method for pattern formation on evolving curved surfaces. We formulate reaction-diffusion equations [**4**] on evolving surfaces using the material transport formula, surface gradients and diffusive conservation laws [**1**]. The evolution of the surface is defined by a material surface velocity. The numerical method is based on the evolving surface finite element method (ESFEM) [**2, 3**]. The key idea is based on the approximation of Γ by a triangulated surface Γ_h consisting of a union of triangles with vertices on Γ. A finite element space of functions is then defined by taking the continuous functions on Γ_h which are linear affine on each simplex of the polygonal surface. To demonstrate the capability, flexibility, versatility and generality of our methodology we present results for uniform isotropic growth as well as anisotropic growth of the evolution surfaces and growth coupled to the solution of the reaction-diffusion system. The surface finite element method provides a robust numerical method for solving partial differential systems on continuously evolving domains and surfaces with numerous applications in developmental biology, tumour growth and cell movement and deformation.

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Poster Session; Friday, July 1, 20:00

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Restricted Occupancy Models for Human Immunodeficiency Virus Neutralization by Antibodies

Viruses are not able to replicate by themselves. They need a host cell, which they manipulate to produce offspring according to the genetic code they provide. To this end, the virus has to enter the cell. The Human Immunodeficiency Virus (HIV) has spikes on its surface that consist of three identical envelope proteins. These spikes attach to target cell receptors and induce the infection of the cell.
To prevent the infection, the immune system elicits antibodies that bind to specific structures on the envelope proteins. If the number of spikes necessary for infection and the number of antibodies binding to one spike such that the spike is rendered non-functional are known, one can estimate the number of antibodies needed to neutralize one virion or a population of virions.
However, the number of spikes on the virion's surface vary from virion to virion and antibodies can bind randomly to the envelope proteins of different spikes. These effects make it impossible to directly determine the number of neutralizing antibodies. We present mathematical models that incorporate these random effects and allow to derive lower and upper bounds for the number of antibodies that have to bind to neutralize a virion or a virion population. In addition, by using restricted occupancy theory, we are able to calculate the mean number of antibodies neutralizing one virion and a population of virions.

Cancer; Tuesday, June 28, 14:30

, Mohammed Shuker
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Numerical simulations of a continuum model for avascular tumor growth

Avascular growth is a benign stage of cancer. Multicellular spheroids serve as powerful 3D experimental model system for the study of this early stage of solid tumor growth. We present results obtained from using a continuum model that we previously developed (Mahmood et al., 2010, 2011). The three cell types considered within the model are: the proliferating cells, able to grow and divide at intervals dependent upon their size, environment and regulation of cell cycle; the quiescent non-dividing cells that may return to the proliferative part of the cycle either by an increase in nutrient concentration or in response to external stimuli such as growth factor; dead cells due to apoptosis or necrosis. We assume a different motile response kinetics of the proliferating and quiescent cells to the available nutrient gradient. Moreover, the model includes viable cell diffusion, diffusion of cellular material, viability inhibitor contributing to the expansion of necrotic centre and process of removal of dead cell. This means that our model is a system of equations of parabolic and hyperbolic types. The numerical simulations are performed using different sets of parameters, including biologically realistic ones, to explore the effects of each of these model parameters on reaching the steady state reflecting growth saturation, the number of viable cells, and the spheroid size.

Acknowledgement: This work was supported by project "CENTER OF EXCELLENCY FOR RESEARCH IN PERSONALIZED THERAPY (CEVYPET)", code: 26- 220120053, co-financed from EU sources and European Regional Development Fund and by project "CENTER OF TRANSLATIONAL MEDICINE" co-financed from EC sources and European Regional Development Fund, by Ministry of Health of the Slovak Republic 2007/57-UK-17.

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Epidemics; Tuesday, June 28, 11:00

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From elaborate to compact seasonal plant epidemic models

Seasonality, or periodic host absence, is a central feature in Plant Epidemiology. In this respect, seasonal plant epidemic models take into account the way the parasite overwinters and generate new infections. The former are termed primary infections while the latter are secondary infections. In the literature, one finds two classes of models: *elaborate* models, where primary infection dynamics are explicit [1, 2], and lower-dimensional, *compact*, models, where primary infection dynamics are implicit [3, 4]. The way compact models may derive from elaborate models has not been made explicit yet.

In this contribution, we show that approximating primary infection dynamics as a fast process compared to secondary infections in two elaborate models translate into two compact forms. Yet, these are less linear than the compact models usually found in the literature. It is only in some particular instances that we find back the latter models. In particular, we show that density dependence in primary infection dynamics has a profound influence on the compact form. Although both models seems to produce fairly similar dynamics, we highlight that there is a structural difference between the two with respect to the co-existence, or competitive exclusion, of different parasite strains.

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Modeling of collective phenomena in biological systems; Saturday, July 2, 08:30

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Discrete modeling of the sinoatrial node automaticity

Each heart cell — myocyte, communicates with the outside world by rapid changes displayed by ion channels. The membrane activity is tranduced directly to the neighboring cells establishing cell-to-cell communication. Because of these cell-to-cell connections the heart tissue is perfectly suited for modeling as a network of interacting units. Differences in intercellular connections are known to be crucial in forming physiologically different parts of the heart tissue.

The rhythmic contractions of the heart begin in the area of the cardiac tissue located on the right atrium called the sinoatrial node (SAN), see [1] for description of SAN physiology. Understanding of the SAN means to known how pacemaker cells maintain the final function, namely, successful pacemaking of the whole heart. Much difficulty in understanding is related to the arrangement of cells — how rather poorly connected cells can produce a signal self-consistent enough to drive the heart contraction. There are two basic approaches to the organization of the SAN cells: the mosaic and gradient models. The first one considers coexistence of two types of cells: nodal and atrial. The second approach assumes the gradual change of properties of individuals cells when moving from the central part of the SAN to its border. The main objective of our presentation is to find whether the SAN automaticity can result from heterogeneity of intercellular links.

The complex cellular processes involved in the SAN functioning are modeled by modified Greenberg-Hastings cellular automaton [2]. Since, there is a consensus that SAN cells are remains of the heart tissue from its very early stage of development, namely from the embryo, then the construction of intercellular connections rooted on stochastical square lattice is physiologically justified. Synchronic activation of the large parts of such network denotes adjusting of cellular excitations into a robust spiral wave [3].

Effects of perturbations in the topology of intercellular connections on periodicity of the system are considered. The focus is how thorough wrinkling of initially flat structure influences the regular beating. Since automaticity of the sinoatrial node relies on a single cell activity, cyclical properties of individual cells are studied. It appears that robust diversity of oscillations of a cell depends on both: properties of intrinsic cellular dynamics and the underlying topology of intercellular connections. Moderate nonuniformity of intercellular connections are found vital for the proper function of the sinoatrial node, namely, to respond effectively to the autonomic system control [4].

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Heart rate dynamics: models and measures of complexity (part I);
Wednesday, June 29, 14:30

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Healthy aging by multifractal analysis of heart interbeat intervals

Heart rate responds dynamically to various intrinsic and environmental stimuli. The response is supposed to be mediated by autonomic nervous system. Multifractal analysis offers a novel method to assess this response. Fractal properties of the power spectra in VLF (and ultra-low-frequency (ULF: $\leq$ 0.0033Hz)) have being analyzed for more than 20 years and they were found to have prognostic significance in cardiac patients [1] though also they were questioned when they were used for an individual [2]. Therefore the reliability of the approach has to be carefully validated.

The method of effective reading of multifractal properties will be described. The method consists of two way analysis pertaining each signal. In parallel, a given signal analysis and integrated signal analysis are performed. Differences between the multifractal spectra received from the same signal are found important in discriminating monofractality from multifractality.

The method is used in study 24-hour ECG recordings of RR interbeat intervals of 48 elderly volunteers, 40 middle-aged persons and 36 young adults in order to assess the effect of aging on autonomic regulation during normal activity in healthy adults. The variability of heart interbeat intervals was evaluated in the VLF band (32-420 RR intervals) to preserve links to standard measures of heart rate variability [1]. The nocturnal and diurnal multifractality was considered separately.

The switch from multi- to monofractality is observed between diurnal and nocturnal series in the group of young adults. That change can be directly related to the circadian alternation in the central mechanisms controlling the temporal organization of cardiovascular system — nocturnal dominance of the vagal tone versus sympathetic main drive during daily activities. With aging the multifractal structure of nocturnal signals declines. Our observations are consistent with [3] that imbalance in the autonomic control due to healthy aging should be related to changes that are emerging from the vagal tone, what in consequence results in increasing activity of sympathetic modulation.

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Cellular Systems Biology; Tuesday, June 28, 17:00

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Discovering motifs in DNA sequences

One of the important aspects of molecular biology is to understand the complex mechanisms regulating a gene expression. One of the steps in the process of exploring regulatory mechanisms is discovering regulatory motifs that influence gene expression. Gene expression is transformed by the interaction of transcription factors with their corresponding binding sites. The purpose of presented algorithm is to detect the conservative motifs in DNA sequences, in order to identify regulatory sites.

New algorithm is presented in this paper that allows discovery of new motifs in a set of related regulatory DNA sequences and also in genome-wide search. This algorithm uses a heuristic approach based on the structure of suffix trie. For representation of motif sequences, we used a position specific scoring matrices (PSSMs), which are widely used for this purpose. In addition, two approaches have been examined: considering prior residue probability of background, and omitting real value probability. Taking into account the actual likelihood of the background during discovering of motifs, improves the quality of found motifs. Proposed algorithm was tested on reference genomes of human and mouse. The results obtained from the algorithm were compared with other known algorithms. The comparison of these algorithms are performed based on the following comparison measurements: nucleotide Performance Coefficien, Site Sensitivit, Site Positive Prediction, and Site Average Performance. From experiments on real biological data sets, we observed that the applications such as genome-wide search can be identified, in which the algorithm behaves better than other existing tools to search for motifs. But in the case of smaller data sets, average values of measurements were comparable to other existing motif finding tools.

Mathematical Models in Eco-epidemiology II; Wednesday, June 29, 11:00

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Infection and biocontrol of an invading competitor

Biological invasions including the spread of infectious diseases have strong ecological and economical impacts. The perception of their often harmful effects has been continuously growing both in sciences and in the public. Mathematical modelling is a suitable method to investigate the dynamics of invasions, both supplementary to and initiating field studies as well as control measures.

Holling-type II and III predation as well as Lotka-Volterra competition models with possible infection of the prey or one of the competitors are introduced. The interplay of local predation, intra- and interspecific competition as well as infection and diffusive spread of the populations can cause spatial and spatiotemporal pattern formation. The environmental noise may have constructive as well as destructive effects.

A plant competition-flow model is considered for conditions of invasibility of a certain model area occupied by a native species. Short-distance invasion is assumed as diffusion whereas long-distance seed dispersal can be stratified diffusive or advective. The variability of the environment due to contingent landslides and artificial causes such as deforestation or weed control leads to the temporary extinction of one or both species at a randomly chosen time and spatial range. The spatiotemporal dimension of these extreme fragmentation events as well as a possible selected harvesting or infection of the invading weed turn out to be the crucial driving forces of the system dynamics.

Mathematical modeling of biomechanical regulation in bone tissue (Session II); Wednesday, June 29, 11:00

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Mathematical Modeling and Analysis of Force-induced Bone Adaptation

In biological systems, all living organisms are able to react to the biophysical signals arising in their environment. To do that, the constituent cells are provided with mechanisms that allow them to perceive biophysical signals and to react accordingly to accommodate to the demanding environment. Bone as a biological system is not exempted from this mechanoresponsive capacity. In the last decades significant progress has been made from the experimental site as well as the medical insights [1], to understand the effects produced by application of mechanical loading on bone tissue and on bone cells. Experimental studies have shown the key role played by mechanical usage on bone tissue adaptation, and the promotion of cellular behaviors, like proliferation, differentiation, or apoptosis. However, the precise biological mechanisms behind the organization and regulation of the site-specific bone adaptation process remain poorly understood.

The functional adaptation of bone is the process whereby bone adapts its mass and structure to withstand changes in biophysical demands. The process of bone remodeling is the suitable mechanism used by bone to renew, repair and maintain bone surfaces along life. In bone remodeling, two cellular activities are highly coordinated to achieve the renewal process at a particular site, mainly resorption and formation. Resorption is the process by which highly specialized cells, the osteoclasts, destroy bone tissue by creating resorption pits, and afterwards release the bone matrix constituents to the blood. Conversely, in the formation process osteoblast cells synthesize and secrete the osteoid, new unmineralized matrix, and afterwards organize as well the osteoid mineralization.

Following the mechanostat hypothesis [2], bone can adapt its shape and structure by the tissue level mechanisms of modeling and/or remodeling. In bone modeling, resorption and formation happen on different bone sites, a process that arises during growth and development. Conversely, in bone remodeling, both cellular activities occur sequentially at the same bone site, with resorption being followed by formation. In adult skeleton, bone remodeling runs in general as a self-maintenance mechanism used to repair microdamage or fractures, or to strengthen a bone surface

supporting increasing mechanical stress. To organize and regulate the sequencing events in remodeling, the involved cells act as a multicellular team which evolves accordingly and is known as the basic multicellular unit or BMU.

To start bone remodeling a bone surface target is activated, maybe due to microdamage reparation or osteocytes apoptosis. Then, the BMU operation starts by recruiting osteoclast and osteoblast progenitors to the site to be resorbed. Osteoclast progenitors differentiate and get fused into multinucleated osteoclasts who are attracted to the site and start resorption. In osteonal remodeling [3], a fully developed BMU contains teams of osteoclasts actively resorbing at the cutting cone, followed by teams of osteoblasts producing and depositing layers of osteoid at the closing cone. The coupling among resorption and formation may happen during the reversal stage coming after resorption, where the site may be prepared for the coming formation phase. During bone remodeling tight organization and regulation of the cellular interactions are required because sustained imbalances in the quantity or quality of the renewed bone can derive in bone disorders compromising the biomechanical integrity and performance of the skeleton.

The bone cells involved in the remodeling process are osteoclasts, osteoblasts, lining cells, and osteocytes. Osteoclasts are cells of hematopoietic origin responsible for bone resorption, whereas osteoblasts are cells of mesenchymal origin that produce and deposit the new matrix. Osteoclasts and osteoblasts are cells found, however, only temporary on bone surfaces. Osteoclasts are found actively resorbing a surface, while osteoblasts are found actively producing new matrix. Instead, osteocytes and lining cells are the osteoblastic lineage cells residing in the bone matrix. Lining cells derive from osteoblasts who have stopped synthesizing osteoid during bone formation and differentiate to a very flat cell covering the bone surfaces. Osteocytes are terminally differentiated osteoblasts, which are embedded into the matrix during the mineralization process. They live in lacunae that are small cavities inside the matrix, and extend their cytoplasmic extensions through the canaliculi. Due to these fingerlike extensions osteocytes keep in contact with other osteocytes within the matrix and other cells on the bone surface, thus forming a highly interconnected network that makes them the suitable cells for sensing and transducing the mechanochemical signals [4].

The understanding of the bone remodeling dynamics and the adaptation of bone to mechanical loading is of relevant scientific interest due to the potential use of physical exercise to counteract aging-induced bone loss and to avoid the decline of bone mass and strength in conditions of bone loss, such as osteoporosis or immobilization. Osteoporosis is a worldwide spread bone disorder where bone strength and mass are highly compromise thus increasing the risk of fractures. For instance, postmenopausal osteoporosis has been associated to a failure of the capacity of bone to maintain bone strength when estrogen levels are diminished [5]. In addition, the fact that astronauts lose bone mass during prolonged spaceflights, or patients in bed rest condition present osteopenia, show the key role play by earth gravity, locomotion and physical activity on the body, specially on the skeleton maintenance [1].

In this work, we employ a systems biology approach to get a better understanding of the process of force induced bone adaptation. To achieve this, firstly a mathematical model describing the adaption of bone due to mechanical and chemical stimuli was developed [6,7], and secondly, system theoretical methods are applied

for the analysis of the complex interactions and the design of treatment therapies for bone disorders [8,9].

The mathematical description focuses on the remodeling process as an essential tissue level mechanism used by adult skeleton to maintaining bone strength throughout life. The main operational stages of the bone multicellular unit during bone remodeling covered are activation, resorption, and formation. In the model, osteocytes are introduced as the main mechanotransducers, sensing the mechanical loading changes and releasing local factors, e.g. nitric oxide and prostaglandins, that influence the interactions among osteoclast and osteoblast cell populations, mainly regulated through the RANKL/RANK/OPG signaling pathway.

For a better understanding of the bone adaptation process, and the identification/discrimination of possible therapeutic targets for remodeling-related bone disorders, a theoretical method for global sensitivity analysis is applied to the mathematical model to explore the effects of parameters/inputs variation on the stationary behavior of bone cells and tissue adaptation. In addition, the use of theoretical methods allows to explore for beneficial effects of combining mechanical and non-mechanical agents in the treatment of particular bone disorders, such as postmenopausal osteoporosis, or bed rest/immobilization.

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The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits II; Wednesday, June 29, 17:00

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Stochastic modelling of cell migration

Cell migration is a central process in normal human tissue development as well as in numerous disease states. Metastatic spread of cancer tumours occurs as a direct result of changes in cell migration, and further insight into the mechanisms behind cell migration is of great importance in cancer research. CMACs (cell-matrix adhesion complexes) are at the heart of the migratory system of the cell; elucidation of CMAC behaviour is essential in understanding cell migration [1] [2]. In this work, quantitative time-series live cell microscopy data are used together with existing knowledge to develop a stochastic model describing the behaviour of the CMAC population of the wild-type cell with respect to CMAC areas and the number of CMACs. New CMACs are born according to a Poisson process and then the subsequent multiplicative growth and decline of CMAC area and final death is described by means of a random walk with a Markov process regime. Analytical results are derived and simulations are performed to validate model performance. It is shown that the model is able to mimic CMAC behaviour with respect to most aspects of the properties described above, and also is able to predict the behaviour of new perturbed experimental conditions.

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Poster Session; Friday, July 1, 20:00

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Models of morphogen transport

Transport of morphogens is a process occurring in the tissue, affecting cell differentiation. In [**?**] authors proposed several mathematical models (systems of PDEs of reaction-diffusion type) of this process. In [**?**] a detailed analysis of two of those models was made in 1D setting. I will present my recent results concerning global in time existence and asymptotic behavior for the 3D setting.

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Information, human behaviour and infection control; Saturday, July 2, 08:30

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The impact of vaccinating behaviour on the natural history of immunization programmes.

Recent theoretical studies have provided increasing evidence that human behaviour can play a critical role in the achievement of public health targets, such as the mitigation of a pandemic influenza outbreak or the success of a vaccination programme for a childhood infection. As for the area of vaccine preventable infections, much of the recent research has focused on the impact of immunization choices - modelled as an evolutionary game with imitation dynamics - on voluntary vaccination regimes, particularly the issue of vaccination free-riding. In this paper we first use a simple transmission model with vaccination payoff modelled as an increasing function of the incidence of vaccine side effects, to interpret historical trends in serious morbidity and mortality from various childhood infections. This allows us to clearly show which are the major killers of vaccination programmes in industrialised countries. These seem mainly to be the technological progress and the ensuing epidemiological transition, which during the last century have brought down to negligible levels the perceived risks of serious disease given infection, and the sustained vaccination programmes conducted in the past, which have brought down to negligible levels the perceived risks of infection. This yields rather pessimistic predictions about the future lifetime of vaccination programmes. Subsequently, motivated by the fact no current vaccination regimes are fully voluntary, we propose a new framework aimed to predict the dynamic effects of the interplay between inter-human and public information on vaccine uptake, based on a modified evolutionary game equation for the vaccinated proportion, including the effort of the public health system as well. The underlying idea is that the hazard of becoming a vaccinator is the sum of two components, one due to information spread through inter-human contacts (e.g. imitation), and one due to information spread by the public health system. Unlike the former, the latter aims to suggest a very small, possibly zero, perceived risk of vaccine side effects, and a larger, possibly prevalence independent, risk of disease. Our main results show that public intervention can play a stabilising role capable to reduce the violence of 'imitation' induced oscillations, to allow for disease elimination, and to even make the so called Disease Free Pure Vaccinators Equilibrium Globally attractive. This suggests that keeping a degree of public intervention in otherwise voluntary vaccination regimes might be the only way to mitigate the pessimistic conclusions reported above.

Mathematical Modeling of Mosquito-Borne Diseases; Tuesday, June 28, 11:00

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A Model for the Spread of Rift Valley Fever in Livestock with Vertical Transmission

Rift Valley Fever (RVF) is a zoonotic infectious disease spread by mosquitoes and transmitted between several animals species and occasionally humans. We present and analyze a new model for mosquito-transmitted disease that includes vertical transmission mechanisms from an infected mosquito mother to infected offspring. In particular, we model the spread of RVF in cattle and mosquito populations, extending existing models for vector-borne diseases to include vertical transmission and an egg/larvae stage. We analyze the importance of vertical transmission in predicting the spread of RVF and discuss how modeling can reduce the uncertainty of the estimates of disease prevalence. We also make this extended model reactive to environmental changes and demonstrate that even if the endemic equilibrium has a low ratio of infectious vectors and animals, a large pulse of vectors resulting from increased hatch and survival rates due to high rainfall events can result in a large epidemic.

Semigroups of Operators in Mathematical Biology I; Wednesday, June 29, 08:30

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Structured population models in metric spaces

Time evolution of a heterogeneous population parametrised by the dynamically regulated properties of individuals can be described by so called structured population models, which are first order hyperbolic equations defined on $\mathbb{R}^+$.

In this talk a new framework for the analysis of measure-valued solutions of the nonlinear structured population model is presented. Existence and Lipschitz dependence of the solutions on the model parameters and initial data are shown using the properties of nonlinear semigroups in suitably chosen metric spaces. The estimates for a corresponding linear model are obtained based on the duality formula for transport equations. The results are discussed in the context of applications to biological data. In particularly, the new framework is applied to describe a process of cell differentiation, which involves discrete and continuous transitions.

The presentation is based on joint works with Piotr Gwiazda (University of Warsaw) and Grzegorz Jamroz (University of Warsaw/University of Heidelberg).

Analysis of mathematical models for cancer growth and treatment, Part I;
Tuesday, June 28, 11:00

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Dynamics of pattern formation in the models of early cancerogenesis

In this talk we will explore a mechanism of pattern formation arising in the processes described by a system of a single reaction-diffusion equation couples with ordinary differential equations. Such models are very different from classical Turing-type models and the spatial structure of the pattern emerging from the destabilisation of the spatially homogeneous steady state cannot be concluded based on linear stability analysis. The models exhibit qualitatively new patterns of behaviour of solutions, including a strong dependence of the emerging pattern on initial conditions and quasi-stability followed by rapid growth of solutions. In numerical simulations, solutions having the form of periodic or irregular spikes are observed. Recently we have proposed models of spatially-distributed growth of clonal populations of precancerous cells, which remained under control of endogenous or exogenous growth factors diffusing in the extracellular medium and binding to the cell surface. We found conditions for emergence of growth patterns, which took the form of spike-type spatially inhomogeneous steady states. This multifocality is as expected from the field theory of carcinogenesis.

In this talk we approach the question of stability of spike solutions, which is essential for their observability in experiments. We study existence and stability of regular spatially inhomogeneous stationary solution of periodic type and of discontinuous patterns.

The talk is a based on a series of joint works with Marek Kimmel (Rice University), Kanako Suzuki (Tohoku University), Grzegorz Karch (University of Wroclaw) and Steffen Härting (University of Heidelberg)

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Discriminative gene selection in low dose radiotherapy microarray data for radiosensitivity profile search

In radiotherapy total dose delivered to targeted tumor tissue is limited to minimize late side effects in normal tissue, which also limits its healing effect. Ability to adjust the dose to the individual patient radiosensitivity with the use of information given after low dose radiation will help in reducing the negative effects of radiotherapy while increasing the efficiency of cancer treatment. In most gene expression studies selection of significant features for sample classification is a common task. The main goal of this step is to discover the smallest possible set of genes that allows to achieve good predictive performance. However, in analysis of cancer patients radiosensitivity, differences between analyzed groups are hardly noticed. Also clinical observations indicate large variations between individuals within group, which provides a need to explore different methods of feature selection.

Examined data contain two groups of breast cancer patients showing clinical differences in their normal tissue late response to radiotherapy. Data pre-processing includes probe sets re-annotation using PLANdbAffy database, tRMA background correction, normalization and summarization. Preliminary data analysis and quality control pointed out strong batch effect, which was corrected using ComBat software.

To select significant genes, which can predict the status of the sample on the basis of the expression profile, we use statistical methods (t-test, modified Welch test, F-test) and recurrent feature replacement methods (Recursive Feature Elimination, fuzzy C-Means RFE). In statistical methods correction due to correlation between genes was applied. We perform comprehensive experiments to compare feature selection algorithms using two classifiers as SVM, with linear and nonlinear kernel, and Naive Bayes. The validation step was divided into 2 stages. Training pilot study patient set, which in opinion of clinicians was more informative, and testing set, which contained the rest of samples, were used to see if there exist gene signature related to radiosensitivity. Multiple random validation procedure using all data was later performed to prove generalizability of selected features.

As a result of applying the above described algorithms, it was possible to construct a classifier that could discriminate patients based on their late response to radiotherapy treatment with 25% error rate using SVM and nonlinear kernel. This

result was proven through multiple random validation. When comparing methodologies of feature selection recruitment modified Welch test which deals with unequal variability of genes between groups performed best, however only with correction due to correlation.

This work was supported by the European Program FP6 - 036452, GENEPIlowRT and Ministry of Science and Higher Education grant no N N519 647840.

Population Dynamics; Wednesday, June 29, 08:30

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Modelling the spatial spread of invasive aliens: process-based models and Bayesian inference

Discrete state-space Markov processes provide a remarkably flexible framework both to describe and infer the behaviour of a broad range of systems in epidemiology and beyond. For many models of interest reversible jump Markov chain Monte Carlo methods are a practical approach to implementing statistically sound parameter estimation for such models when, as is typically the case, only partial observations are available. We consider the application of such inference approaches, applied with spatial epidemic models, to describe the spread of invasive species at large spatial scales. In such applications local environmental characteristics determine susceptibility (suitability for the invasive species) which emphasises the role of landscape heterogeneity.

In particular we present a generic Bayesian approach to parameter inference in a grid-based stochastic, spatio-temporal model of dispersal and establishment describing the invasion of a region by an alien plant species. The method requires species distribution data from multiple time points, and accounts for temporal uncertainty in colonisation times inherent in such data. The impact on colonisation suitability of covariates, which capture landscape heterogeneities, is also inferred. The model and inference algorithm are applied to British floristic atlas data for Heracleum mantegazzianum (giant hogweed), an invasive alien plant that has rapidly increased its range since 1970. Using systematic surveys of species distribution across a 10km grid covering the British Isles, we infer key characteristics of this species, predict its future spread, and use the resulting fitted model to inform a simulation-based assessment of the methodology.

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Hypoxic Migratory Cell Waves around Necrotic Cores in Glioblastomas: A Mathematical Model

Malignant gliomas are the most common and deadly brain tumors. Survival for patients with glioblastoma (GBM), the most aggressive glioma, although individually variable, is in the range of 10 months to 14 months after diagnosis, using standard treatments which include surgery, radiotherapy, chemotherapy (temozolamide and antiangiogenic drugs such as bevacizumab) [1]. GBM is a rapidly evolving astrocytoma that is distinguished pathologically from lower grade gliomas by the presence of necrosis and microvascular hyperplasia. Interestingly, necrotic foci are tipically surrounded by a population of rapidly moving tumor cells that superimpose themselves on a more stationary population, causing increased cell density, known as "pseudopalisades" [2, 3]. Evidence suggests that this tumor cell migration is caused by a vaso-occlusive event where the local tumor blood vessels no longer provide the necessary oxygen supply. This leads to the formation of a wave of tumor cells actively migrating away from central hypoxia (oxygen deprivation) that arises after a vascular insult. Indeed, pseudopalisading cells show nuclear expression of hypoxia-inducible factor 1α, consistent with their hypoxic nature [2, 3].

We have developed a mathematical model that incorporates the spatio-temporal interplay among two tumor cell phenotypes, a necrotric core and the oxygen distribution. Our scenario consists of the tumor cells embedded within two blood vessels. We will assume that the hypoxic phenotype is the migratory one but non-proliferative, whereas the normoxic is less migratory but proliferative [4, 5]. In addition, our model takes into account the switching mechanisms between both phenotypes when the local oxygen levels cross a threshold value characteristic of hypoxia. Our numerical simulations reveal the formation of a superimposed travelling wave of hypoxic cells that qualitatively reproduces the experimentally observed patterns. This suggest that our model could be further extended to include the selective action of radiotherapy on the tumor cells depending on their oxic state.

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Modelling dengue fever epidemiology; Saturday, July 2, 08:30

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Why dengue and yellow fever coexist in some areas of the world and not in others?

Urban yellow fever and dengue coexist in Africa but not in Asia and South America. In this paper we examine four hypotheses (and combination of them) advanced to explain the absence of yellow fever in urban areas of Asia and South America. In addition, we examine one further hypothesis that would explain the coexistence of the infections in Africa and at the same time explaining why they do not coexist in Asia and South America. The hypotheses advanced to explain the nonexistence of yellow fever in Asia and South America are: the risk of importation to Asia of a yellow fever viraemic person is very low; the Asian Aedes aegypti is relatively incompetent to transmit yellow fever; there would exists a competition between dengue and yellow fever viruses within the mosquitoes, as suggested by some in vitru studies, in which the dengue virus always wins; there is an important cross-immunity between yellow fever and other flaviviroses, dengue in particular, such that a person recovered from a bout of dengue would have his/her susceptibility to yellow fever diminished. This latter hypothesis is called hereafter the "Asian hypothesis". Finally, we hypothesize that the coexistence of the infections in Africa is due to the virtual absence of the mosquito Aedes albopicuts, which competes with Aedes aegypti, in Africa. We call this latter hypothesis the "African hypothesis". We construct a model of transmission that allows all the above hypotheses to be tested. We conclude that the Asian and the African hypotheses can explain the observed phenomena. The other hypotheses do not explain the observed phenomena.

Mathematical modeling and simulations of angiogenesis I; Wednesday, June 29, 08:30

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Parameter sensitivity investigation of a mathematical model of glioma angiogenesis via Latin hypercube sampling.

Malignant glioblastoma multiforme (GBM) is a relatively rare cancer with a very poor prognosis. It is unique among cancers in that the tumors are quite diffuse and infiltrative, but do not metastasize out of the CNS. This diffuse nature, as well as its location in the brain, presents many challenges for treatment and disease monitoring. Following the development of anti-angiogenic agents in the past few years, there has been much hope that this form of treatment might make great strides in the treatment and management of malignant glioma, but clinical response to date has been disappointing. Patients often show a strong initial response on MRI, with imageable tumor receding relatively soon following treatment initiation. However, after some time they all progress, often with more diffuse, wide-spread disease than prior to anti-angiogenic treatment. To better understand the role of angiogenesis and anti-angiogenic therapy in GBM patients, we have created a proliferation-invasion-hypoxia-necrosis-angiogenesis (PIHNA) mathematical model of glioma growth with angiogenesis and have adapted it to simulate anti-angiogenic therapy. Based on our clinically validated, extensive work with the proliferation-invasion (PI) model of glioma growth (1, 2, 3) this model was developed to simulate the effects of hypoxia on vascular recruitment in glioma. It has been correlated with FMISO PET imaging data (4), and provides a basis from which we can better understand the effects of anti-angiogenic treatment on vascular recruitment, as well as the tumor environment. Here we present our use of a sensitivity analysis technique incorporating latin hypercube sampling (LHS) to vary parameters against each other and determine which parameters in the model have the most significant influence on hypoxic burden and how treatment parameters fit in. This knowledge allows us to better assess the significance of anti-angiogenic therapies on tumor growth patterns and give insight into the relationships between these factors and the tumor microenvironment to enhance combat and control of the disease.

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Moving Organisms: From Individuals to Populations; Wednesday, June 29, 17:00

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Profits from noise: the example of E. coli motion and chemotaxis

E. coli bacteria propel themselves through flagellar rotation. The control of the flagella is given through a rather simple signaling pathway, involving only a very small number of enzymes. Despite its simplicity this signaling pathway regulates a number of complex behaviors like chemotaxis, adaptation, and even Lévy walks. A Lévy walk is a special type of a random walk, characterized by a power-law run length distribution. It has been proven to represent the optimal search strategy to find randomly located and sparse targets. Interestingly, in *E. coli* bacteria the Lévy walk is a result of noisy fluctuations affecting the signaling pathway. We use a model of the signaling pathway given in the form of differential and algebraic equations, augmented by a stochastic term, to study the influence of noise on the concentration dynamics and the behavior of single cells and populations. Based on the model we derive the power-law run length distribution analytically in dependence on and statistical properties of the noise and properties of the signaling pathway. Our expression yields a power-law exponent of -2.2 which coincides with experimental data. We also use the model to simulate chemotactic behavior of large populations in different chemical landscapes. We show that also chemotactic behavior profits from noise, as it increases bacterial motility and behavioral variability.

Crowd Dynamics: Modeling, Analysis and Simulation (Part 1); Wednesday, June 29, 11:00

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Handling of congestion in crowd motion modeling

We propose a general framework to incorporate congestion in the modeling of crowd motion in evacuation situations. This approach can be seen as a first order (in time) counterpart of the evolution problem associated to the collective motion of rigid spheres (or discs) with a non elastic collision law. In its simpler, microscopic, form (see [**4**]), the approach we propose is based on the definition of a desired velocity (corresponding to the velocity one would have in the absence of others); the actual velocity is then defined as the projection of this desired velocity onto the set of feasible velocities (velocity which do not violate the non-overlapping constraints between individuals). This model fits into the general framework of sweeping processes by convex sets [**5**], and its generalization to non-convex sets [**1**]. Well-posedness results rely on a so called *catching up algorithm*, which follows a prediction-correction strategy, where the correction consists in projecting a configuration which violates the constraints onto the set of feasible configurations.

We proposed recently a macroscopic version of this approach ([**2**]): the crowd is described by a density which is subject to remain below a maximal value (congestion). We shall present how the general framework of optimal transportation endows the space of densities with a natural distance (Wasserstein distance) which makes it possible to generalize the catching up approach to this non-Hilbertian setting [**3**].

We shall address the links and deep differences between micro and macro approaches, from both mathematical and modeling standpoints.

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Poster Session; Friday, July 1, 20:00

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Mathematical Modelling of Cancer Ecology

We model the metabolism and behaviour of a developing tumour in the context of its microenvironment, with the aim of elucidating what drives the hallmarks of malignancy [1]. The multiscale, multistage, highly nonlinear nature of cancer progression [2] calls for a dual modelling approach that can link continuous tissue-level spatiotemporal patterns with discrete cell-level adaptations at the tumour-host interface. Of particular interest is the acid-mediated invasion hypothesis [3], which suggests that tissue hypoxia, adoption of the glycolytic phenotype [4], and acquisition of resistance to acidic byproducts of the glycolytic phenotype comprise a critical stage in tumour progression. Many open questions remain concerning the details of this hypothesis and how it fits into the somatic evolution of cancer, illustrating just one of many research avenues for modelling the somatic evolution of cancer in general. We have generalised an existing continuum model of the acid-mediated invasion hypothesis [5] by considering additional, potentially important, biological features of cancer invasion, such as realistic acid-induced cellular death terms and cellular competition. Using both analytical and numerical methods, we firstly explore how a wave of tumour cell invasion is influenced by the acquisition of acid resistance, with further studies investigating parameter sensitivity and the impact of modelling invasion with more than one spatial dimension.

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Epidemic models: Networks and stochasticity II; Thursday, June 30, 11:30

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Stochastic amplification in an epidemic model with seasonal forcing

In this talk I will discuss, using the formalism of master equations, the nature of the stochastic dynamics which appears in models of population biology, and in particular childhood epidemics. When they contain a large number of constituents, the behaviour of these models may be analysed using an expansion in the system size. To leading order the deterministic analogues of the models can be compared to the equations which are normally written down on phenomenological grounds, for example the SIR (Susceptible-Infected-Recovered) differential equations. At next-to-leading order a simplified stochastic description is obtained. Attention will focus on systems for which the deterministic description fails to predict cycles, but where large cycles are found at next-to-leading order. These cycles have their origin in fluctuations due to the discrete nature of the system components, and are much larger than would naively be expected because they are amplified by a resonance phenomenon. The application of these ideas to the SIR model with term-time forcing will be described.

Population Dynamics; Tuesday, June 28, 11:00

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Macroparasites in Managed Systems: Using mathematical models to help reduce the Impact of *Argulus foliaceus* in UK Fisheries

Argulus foliaceus is a macroparasite which reduces the aesthetic appeal and catchability of rainbow (Oncorhynchus mykiss) and brown (Salmo trutta) trout in still-water fisheries across the UK; infection is detrimental to fish welfare, can lead to loss of revenue, and impacts negatively on the reputation of the affected fisheries. Current methods of control can be both extreme and ineffective, with the parasite often surviving in surprising circumstances, despite constant, expensive treatment.

The aim of this talk is to present mathematical models, in the form of coupled non-linear ODEs, which describe the relationship between argulids and their hosts, incorporating reduced catch rates and several different stocking methods. Fishery managers can stock fish into their lakes in a number of different ways in order to make sure that anglers catch enough fish and want to return to their fishery. This talk will investigate the relationship between those stocking methods, the response of the fish to parasitism and the number of parasites in the lake. These combine to have a - sometimes counterintuitive - knock-on effect on the number of fish caught and hence the economic viability of the fishery.

Epidemics; Tuesday, June 28, 17:00

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Tuberculosis in Russia: comparison of TB control programmes

Tuberculosis is recognized as a major global public health problem, so development of TB control strategies and estimation of their efficiency are important tasks. Mathematical modelling can be a tool for solving these problems.

We compared control programmes for 14 regions related to the Central Federal District of Russia. The initial values of indicators for monitoring TB control programmes were obtained from data analysis [1]. Average smear-positive case detection rate equals 74%, average treatment success rate equals 78%, average smear-negative case detection rate equals 34%.

We considered two TB control programmes. The programme 1 is recommended by WHO, the targets of programme are detection of 80% of new smear-positive cases and cure of 85% of such cases. Russian health system considers two consecutive stages of tuberculosis: smear-negative and smear-positive. Detection of smear-negative cases is an important part of the Russian TB control programme and therefore we considered programme 2 focused on improvement of smear-negative case detection. The target of programme 2 is detection of 40% of new smear-negative cases.

To compare control programmes we used a mathematical model that describes the spread of TB in population of Russia, the values of model parameters were obtained from model fitting [1]. To analyze sensitivity of model solution to changes in model parameters we used a method of adjoint equations, also we obtained formulas for calculation of changes in basic epidemiological indicators [2].

The changes in TB mortality rate, TB incidence and number of people who infected by mycobacteria per year were calculated for each programme. Programme 1 is more effective than programme 2 in 9 regions and less effective in 3 regions. They are approximately equal in 2 regions. The results obtained show that type of control programme should be chosen separately for each region after analysis of epidemic situation.

The technique developed can be used to estimate the efficiency of other TB control programmes that were not considered in this study. It can be a usefull tool to choose the most effective programme.

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Connectivity and diffusion for *Heliconius* species in a seasonally dry fragmented habitat

In a fragmented landscape, the capability of populations to move between habitat patches, called functional connectivity, is influenced by the nature of the intervening matrix and how organisms respond to it. Models usually treat the matrix as a fixed category and fail to appreciate the possibility of dynamic matrix types. We studied the role of seasonal changes in matrix quality, given that it differs between dry and wet seasons in the seasonal tropics. The duration of the favorable period for dispersal, the species' ability to disperse and the distance between patches could be important factors determining patch connectivity. We explored these connections by employing a diffusion model to a one-dimensional landscape subjected to periodical fluctuations in matrix quality; diffusion was curtailed in the dry season and permitted in the wet season. Our model predicts that, given a particular organism's lifetime and diffusion constant, connectivity will depend on the relation between the duration of the dispersal season and the time for the population to fully extend into the matrix. We parameterize our model with demographic data from *Heliconius* butterflies, finding that the model successfully describes connectivity between habitat patches and so it could be used to model dispersal of other organisms in seasonal environments and to help guide restoration efforts and design of protected areas in the tropics.

Cancer; Wednesday, June 29, 11:00

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Mathematical modelling of metabolic symbiosis in tumors

In the 1920s the findings by Otto Warburg's highlighted the fundamental differences in the metabolism of tumor cells. However, the oncogene revolution somehow pushed tumor metabolism to an ancillary level in cancer research. It is currently becoming clear that many key oncogenic signalling pathways converge to adapt tumor cell metabolism to support growth and survival, and some of these alterations seem to be required for malignant transformation [1, 2, 3].

The abnormal tumor microenvironment has a major role in determining the metabolic phenotype of tumor cells. Tumor vasculature is irregular and malfunctioning, creating spatial and temporal heterogeneity in oxygenation, pH, and the concentrations of glucose, lactate and many other metabolites. Under such varying and extreme conditions, adaptive responses are induced that contribute to the switching metabolic phenotype of malignant cells greatly influencing tumor progression. Although aerobic glycolysis (the Warburg effect) is the best documented metabolic phenotype of tumor cells, it is not a universal feature of all human cancers. Moreover, even in glycolytic tumors, oxidative phosphorylation is not completely shut down.

Hypoxic cells use glucose for glycolysis, producing large amounts of lactate and exporting it via monocarboxylate transporters (mainly the isoform MCT4), a family of proteins that when expressed in the plasma membrane are responsible for the transport of different types of molecules [4,5]. Because of the accelerated metabolism of tumor cells, these transporters are up-regulated in many different types of cancers [2,4,6]

This fact has been recognized in the last few years as opening a potential target for therapies since blocking the activity of these transporters might lead to different scenarios leading to the death of the tumor cell [2,7-10]

It has been recently demonstrated [10] that oxygenated cells within the tumor can import extracellular lactate using another transporter (MCT1) to fuel respiration, preserving glucose for use by the hypoxic cells and regulating the medium pH. This metabolic symbiosis between oxidative and glycolytic tumor cells that mutually regulate their access to energy metabolites and pH makes the tumor progression very robust. Furthermore, it has been shown in [10] that inhibition of MCT1 induces a switch on oxidative cells from lactate-fueled respiration to glycolysis. As a consequence, hypoxic cells die from glucose starvation rendering the remaining better-oxygenated cells sensitive to irradiation and other therapies.

Similar symbiotic phenomena between the tumor and its altered microenvironment have been reported in other tumor models [11,12].

In this communication we will present a mathematical model of tumor cells behavior in vitro able to describe the glucose and lactate uptake in different scenarios. The model fits the in-vitro experiments of Ref. [10], together with other measurements reported in the literature [13], as well as our own experiments with glioma cell lines.

We will discuss how to extend the in-vitro model to incorporate other phenomena present in cancers such as hypoxia and reoxygenation. Finally, it will be examined how these mathematical models can assist in the design of optimized combination therapies with radiation and inhibitors of monocarboxylate transporters.

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Computational toxicology and pharmacology - in silico drug activity and safety assessment; Saturday, July 2, 11:00

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Artificial neural networks for carditoxicity prediction of drugs - practical considerations

Introduction Early toxicity prediction for potential drugs is considered as a necessary safety measure regarding recent withdrawals of many substances from the pharmaceutical market. The latter was substantially based on the identified cardiotoxicity related to the inhibition of the potassium channels encoded by hERG (the human ether-a-go-go related gene). Thus, the drugs affinity to hERG channels is considered now as one of the major screening factors for potentially dangerous substances. There are theories describing relationships between hERG channels blocking activity and chemical structure but they often lack of physiological/pathological factors and drug concentration influence. Thus, it is feasible to use empirical modeling to fill this gap. The aim of this work was to create predictive model for chemical substances affinity to hERG channels by means of artificial neural networks (ANNs).

Materials and methods Database used for the modeling purposes was recently published and is freely available from the CompTox project website (www.toxportal.net). Input data were derived from the published in vitro experiments. Inputs represented in vitro experiment settings, chemical descriptors of drugs and drug concentration. Output was simply percent of hERG channel inhibition (range

0 to 1). Final set contained 1969 records describing 200 drugs. Initial number of inputs was 109. Enhanced 10-fold cross validation (10-cv) was applied, where whole drugs information was excluded from test sets. For external validation a test set of 193 records (25 substances) for drugs both previously present (different in vitro settings) and absent in the native dataset was used. Drugs chemical structures were drawn in MarvinSketch or downloaded from PubChem Compound database. The molecules were structurally optimized with use of molconvert command-line program included in Marvin Beans package. Resulting *.sdf files were the subject to descriptor calculations by cxcalc program with selected 41 plugins. The default parameters were used in both cxcalc and molconvert programs. Multi-layer perceptrons (MLPs) and neuro-fuzzy ANNs (NFs) were trained with use of back-propagation (BP) algorithm with momentum, delta-bar-delta and jog-of-weights modifications. Various activation functions were tested: hyperbolic tangent, logarithmic, logistic and linear. MLPs architectures were varied from 1 to 6 hidden layers and up to 200 nodes in each layer. For NFs of Mamdani (multiple input single output) MISO type only one layer was applied. Adjacent layers were fully interconnected. Sensitivity analysis was performed in order to reduce initial number of inputs to the crucial variables set by means of iterative algorithm with gradual inputs reduction and models predictive performance assessment. The latter was generalization error estimated by means of 10-cv with root mean squared error (RMSE) measure. Ensemble ANNs systems were applied and combined by simple average of their outputs in order to improve predictability of the model.

Results The input reduction procedure resulted in 39 parameters describing in vitro setting (8), drug physico-chemical properties (30), and concentration (1). The best ANNs architectures found were as follows: (1) ANN with 3 hidden layers with 15, 7 and 5 nodes in each one respectively and logistic activation function; 2) ANN with 2 hidden layers with 20 and 10 nodes. The resulting 10-cv RMSE was 0.22 with respect to the validation data set RMSE = 0.2. This result, although not satisfactory seems to be final with the available data representation. Future research will be devoted to the improvement of the model by enhancing input data by new factors/variables, if available.

Cancer; Friday, July 1, 14:30

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Modeling of Tumor Cell Dynamics with Individual-based Lattice-gas Cellular Automata

Malignant tumors can be considered as populations of interacting cells with a high amount of phenotypic heterogeneity. To model cooperative phenomena (e.g. cancer growth) in interacting cell populations, lattice-gas cellular automaton (LGCA) models are increasingly used. Major advantages of LGCA models are that they admit computationally efficient simulations and often analytical treatment of the modeled problem. However, it has not been possible so far to distinguish individual biological cells in LGCA models making them unsuitable to model phenomena where the explicit description of individual cells is required. However, lattice-gas cellular automata have been successfully applied to model specific tumors without specifically considering individual cells, e.g. growth of glioblastoma tumors. Nonetheless, there are processes during tumor formation for which a "classical lattice-gas model" is unsuitable. One such process is the invasion of surrounding tissue by single tumor cells, a prerequisite for the formation of metastasis.

We propose an extension to (classical) lattice-gas cellular automata which allows the identification and tracking of individual cells. In particular, we derive stochastic differential equations (Langevin equations) corresponding to specific LGCA models. The LGCA model together with the knowledge of the corresponding Langevin equation allows computationally efficient simulations and feasible analytical treatment of the dynamics of individual cells in populations of interacting cells. Furthermore, our proposed approach facilitates the construction of individual-based LGCA models with cell-dependent dynamics. This also supports the incorporation of LGCA models into multi-scale models which consider processes at sub-cellular and cellular scales.

We present applications of our individual-based LGCA appoach to the following examples: random walk, adhesion, and collective motion. Furthermore, we use an individual-based LGCA model to investigate conditions for the onset of tissue invasion by single tumor cells.

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Mathematical Modeling and Numerical Simulations for the Influence of Heat Shock Proteins on Tumour Invasion

Invasion is a key property of tumor cells; thereby, they encounter a large variety of soluble and substratum-bound factors which can influence the different stages of their migration. There are at least two mechanisms promoted by such factors: chemotaxis and haptotaxis. These in turn are influenced by the intracellular dynamics. In our talk we focus on the effect of heat shock proteins (HSP), a class of functionally related proteins whose expression is enhanced when cells are exposed to elevated temperature or other stresses and which have been recently proposed to influence cancer cell migration. Our mathematical model has a multiscale character, accounting both for the microscopic, intracellular level on which these proteins are acting and for the macroscopic level of cell population. It consists of a system of reaction-diffusion equations for the density of cancer cells, of the extracellular matrix and the concentration of matrix degrading enzymes, which is then coupled with a delay differential equation for the HSP dynamics. We propose several different ways for modeling the time lag and perform numerical simulations in order to assess the effect of our choices on the behaviour of the system.

Epidemics; Tuesday, June 28, 17:00

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Did seasonal influenza vaccination increase the risk of pandemic influenza infection?

Recent studies have suggested that vaccination with seasonal influenza vaccine resulted in an apparent higher risk of infection with pandemic influenza H1N1 2009. A simple mathematical model incorporating strain competition and a hypothesised temporary strain-transcending immunity is constructed to investigate this observation.

Results of the model over a range of reproduction numbers and effective vaccination coverage confirm this apparent increased risk in the Northern, but not the Southern, hemisphere. This is due to unvaccinated individuals being more likely to be infected with seasonal influenza (if it is circulating) and developing hypothesised temporary immunity to the pandemic strain. Because vaccinated individuals are less likely to have been infected with seasonal influenza, they are less likely to have developed the hypothesised temporary immunity and are therefore more likely to be infected with pandemic influenza. If the reproduction number for pandemic influenza is increased, as it is for children, an increase in the apparent risk of seasonal vaccination is observed. The maximum apparent risk effect is found when seasonal vaccination coverage is in the range 20-40%

Only when pandemic influenza is recently preceded by seasonal influenza circulation is there a modelled increased risk of pandemic influenza infection associated with prior receipt of seasonal vaccine.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -I; Tuesday, June 28, 11:00

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Cell-based modeling of plant tissues using VirtualLeaf

Plant organs, including leaves and roots, develop by means of a complicated, multi-level cross-talk between gene regulation, patterned cell division and cell expansion, and tissue mechanics. In contrast to the cells in many animal tissues, plant cells cannot migrate and, with very few exceptions, they cannot slide past each other. Consequently, plant morphogenesis depends entirely on patterned cell division, cell expansion, and cell differentiation. Thus plant development requires different cell-centered models than those developed for animal development, in which cell migration and tissue folding play a primary role. We will present a cell-centered computer-modeling framework for plant tissue morphogenesis that we named *VirtualLeaf* [**1**]. We will illustrate the current use of VirtualLeaf with examples of auxin-driven vasculature development, determination of leaf shape, and meristem growth. VirtualLeaf defines a set of biologically intuitive C++ objects, including cells, cell walls, and diffusing and reacting chemicals, that provide useful abstractions for building biological simulations of developmental processes. VirtualLeaf-based models provide a means for plant researchers to analyze the function of developmental genes in the context of the biophysics of growth and patterning. VirtualLeaf is an ongoing open-source software project (http://virtualleaf.googlecode.com) that runs on Windows, Mac, and Linux.

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Mathematical modeling and simulations of angiogenesis II; Wednesday, June 29, 11:00

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Cell-based modeling of angiogenic blood vessel sprouting: cell-ECM interaction and tip-cell selection

Angiogenesis is a topic of intensive experimental investigation so its phenomenology and the molecular signals contributing to it have been well characterized. Yet it is poorly understood how the biological components fit together dynamically to drive the outgrowth of blood vessels. Cell-based simulation models of angiogenesis describe endothelial cell behaviour in detail, help analyze how cells assemble into blood vessels, and reveal how cell behaviour depends on the microenvironment the cells themselves produce. Our previous simulation models, based on the Cellular Potts model, have shown that the elongated shape of endothelial cells is key to correct spatiotemporal in silico replication of vascular network growth [**1**]. We also identified a new stochastic mechanism for angiogenic sprouting [**2**]. Here I will briefly discuss new insights into the role of cell shape and stochastic motility during vascular branching. Then I will present recent results on the role of tip cells, suggesting that tip cell-stalk cell interactions accelerate angiogenic sprouting. I will also discuss our recent cell-based modeling studies of cell-extracellular matrix interactions during angiogenesis.

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Speciation; Wednesday, June 29, 08:30

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Darwinian speciation on a regulated landscape

Darwin envisioned speciation as a gradual transformation from within-species diversity to between species one, driven by the fitness-advantage of reduced competition via niche-segregation. We identify three issues why Darwins suggestion has been considered problematic since the New Synthesis: I: The notions of niche and reduced competition have no meaning in the context of a rigid adaptive landscape. Instead, one has to consider the landscape (i.e. the fitness function) as a function of the phenotype-distribution in a functional analytic context. The functional derivative of this map is the competition function with the correct biological meaning. The adaptive dynamics phenomenology, including evolutionary branching, can be derived from this setup. II: The observed often-allopatric nature of speciation seems to exclude a role for competition. However, the theory of structured populations allows considering spatially distributed populations as a single population with an over-all fitness value. Therefore, we can define the adaptive landscape on the large spatial scale and apply the considerations above for allopatric and parapatric speciation modes analogously to the sympatric case. III: Biological species concept declared reproductive isolation as the defining issue of speciation. In our picture emergence of isolation is secondary to ecological segregation on the regulated/changing landscape. As selection for ecological divergence is caused by a fitness minimum, it is always accompanied by a selection pressure for isolation. Whether this pressure results in an evolutionary buildup of reproductive isolation depends on the availability and genetic organization of the possible isolating mechanisms. Considering these three issues together leads us to conclude that Darwins original idea is still the most parsimonious theory of speciation. Species diversity is necessarily based on competition-reducing niche segregation, i.e. segregation with respect to the way of being regulated. This structure translates to the concept of regulated adaptive landscape, providing selection pressure for competition-reducing branching evolution, which may, or may not be related to spatial segregation.

Fractals and Complexity I; Wednesday, June 29, 14:30

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Fractality of chromatin

The extension of the fractal concept towards biology and medicine has improved our understanding of functional properties and the dynamics of physiological phenomena in living organisms Fractals are very useful to characterize properly the complexity of tissues by describing relevant underlying design principles [1]. Fractality has evolutionary advantages. Structures with fractal features can be built by simple, iterative programs. Fractal banching is a simple and efficient way for the construction of complex connections resulting in short distances for transport. Fractal foldings of membranes permit to create a large surface area within a very small volume. Power law organization of physiological systems increase the capacity of adaptation in the case of changes in the environment [1]. Therefore we can expect that fractality can also be found in the organization of the genome and the epigenome. Several investigators showed the presence of self-similarity in DNA sequences. Experimental data support the concept of a fractal organization of chromatin. In intact interphase chicken erythrocytes, spectra obtained by small angle neutron scattering. revealed a constant fractal dimension of the protein component, and a biphasic DNA organization, with a fractal dimension on lower scales and a different one on the larger scales [2]. Fractal structures can be created in polymers by iterative processes for instance by repeated folding during condensation. Thus a polymer can be packed in a small volume without entanglements, facilitating rapid unravelling when necessary. Recent experiments suggest that this process applies also to chromatin leading to a genome organization in form of a spatial segregation of open and closed chromatin with knot-free fractal globule formations[3]. All these studies support the concept of a fractal nature of DNA, nuclear chromatin and the surrounding nucleoplasmic space, i.e. a fractal organization of the nucleus. Morphologists, using light and electron microscopy, are demonstrating indirect evidence for the fractal organization of chromatin for nearly two decades . They differentiate basically two distinct chromatin conformations: the uncondensed euchromatin and the much denser and darker heterochromatin, which is usually considered to be transcriptionally less active. Alterations of the nuclear architecture reflect genomic and non-genomic changes, which are very common in tumor cells. Genomic changes may be point mutations translocations, or amplifications or alterations of the chromosomal position. Furthermore malignant tumors show widespread epigenetic changes including global hypomethylation, as well as focal hypermethylation of multiple CpG island gene regulatory regions. Hypomethylation is associated with decondensing of the chromatin structure and induces chromosomal instability. A more aggressive behaviour is usually observed in genetically unstable neoplasias with an increasing number of genetic or epigenetic changes. Therefore unstable tumors are expected to show a more complex chromatin rearrangement, with a mixture of many chromatin areas with varying density (lighter and darker), equivalent to a higher fractal dimension in the computerized image analysis[1]. Clinico-pathologic studies demonstrated that an increased fractal dimension of chromatin at diagnosis

was an independent adverse prognostic factor for survival of patients with different malignant neoplasias, such as multiple myeloma , squamous cell carcinoma of the oral cavity squamous cell carcinoma of the larynx , and malignant melanoma of the skin [4-7]. Therefore we may conclude that the complexity of the chromatin architecture in neoplastic cells may reveal important prognostic information. In summary, fractal characteristics of the nucleus are essential for its function and are reflected in its chromatin structure, which may accompany pathologic processes , such as carcinogenesis and tumor progression.

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Bridging the Divide: Cancer Models in Clinical Practice; Thursday, June 30, 11:30

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Optimised cancer treatment using cell cycle synchronisation with heavy ion irradiation

Cancer is a leading cause of death worldwide. As a consequence a multitude of experimental and mathematical studies on cancer growth and a diversity of treatments are being developed. Among these is tumour irradiation with heavy ions. While this novel methodology was restricted to research institutes for a long time, this treatment became a full part of clinical reality now.

We present an agent-based approach to the modelling of cellular dynamics within tumour spheroids that is based on experimentally accessible parameters and thus is able to take advantage of experimental data from irradiation experiments. As the model architecture is lattice-free and average-free, it can be considered to be a realistic representation of tumours. The model grows a tumour from a single malignant cell and the dynamics of tumour growth in response to irradiation protocols can be tracked. As the model is single cell based we are able to provide an in depth analysis of all possible observables ranging from the cell cycle phase, pressure inside the spheroid, nutrient supply and limitations, up to genetic expression profiles for the intracellular network. Target of our study is a detailed examination of the dynamical reaction of tumours to heavy-ion irradiation treatment.

It is found that irradiation treatment induces a variety of dynamical reactions within a tumour. Reoxygenation of the tumour volume and a decrease in pressure due to cell death lead to excessive regrowth after irradiation. As expected fractionation of the radiation dose changes the degree of tumour control considerably depending on the applied fractionation scheme. A pronounced resynchronisation of the cell cycle within the tumour after irradiation is found which could be exploited in order to administer follow-up treatments in accordance to the cell's most radiosensitive phases. This result has direct implications for experimental studies and eventually for clinical trials.

Connecting microscale and macroscale models of cellular migration;
Tuesday, June 28, 17:00

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From particles to PDEs: continuum approximations to models of cellular migration

Cell migration is a fundamental process in biology. Examples range from the development of multi-cellular organisms, through to the emergence of complex spatial patterns in bacterial populations. Mathematical models of cell migration can help increase our understanding of the underlying biology. However, the models that capture the molecular scale interactions are typically rather complex and can be difficult to analyze. Here, we explore this problem by developing a model based on Langevin dynamics, whereby short-range intercellular interactions are represented using an appropriate potential function. Following Newman and Grima (2004), we obtain a mean field approximation to our model, this being an integro-partial differential equation. By exploiting the biologically plausible limit of intercellular interactions occurring on infinitesimally small length scales, we derive a system of partial differential equations that can approximate the mean-field behaviour of the original Langevin model and and is amenable to analysis. We will show how the molecular scale details (represented by our choice of interaction potential) are reflected in the PDE approximation. An analysis of the resulting patterns will be given. Relevant applications, such as cell-sorting and chemotaxis, will also be discussed.

Delay Differential Equations and Applications I; Friday, July 1, 14:30

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Delayed protein degradation does not cause oscillations

It is well known that time delays may cause oscillations in solutions of ordinary differential equations. We would like to point out that the presence of oscillations depends on particular causes of a time delay.

Models with time delays may be divided into two families [1,2]. In social-type models, where individuals react to the information concerning the state of the population at some earlier time, we should expect oscillations. On the other hand, in biological-type models, where some changes already take place in the population at an earlier time, oscillations might not be present for any time delay. We will briefly review two specific examples of evolutionary games - replicator dynamics with time delay [1].

Our main goal is to show that delayed degradation does not cause oscillations as it was recently argued [3]. To do so we propose a new methodology to deal with time delays in biological systems and apply it to simple models of gene expression with delayed degradation [4].

We develop a systematic analytical treatment of stochastic models of time delays. Specifically, we take into account that some reactions, for example degradation, are consuming, that is once molecules start to degrade they cannot be part in other degradation processes. It follows from our rigorous analysis that one should look for different mechanisms than just delayed protein degradation to explain causes of oscillations observed in certain biological experiments.

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Modeling of immune responses and calcium signaling IV; Saturday, July 2, 08:30

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Simple stochastic models of gene regulation

We will discuss simple models of gene regulation. We assume that the number of mRNA and protein molecules is small and therefore to describe biochemical processes of transcription, translation, and degradation, we use birth and death processes. We linearize Hill functions which describe regulation, use the generating function approach to the Masters equations, and show that translational repression contributes greater noise to gene expression than transcriptional repression [1].

Our main goal now is to derive analytical expressions for the variance (noise) of the number of protein molecules in models where changes of the DNA state between an active and inactive one are governed by birth and death processes whose intensities depend on the number of protein molecules [2]. We will discuss different approaches to the problem of closure of an infinite chain of equations for moments of the protein probability distribution and apply it to systems with two gene copies [3].

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Recent developments in the study of Lotka-Volterra and Kolmogorov systems; Saturday, July 2, 14:30

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Permanence for Kolmogorov competitive systems of PDEs

This talk is about recent results on permanence for Kolmogorov reaction–diffusion systems of partial differential equations (PDE)

$$\frac{\partial u_i}{\partial t} = \Delta u_i + f_i(t, x, u_1, \ldots, u_N)u_i, \qquad 1 \leq i \leq N,\ t \in [0, \infty),\ x \in \Omega.$$

Here $u_i(t, x)$ measures the population density of the i-th species at time t and spatial location x, and Ω is a bounded habitat. The system is endowed with appropriate boundary conditions.

Systems are assumed to be *competitive*, which means that $\partial f_i/\partial u_j \leq 0$ for $1 \leq i, j \leq N$, $i \neq j$ (usually much more will be assumed).

Permanence (sometimes called *uniform persistence*) means that any positive solution of the system becomes bounded away from zero, where the ultimate bound is independent of the solution.

We will give a survey of results on permanence for Kolmogorov competitive systems of PDEs, in particular with general dependence on time. Especially, connections with invasibility will be addressed.

Mathematical modeling and simulations of angiogenesis I; Wednesday, June 29, 08:30

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Image Driven Computational models of Cell migration

Cell migration has been identified as one of the fundamental mechanisms driving embryogenesis, organ development, angiogenesis and tumor invasion. We develop computational models of cell migration and tissue infiltration to assist related experimental studies. Continuum models are developed to capture migration of cell agglomerates at the tissue level resolution and a discrete particle model enables for the exploration of cell migration on a cellular scale.

The models are validated against a set of in-vitro and in-vivo model systems. In order to facilitate the validation process, we develop a set of computational tools that allow for the extraction of relevant statistical metrics on biological experiments. Curvelet based image reconstruction is used for vessel network and cell membrane segmentation and Particle Image Velocimetry (PIV) on in-vitro experiments to register mass transport in migrating cell layers. We combine these methods and present a robust algorithm for in-vitro cell shape tracking of multiple cells.

References.

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Evolutionary Ecology; Friday, July 1, 14:30

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Beyond mutation surfing: adaptation during invasions

We use stochastic simulations to model invasion of new territory by a population that evolves by natural selection to the novel environment, as well as by drift. Previous studies have resulted in competing claims to the effect that the process of invasion may either promote or inhibit adaptation. By comparing adaptation in invading and established populations, we identify conditions under which invasion facilitates adaptation (when compared with evolution in an established population), as well as regimes in which invasion impedes adaptation. We also discuss the extent to which analytical models can provide insight on this problem.

Poster Session; Friday, July 1, 20:00

Harriet Mills
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Caroline Colijn
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Pathogen spread on coupled networks: effect of host and network properties on transmission thresholds

In recent years network models have been extensively used to study how spreading dynamics in human populations, such as the dynamics of an infectious disease, a rumour or even a behaviour, depend on how individuals are connected to each other. Real populations are connected via a large variety of networks; respiratory, sexual or online social networks to name just a few. These networks, though generally of very difference structure, are not always independent and interactions on one may influence interactions on another. For example, HIV is spread over a sexual network and TB over a respiratory network, infection with HIV raises the risk of progressing from latent to active TB, potentially increasing transmission rates of TB across the respiratory network. Here we develop the theory behind network models. First we consider two processes spreading on two distinct networks. Process B spreads only over network b, but process A spreads over both networks, with a reduced transmission rate over network b. We examine how the amount of transmission of process A over network b affects the epidemic, and find that even a small amount of transmission across another network can greatly influence the epidemic size. Secondly, we consider how different host types in the population affect the epidemic threshold of a disease over one network. We apply these frameworks to our motivating example of HIV and TB.

Fractals and Complexity II; Wednesday, June 29, 17:00

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Mathematical model of box-counting analysis in the human dentate nucleus during development

Many disorders of the cerebellum may be developmental in origin. In order to recognize impaired development and better to understand the etiology of various neurological disturbances of the cerebellum, a precise timetable of the cellular events that take place during normal development is needed. Therefore, the binary and skeletonized two dimensional neuronal images of Golgi impregnated sections of the human dentate nucleus at various gestational periods were subjected to fractal analysis in order to investigate the morphology of these cells during development. Since the results showed that both parameters increased during gestation, a mathematical model which quantitatively describes changes in morphology of neurons from the human dentate nucleus during development is proposed. While the binary fractal dimension linearly increased with gestational time, the skeletonized fractal dimension increased with time exponentially. The findings of the present study are generally in accordance with previous qualitative data and provide better understanding of the formation of the neuronal circuitry of the human dentate nucleus.

Structure and Dynamics of Biochemical Reaction Networks II; Tuesday, June 28, 17:00

Maya Mincheva
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Oscillations in Biochemical Reaction Networks

Understanding the dynamics of interactions in complex biochemical networks is an important problem in modern biology. Biochemical reaction networks are modeled by large nonlinear dynamical systems with many unknown kinetic parameters, which complicates their numerical analysis. Important properties, such as the potential of a biochemical reaction network to oscillate can be determined by the network's structure. We will discuss a new graph-theoretic condition which includes the negative cycle condition for oscillations as a special case.

Recent advances in infectious disease modelling I; Saturday, July 2, 11:00

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Impulsive differential equations and their application to disease modelling

Many evolutionary processes are characterized by the fact that at certain moments of time they experience a change of state abruptly. These processes are subject to short-term perturbations which act instantaneously; that is, in the form of impulses. Thus, impulsive differential equations - differential equations involving impulse effects - appear as a natural description of observed evolution phenomena of several real-world problems. We will discuss how to solve linear homogeneous and non-homogeneous impulsive differential equations as well as non-linear autonomous impulsive differential equations. We will also give an overview of existence and uniqueness of impulsive systems as well as the issues that arise with stability. We illustrate using a model for HIV drug therapy.

Developmental Biology; Thursday, June 30, 11:30

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The combined mechanisms of the reverse fountain and the reflected flow provide for self-organization and maintenance of the root apical meristem

The phytohormone auxin is critical for patterning and morphogenesis in plants. In plant roots, auxin maxima coincide with the sites of the root apical meristem (RAM) initiation and functioning. By today, the two main mechanisms of the auxin distribution formation in the root tip were proposed. The reverse fountain mechanism is based on a specific RAM structure in which each cell has a specified set of directions of auxin efflux. A stable location of the auxin maximum in silico is provided for by a reflux of auxin from the basipetal flow back to the acropetal flow all along the meristem, which transports auxin in a loop. The reflected flow mechanism is based on the auxin-dependent regulation of auxin acropetal flow: low auxin concentrations activate the transcription of PIN1 genes, whereas the high concentrations induce degradation of PIN1 proteins [2]. The mechanism explains self-organization of the auxin distribution pattern in an array of functionally identical cells acquiring cell type specialization due to auxin regulation of the level of PIN1 proteins in these cells. We suggested that the reverse fountain and the reflected flow mechanisms are complementary in root development. In particular, only the reflected flow mechanism operates at the very early stages of root development. At later developmental stages, an anatomical structure forms and provides for the functioning of the reverse fountain mechanism that serve for more robust maintenance of the auxin maximum in the RAM. However, the reflected flow mechanism does not disappear, revealing itself if RAM structure is disrupted or the environment changes. To test the hypothesis we combined both mechanisms in 2D mathematical model. This model describes (1) auxin flow from the shoot; (2) auxin synthesis that is positively regulated by auxin itself; (3) irreversible loss of auxin (degradation); (4) auxin diffusion, providing for an isotropic distribution in the root; synthesis and degradation depending on auxin concentration of (5) PIN1, (6) PIN2, (7) PIN3; (8) active auxin transport mediating by PINs proteins; (9) growth and division of root cells. Two cell types are considered in the 2D model: central cylinder and epidermis. For the central cylinder cells the processes (1-5,7-9) are considered and described as in [2]. For the epidermal cells the processes (2-4,6-9) are considered. As auxin transporters carry out different, often redundant, functions in specialized tissues, we introduced to the model some simplifications. Only three auxin carriers are considered: PIN1 transports auxin acropetally, PIN2 mediates basipetal auxin flow as well as lateral transport from basipetal back to

acropetal flow, PIN3 regulates auxin redistribution in the root cap. Thus, PIN proteins have the following locations in the cells: PIN1 is localized at the basal side of the central cylinder cells, PIN2 at the lateral internal and apical sides of the epidermal cells and PIN3 at all sides of potentially all cells. For the processes (1,3-5,8-9) the parameter values were taken from [2]. Other parameters were estimated so that: (1) PIN2 is expressed predominantly in epidermal cells with low auxin level; (2) PIN3 expression domain is localized in the zone of high auxin level; (3) auxin synthesis rates are high in the cells with high auxin level. With this set of parameters and initial uniform auxin distribution, the model provides steady-state auxin distribution pattern that agree well with the experimental data. The mechanism of auxin distribution self-organization found in the resulting stationary solutions is the following. At the first step, auxin maximum is generated in the central cylinder cell array at the distance from the root end under the reflected flow mechanism. As a result, the zone of high auxin level in the root tip is organized where PIN3 and auxin synthesis rate are high. Second, the PIN3-mediated auxin redistribution is switched on in the root tip, and auxin moves to PIN2-mediated basipetal flow in epidermis. Third, As PIN2 is localized on the lateral internal cell sides in epidermis, the reflux of auxin from the basipetal flow back to the acropetal flow starts to work. Finally, the auxin gradient associated with the maximum is formed under the reverse fountain mechanism which finishes formation of auxin distribution pattern. In numerical experiments we showed that the 2D model reveals both the robustness to the developmental processes from the reverse fountain mechanism [1] and the plasticity to the environment changes from the reflected flow mechanism [2]. Based on these advantages the 2D model gave new predictions about the positional information in root patterning that can be checked in the experiments. The 2D model of auxin distribution in root can be a powerful tool for investigation of root development in silico.

The work was partially supported by the RAS programs A.II.5.26, A.II.6.8, B.27.29, SB RAS 107, 119, and RFBR 10-01-00717-,11-04-01254-.

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Level crossings in biological time series

Kedem in his research [**1**] made use of zero crossings theory in time series analysis. Zero crossings are remarkably simple and effective tool to examine the autocorrelation structure of time series. The application of nonlinear binary transformation of time series allows to retain information contained in the autocorrelation function of the original data. Kedem (1989) found relation between first order autocorrelation and the expected zero crossings rate. In the case of zero mean stationary Gaussian time series there exist explicit formula (*cosine formula*), connecting the first order autocorrelation ρ_1 and the expected number of zero crossings $E[D]$. The relationship looks as follows

$$\rho_1 = \cos(\frac{\pi E[D]}{n-1}).$$

Cosine formula is therefore very useful for the estimation purposes. Having given the number of zero crossings, we can estimate first order autocorrelation in a very simple and fast way. Using Electroencephalogram (EEG) signal we ilustrate how accurate the cosine formula is. We also answer the question how far precisely we can compute the first order autocorrelation using zero crossings.

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Mathematical Modelling of Macromolecules and Molecular Aggregates;
Saturday, July 2, 14:30

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Global optimization analysis of viral capsids and amide planes

A scheme of Combinatorial Optimization (CO) is introduced in order to describe the geometrical pattern of the macromolecular structures like A-DNA and molecular aggregates like Tobacco Mosaic Virus (TMV). Backbone sequences of internal atom sites are seen to be associated to sequences of Steiner points of an Euclidean Steiner Tree Problem. The agreement with experimental data is 94.6% and 98.2% for A-DNA and TMV, respectively.
Another CO scheme in which the Steiner points have a fundamental role, is the introduction of an objective function which minimum will lead to the confirmation of the existence of Amide planes in protein structure. This is a Mathematical Programming approach such that the variables are small perturbations of bond and dihedral angles. Objective function and constraints are derived only from knowledge of the 3-dimensional molecular structure.
These results provide excellent examples of robust methods of optimization as applied to the study of geometrical modeling of biopolymers and molecular aggregates.

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Lattice Gas Cellular Automata modeling of lineage dynamics and feedback control

This study is important in understanding the mechanism and dynamics of some biological problems such as tumor invasion and wound healing. Firstly, we describe microscopically the model and we derive the corresponding mesoscopic approximation, via the mean field assumption. In the following, we upscale our model providing a PDE which serves as a macroscopic manifestation of the underlying cellular interactions. We focus on investigating the speed and the structure of the invasion front, using the above mentioned approximations, as functions of the underling cell phenotypes and microenvironmental factors (i.e. nutrients).

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Developmental Biology; Saturday, July 2, 11:00

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Coding design of positional information for robust morphogenesis

Robust positioning of cells in a tissue against unavoidable noises is important for achieving normal and reproducible morphogenesis. The position in a tissue is represented by morphogen concentrations, and cells read out them to recognize their spatial coordinates. From the engineering viewpoint, these positioning processes can be regarded as an information coding. Organisms are conjectured to adopt good coding designs with high reliability for a given number of available morphogen species and their chemical properties. To answer quantitatively the questions, how good coding is adopted? and when, where, and to what extent does each morphogen contribute to positioning?, we need a way to evaluate the goodness of coding. In this paper, by introducing basic concepts of computer science, we mathematically formulate coding processes in morphogen-dependent positioning, and define some key concepts such as encoding, decoding, and positional information and its precision. We demonstrate the best designs for pairs of encoding and decoding rules. We also discuss the applicability of our theory to biological data.

Mathematical modeling of biomechanical regulation in bone tissue (Session I); Wednesday, June 29, 08:30

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BMU remodelling simulation using reducer order method

Adam Moroz, Mikhail Goman, David I. Wimpenny BMU remodelling simulation using reducer order method The bone remodelling process, performed by the Bone Multicellular Unit (BMU) is a key multi-hierarchically regulated process, which provides and supports various functionality of bone tissue. It is also plays a critical role in bone disorders, as well as bone tissue healing following damage. Modelling of bone turnover processes could play a significant role in helping to understand the underlying cause of bone disorders and thus develop more effective treatment methods. The reducer order approach to modelling of bone turnover, based on the osteocyte loop of regulation, have been employed, thin wide range of rate parameters using the Monte Carlo method. The optimal control framework for regulation of remodelling has been discussed. The study illustrates the complexity of formalisation of the metabolic processes and the relations between hierarchical subsystems in hard tissue where a relatively small number of cells are active.

Stem cells and cancer; Wednesday, June 29, 14:30

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Tumor Growth Kinetics Modulated by Generational Lifespan of Non-Stem Cancer Cells

Numerous solid tumors are heterogeneous in composition. While growth is driven by cancer stem cells (CSCs), the reported relative frequencies of CSC versus non-stem cancer cells span wide ranges within tumors arising from a given tissue type. We have previously shown that tumor growth kinetics and composition can be studied through an agent-based cellular automaton model using minimal sets of biological assumptions and parameters. Herein we describe the pivotal role of the generational lifespan of non-stem cancer cells in modulating solid tumor progression. Although CSCs are necessary for expansion, tumor growth kinetics are surprisingly modulated by the dynamics of the non-stem cancer cells. Our findings suggest that variance in tumor growth curves and CSC content of solid tumors may be attributable to the proliferative capacity of the non-stem cancer cell population that arises during asymmetric division of CSCs. Remarkably, slight variations in proliferative capacity result in tumors with CSC fractions differing by multiple orders of magnitude. Larger proliferative capacities yield migration-limited tumors, as the emerging population of non-stem cancer cells spatially impedes expansion of the CSC compartment. Conversely, lower proliferative capacities yield persistence-limited tumors, with symmetric division frequency of CSCs determining tumor growth rate. Intermediate proliferative capacities give rise to fastest-growing tumors, indicating a between self-metastatic growth through symmetric CSC division and the availability of space facilitated by removal of senescent non-stem cancer cells. Our results offer novel explanations for the large variations in CSC ratio reported in the literature, and highlight the importance of non-stem cancer cell dynamics in the CSC hypothesis.

Poster Session; Friday, July 1, 20:00

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Modelling Homeostatic Responses

In this poster I will derive a set of differential equations describing the dynamics of a cellular frustrated system. I will concentrate on how the system is capable of performing immune responses that drive the system back to homeostatic control. In this way we show that cellular frustrated systems can respond to endogeneous or exogenous perturbations. The immunological significance of these results will be discussed, in particular in connection to autoimunity or tumour elimination.

Population Genetics; Wednesday, June 29, 14:30

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Conditions for extinction of some lethal alleles of X-linked genes

Some lethal alleles of certain genes can cause the death of the organisms that carry them. Some of these alleles, as could be that responsible of hemophilia, correspond to genes linked to sex chromosomes, especially to X chromosome. If these alleles are dominant, all the carriers die so they are rarely detected due to their rapid elimination from populations. However, recessive lethal alleles only cause death of carrier males and homozygous carrier females, though the last ones must be daughters of a carrier male, so they rarely exist. Heterozygous carrier females are able to live and reproduce. They do not phenotypically express the genetic condition but can pass the lethal allele onto offspring.

In this work, we introduce a multitype bisexual branching process for describing the evolution of the number of individuals carrying the alleles, R and r, of a gene linked to X chromosome. The R allele is considered dominant and the r allele is assumed to be recessive and lethal. Females can have two genotypes: homozygous, RR, and heterozygous, Rr, whereas only R males are able to live. Homozygous and heterozygous females have identical phenotypes so males do not know the genotype of their mates, it can be said that they made a "blind" choice among the two genotypes.

In such a model, we take into account that the offspring of a couple with a homozygous female do not carry the lethal allele. However, couples with heterozygous females can give birth to RR and Rr females and R and r males. Since r males die, Mendelian inheritance ratios of these couples are altered. The total offspring of each couple is modeled through a random variable whose probability distribution is supposed to be different for homozygous and heterozygous females.

We use this model to study the extinction probability of one of these lethal alleles, i.e. under which conditions it will eventually disappear and when it will survive along the generations. Such conditions are expressed in terms of the parameters of the model. In case of non extinction, we investigate the evolution of the number of carriers of such alleles.

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Population Dynamics; Tuesday, June 28, 17:00

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Adaptation to a given habitat as a factor influencing dynamics and evolution of model populations.

We investigate the conditions under which a model population can survive in a given habitat, colonize a new (spatially separated) habitat and is able to co-exist with a population living in a neighbouring habitat.

Each habitat is represented by a square lattice and a model phenotype, describing the phenotype of an individual that is fully adapted to the considered habitat. The populations are composed of individuals that move over the lattice, mate, produce offsprings and die. The individuals are characterized by their genotypes, phenotypes and ages. The individuals adaptation to a given habitat depends on the number of its phenotypic features that are the same as the corresponding features of 'the model phenotype' according to a power function with some exponent n. The value of the adaptation is related to the individuals probability of survival.

We discuss the influence of the value of n on the population dynamics and its genetic and phenotypic variability. In particular, we compare the situations when: $n>1$ (briefly, in this case only the individuals that are quite similar to the model phenotype can survive easily) and $0>n>1$ (here, even small similarities between the phenotype of the considered individual and the model phenotype may be significantly advantageous for survival). For co-existing populations, possibilities of formation of hybrid zones of different shapes are also investigated. Computer simulations based on the standard Monte Carlo technique are performed.

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Poster Session; Friday, July 1, 20:00

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Modelling calcium transients in plant pathogen defence reactions

Recognition of so-called pathogen-associated molecular patterns (PAMPs) triggers the plant immunity. As a first line of defence the production of reactive oxygen species (ROS) is started. ROS are able to kill the invading pathogen and to crosslink cell wall components forming a barrier to block the infection. The plant receptors perceive the PAMPs on the cell surface and transfer a signal into the cell. As a consequence, the release of calcium from internal stores is mediated, generating a spike of the cytosolic calcium concentration. This increase depends on the type of elicitor and can differ in lag time, magnitude, peak time, intensity and duration. The project focuses on the establishment of a mathematical model and the simulation of the cytosolic calcium signals upon pathogen contact and also should be expandable for integrating other components of this signal transduction chain. Initially, the cytosolic calcium levels are measured in aequorin-transformed tobacco cell cultures. Simultaneously, the cytosolic calcium concentration is mathematically described, based on a system of differential equations. The MatLab software is used for running simulations. The simulations imply the variation of different sets of parameters to describe the different kinetics of calcium transients, dose-response-relationship curves and additionally reproducing the refractory behavior of the cytosolic calcium increase for comparison with the measured datasets.

Cancer; Saturday, July 2, 14:30

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Predicting pseudoprogression in glioblastoma patients: A mathematical and clinical perspective

Background: Glioblastoma multiforme (GBM) is a highly invasive primary brain tumor that diffusely invades the surrounding normal appearing tissue and yields short life expectancies despite aggressive treatment. A combination of chemo and radiation therapies is the standard of care for newly diagnosed GBM. However, published data estimate that 20%-50% of progressive enhancement on MRI occurring within 12 weeks post chemoradiotherapy is the result of pseudoprogression (Psp) and does not indicate true progression (TP) of disease. Though many novel methods and modalities are currently being evaluated to distinguish Psp from TP, there is no widely accepted noninvasive mechanism to predict Psp in individual patients.

Methods: A reaction-diffusion model has effectively quantified the net proliferation () and invastion rate (D) (P-I) of untreated glioma growth and invasion. We investigate the application of the P-I model as a mechanism to predict which patents will be more likely to experience pseudoprogression and true progressive disease. The pre- and post-chemoradiotherapy MRI scans of 57 patients were reviewed retrospectively.

Results: Eleven of the 57 patients were clinically confirmed to exhibit pseudoprogression and 46 patients were confirmed to exhibit true progression. These patients were then evaluated based on model-generated parameters of the net migration (D) and proliferation rates () of each patients glioma tumor. Of the 11 Psp patients, 9 (82%) had pretreatment D/<1 mm2, and of the 46 TP patients, 33 (72%) had pretreatment D/>1 mm2.

Conclusion: A pre-treatment D/rho<1 mm2 reflects a more focal, less invasive tumor that is more likely to be highly vascularized and hypoxic. Thus, in a post chemotherapy environment, such tumors may be more prone to enhanced edema due to the increased permeability of the tumor vasculature and more likely to exhibit enhancement on radiographic imaging. Though additional investigation is necessary to determine if this relationship persists, preliminary results suggest the application of the P-I model to patient-specific pre-chemoradiotherapy MRI data provides model-derived parameters that may offer a quantitative mechanism to help predict which patients are more likely to experience pseudoprogression.

Ecosystems Dynamics; Tuesday, June 28, 11:00

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Modeling the Spread of *Phytophthora*

The genus *Phytophthora de Bary* is a well-known group of fungus-like pathogens with algal relatives which are the causal agent of the most devastating plant diseases. Herbaceous crops like potatoes as well as woody crops like citrus or even trees in natural forests fall prey to them and cause tremendous pecuniary and ecological losses each year which attract a lot of interest in the investigation of the behaviour and the spread of *Phytophthora*.

We consider a model for the morphology and growth of *Phytophthora* using the example of *Phytophthora plurivora* utilizing a correlated random walk describing the density of tips. This correlated random walk incorporates some non-standard aspects, as growth and change of direction are intertwined, and the spread of newly split tips is delayed (apical dominance).

First we investigate running fronts, especially questioning the effect of this delay, for uniform- as well as non-uniform turning kernels. We find that this delay primarily influences the slope of the front and therewith the way of spatial appropriation, and not its velocity. This theoretical prediction is confirmed by experimental data of *Phytophthora* growing in Petri dishes.

The second question we are dealing within this talk is concerning the manner tips are interacting, especially the point why tips stop to grow "behind" the interface of the front, respectively in confrontation experiments at the interface between two colonies. The combination of experimental data about the spatial structured time course of the glucose concentration and simulations of a model taking into account both, tips and glucose, reveals that nutrient depletion is most likely the central mechanism of tip interaction and hyphal growth. We presume that this is the growing mechanism of this *Phytophthora* in infected plant tissue and this the pathogen will sap its hosts via energy depletion and tissue destruction in infected areas.

Poster Session; Friday, July 1, 20:00

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Analysis of p53 transactivation on different Response Elements

p53 is the guardian of the genome, it acts as a transcription factor regulating the production of several proteins upon DNA damage. Maybe this is the most investigated protein in human cells, still the exact mechanism how p53 binds to response elements (REs) in the DNA is still unclear. A yeast-based essay enables us to investigate its binding dynamics to REs of highly important targets. We collected time courses of transcriptional activity at various REs by measuring luminescence induced by p53 regulated promoters at various p53 induction levels. We created a mathematical model for the molecular interactions of p53 dimers and their binding to REs. Alternative versions of the model contain possible proposed binding orders and interactions. We perform large scale parameter estimation to identify which model can give such parameter sets that fits the experimental measurements. Initial results revealed that earlier time points need to be measured to allow proper fitting. We observed that, some parameters show low sensitivity at all p53 induction levels. Thus we narrowed down on a subset of parameters from the initial set and run the estimation by fitting all the measured REs together and observed the intra RE and inter RE variations in the parameters. With the parameter estimation we plan to identify the details of p53 RE binding events. The emerging modeling results will be further validated experimentally.

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A multi-scale analysis of the influence of hormonal cross-talk: cell-fate determination in *Arabidopsis thaliana* root development

Root growth and development in *Arabidopsis thaliana* are sustained by a specialised zone termed the meristem, which contains a population of dividing and differentiating cells that is functionally analogous to a stem cell niche in animals. The size of the meristem is regulated by the balance between cell division and cell differentiation, and this balance is controlled antagonistically by the hormones auxin and cytokinin. Local accumulation of auxin promotes cell division, whereas high cytokinin concentrations promote differentiation. The cross-talk between these two hormones is controlled by a genetic regulatory network.

As a first step of our analysis, we propose and compare with experimental observations a single-cell, deterministic mathematical model of this regulatory mechanism. We show that, although genetic mutations can reproduce qualitatively the effects of varying auxin and cytokinin supply on their response genes, the general response of the network is different and an analysis based on the ratio between these two hormones may be misleading.

Recently, gibberellin has been shown to be relevant in determining the adult size of the meristem by interacting with auxin and cytokinin. We propose a multi-scale model of this interaction and we validate the results of our simulations with experimental data. We conclude that a multi-scale investigation can provide insight into the signalling network controlling meristematic activity, by enabling the study

of the dynamical response of the network in different tissues and the identification of potential missing components.

Multiscale modelling of biological systems: the Chaste framework;
Tuesday, June 28, 11:00

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Using Chaste to simulate a multiscale problem in developmental biology

During somitogenesis the posterior PSM segments at regular time time intervals into blocks of epithelial cells called somites. A clock and wavefront mechanism is the widely accepted model for this process, with cellular clocks and a travelling molecular wavefront determining when and where the somites form, respectively. Recent experimental findings in zebrafish have highlighted the fundamental role of Notch-Delta signalling in the coupling of neighbouring cellular oscillators. Using the framework of phase coupled oscillators to model the Notch-Delta coupled molecular oscillators, we demonstrate how oscillator coupling alone is sufficient to yield a range of experimentally observed results. A notable feature of the considered phase-coupled framework is that the clock and wavefront are not separate entities, rather the wavefront that slows clock oscillations is a gradient in clock phase.

Cell movements in the chick PSM have recently been quantified: cells are most motile in the posterior PSM while cell densities are largest anteriorly. Using a cell-based model implemented in Chaste, we investigate the interaction between three tightly-coupled processes: embryo elongation, embryo convergence and cell proliferation. Results from the numerical simulations are compared with available experimental data and the model is used to suggest further experimental studies.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents I; Tuesday, June 28, 17:00

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The use of viral dynamics modeling to optimize the design of a Phase Ib trial, facilitate its analysis, and inform the decision making for the development of directly acting HCV compounds

Hepatitis C virus (HCV) causes a chronic infection of the liver, and leads to fibrosis, cirrhosis, and in some patients to hepatocellular carcinoma. Current standard of care (pegylated interferon plus ribavirin for 48 weeks) is an arduous regimen for the patient and has a cure rate of only 50 % in genotype 1 (GT 1) patients. Therefore, in recent years there has been significant effort to develop directly acting antivirals that will have a substantially higher rate of cure and require a shorter period of treatment. This presentation will describe how we used pharmacokinetic and viral dynamics modeling to design the duration of treatment in a Phase Ib clinical trial of an HCV NS5B polymerase inhibitor in GT 1a, 1b, and 3 patients, and to determine the optimal sampling times both during and after treatment. Quantitative analysis of the resulting viral load data led to a much clearer understanding of the response across genotypes and supported the decision making process in clinical development.

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Data analysis and mathematical modeling of internal duplication process in multi-domain proteins

Multi-domain proteins have likely been shaped by selective genome growth dynamics during evolution. Emergence of new protein domains allows to perform new functions as well as to create polypeptide structures that fold on a biologically feasible time scale. Although the dynamics of genome growth through shuffling of protein domains have been studied extensively over decades, recent experimental observations of a significantly large number of domain repeats of several domains from the same family suggests that one more process involving domain recombination may still remain hidden [**1, 2**]. Here we examine the protein domain statistics retrieved from Pfam, SMART, Gene3D, ProDom and TIGRFAMs databases and consisting of 68 eukaryotic, 56 archaeal, and 929 bacterial organisms. We show that this analysis confirms earlier observations [**3**] and extends them to numerous organisms in the three kingdoms of life. The results show that the number of total protein domains and the number of domain families in a protein are governed by different statistical laws. While the former follows a power-law distribution, the latter exhibits an exponential statistics. We develop a methodology and propose an evolutionary dynamics model, based on a rate equation formalism, and consisting of domain fusion, mutation, protein duplication and internal duplication processes. We then demonstrate that these distinct distributions are in fact rooted in the internal domain duplication mechanism. The analytical results derived from the evolutionary dynamics model as well as computer simulation show that this domain-repeats event generates a wide number of domains in a protein while at the same time preserving a thin number of domain families across proteome species. To our knowledge, this is the first mathematical model of protein domain evolution that explicitly takes into account the effect of internal duplication mechanism and provides analytical solution. These findings bring in our view new insights into the fundamental mechanisms governing genome expansion with potential implications in the development of protein interaction network models and related evolutionary studies.

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Reports from US - African BioMathematics Initiative: Conservation Biology; Saturday, July 2, 14:30

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Canine Distemper Virus (CDV): Methods for modeling spillover infections for African Wild Dogs (Lycaon pictus) in a multi-host community

Canine Distemper Virus (CDV) is a potentially lethal morbillivirus spread via aerosol. It is common in domestic dogs and also affects many wild carnivores, including lions, hyenas, jackals and African wild dogs (AWDs). The AWD is a critically endangered canid that is known to experience high mortality from epizootics of CDV. AWDs are only known to survive in protected areas in Africa, which they share with lions, hyenas and jackals. Inter-species interactions at shared kill sites provide an opportunity for CDV to spill over from one infected species to another susceptible species. We aim to examine how CDV is transmitted between four different host species (lions, jackals, hyenas and AWDs) within a reserve.

We constructed a heterogeneous deterministic SEIR model to establish a disease-free equilibrium for each species. We then introduced stochasticity to our model to understand how CDV spreads through multispecies metapopulations. Stochasticity was introduced in the infection process and in the inter-species contact process. Due to variation in collection techniques for demographic data in the literature, our model was compromised since data for some species may already reflect the endemic state of the disease while other species are potentially disease-free. Nevertheless, our model demonstrates a valid method for determining the sources and sinks of disease in a multi-host metapopulation. We also plan to build a contact network model to avoid the issue of mixing endemic host populations with disease-free host populations. These models could be applied to other metapopulation systems to study or prevent disease spillovers between neighboring populations.

Mathematical models of gene regulation; Tuesday, June 28, 11:00

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Calibrating stochastic models of transcriptional bursting in single mammalian cells

In both prokaryotes and eukaryotes, stochasticity in the dynamics of mRNA and protein expression has important consequences on gene regulation and on non-genetic cell-to-cell variability. Here, we show how discontinuous transcription of mammalian genes leads to broad spectra of temporal bursting in mRNA synthesis. To monitor transcription at high temporal resolution, we designed chromosomally-integrated vectors encoding a very short-lived luciferase in combination with ultra-sensitive bioluminescence microscopy. These data enabled us to develop and calibrate a probabilistic model of gene expression to estimate gene-specific transcription burst sizes and switching rates. The model was further used to deconvolve the time traces, which showed that rapid bursting at timescales of tens of minutes may be an intrinsic property of transcription in mammalian cells, and lead to the characterization of refractory periods of variable duration in the inactive state. Experiments in which the regulatory elements were modified showed that the bursting kinetics was markedly altered by sequence modifications of cis-regulatory sequences. This high temporal resolution monitoring of transcription is readily applicable to many systems; including the circadian oscillator in which we show that increased bursting frequency precede maximal burst sizes by few hours.

Mechanics of the cytoskeleton and cortical actin at the cellular level;
Saturday, July 2, 08:30

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Actin binding proteins govern the range of polarizing cortical flows in *C. elegans* zygotes

Establishment of polarity is essential for conferring different developmental fates to the dividing cells of an embryo. In *Caenorhabditis elegans* one cell embryos, antero-posterior polarization is facilitated by long-ranged flow of the actomyosin cortex. Even though the flowing cortex contains many actin binding proteins (ABPs) that contribute to its structure and dynamics, there are only a limited number of mechanical properties that are important at large length and time scales relevant for polarization, for example contractility and cortical viscosity (Mayer, Bois, Depken, Jülicher, Grill, 2010). Importantly, this suggests that there is only a reduced spectrum of cortical flow phenotypes that one might expect to obtain by modulating these few mechanical properties through different molecular mechanisms. To bridge the gap between molecular and cellular scales, we here sought to investigate which cell-scale mechanical properties are controlled by which ABPs. We devised a candidate RNAi screen of ABPs and found that several ABPs affect cortical flow. This was achieved by analyzing myosin foci size and density and several flow characteristics, such as peak velocities and spatio-temporal velocity-velocity correlations, for each ABP knockdown. The velocity-velocity correlations provided us with an estimation of the characteristic hydrodynamic length of cortical flow, which describes the extent to which flows are long-ranged. Interestingly, all those ABPs that displayed a detectable cortical flow phenotype did so through affecting this hydrodynamic length. RNAi either resulted in short-ranged flows, indicative of a less viscous cortex, or it resulted in flows that were longer-ranged than wild type, indicative of a cortex that is more viscous that under wild-type conditions. Our results suggest that the characteristic hydrodynamic length is a central physical property subject to precise regulation. They also point towards a type of "mechanical redundancy" in animal development, with many molecular mechanisms affecting the same cell-scale physical property.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents II; Wednesday, June 29, 08:30

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Mathematical models of the intracellular replication and within host evolution of HBV and HCV

Hepatitis virus type B (HBV) is a major causative agent of acute and chronic hepatitis. Especially, chronic hepatitis is a major risk factor of liver cirrhosis and hepatocellular carcinoma. During the long time course of chronic hepatitis, severity of hepatitis varies depending on the viral load. It is important to estimate the viral kinetics of HBV for the prediction of the outcome of hepatitis. Though the detailed mechanism of HBV replication is revealed according to the development of molecular biological technique, how reproduction rate of HBV is determined in single cell level had not been clear yet. To investigate the intracellular replication dynamics of HBV, a mathematical model of HBV replication process is constructed. And how the long time course of hepatitis is affected by within host evolution of HBV was investigated by using an evolutionary simulation [1]. From the analysis of our model, the condition for the exacerbation of hepatitis during the chronic hepatitis is obtained. It is shown by our model that the waiting time for release of newly produced virion from infected cell plays critical roles for determining the clinical course of hepatitis. Now, a mathematical model of HCV is additionally constructed to compare with HBV.

In the intracellular replication of virus, the viral genome should play several distinguished roles, as a template of the genome replication, as a component of the viral particle and as a template for the viral gene expression. Because it is impossible to simultaneously play many roles, it is necessary to optimally distribute the viral genome to these roles for the efficient replication. The optimum distribution of genome is common problem for many viruses. HBV is DNA virus, on the other hand, HCV is the positive strand RNA virus, and their replication patterns are quite different. HBV and HCV respectively achieve the optimum distribution of genome by different regulatory mechanism. The intracellular replication dynamics of HBV and HCV are drastically changed by the distribution of genome. I would like to show how the replication dynamics of HBV and HCV is affected by the distribution of their genome. And I would like to discuss how the long time course of chronic hepatitis is affected by the intracellular dynamics and within host evolution of HBV and HCV in this mini-symposium.

References.

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Turing !! Turing?? on morphogenesis via experimental and theoretical approaches; Wednesday, June 29, 17:00

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The Mechanism To Establish Robust Left-Right Asymmetry

A development of animal body proceeds under the intrinsic noise (gene expression, protein interaction, cell migration etc.) and the extrinsic noise (environment). In spite of existence of so much noise, an animal development proceeds robustly and C.H.Waddington called a stability of a development, "Canalization". Of course, left and right determination in the mouse is not exception and canalization of L-R development attains 99.99 %.

Our body has many internal organs that show asymmetric morphologies about left-right axis and these morphologies play important roles in its function, such as the heart, liver, stomach and intestine. Recently, mechanisms to establish L-R asymmetry in the mouse embryo have been elucidated by using genetics and molecular approaches. In the mouse embryo, the small leftward fluid flow in the node produces first asymmetric information along L-R axis and the left-side specific genes are expressed in the left lateral plate mesoderm subsequently.

Although some cascades of gene expressions were studied, it is unknown how robust expressions of left side specific genes are established from the small asymmetric water flow in the node. Nodal and Lefty, two members of the transforming growth factor-β super family of proteins and are expressed in the lateral plate mesoderm, have been implicated in Turing system. Turing system is a mathematical model that consists of two diffusible molecules and may underlie pattern formation during development. We have now examined the potential role of Turing system in left-right patterning both by experimentally manipulating Nodal and Lefty gene expression in the mouse embryos and by constructing a mathematical model.

Our results suggest that an initial small difference in the level of an activating signal between the left and right sides of the embryo is amplified and converted into robust asymmetry by Turing system involving Nodal and Lefty.

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Analysis of a characteristic equation for a Delay Equation from cell population dynamics

We present Delay Equations describing age-structured cell population dynamics where the cell population is divided into proliferative and quiescent cells. We derived a characteristic equation for an interior equilibrium and analyzed the model in the framework of [**1, 2**]. We will show how to use the characteristic equation to determine stability boundaries for the interior equilibrium in two-parameter space.

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Ecosystems Dynamics; Tuesday, June 28, 14:30

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Intraguild Predation in a Source–Sink Metacommunity

Dispersal of organisms in a heterogeneous landscape strongly influences the persistence of indirectly interacting populations. The source–sink habitat structure is one of the major mechanisms to promote coexistence of locally exclusive competitors. It is known that two populations that interfere with each other (Takeuchi 1989) or compete exploitatively (Namba and Hashimoto, 2004; Abrams and Wilson, 2004) or apparently (Namba, 2007) in spatially heterogeneous metacommunities can coexist regionally even if one of them is locally inferior in both patches.

Here, I consider a Lotka-Volterra model of intraguild predation in two patches that have different environmental conditions and are connected by dispersal:

$$\begin{aligned}
\frac{dR^i}{dt} &= \left\{r^i - a_{RR}R^i - a_{RC}C^i - a_{RP}P^i\right\}R^i, \\
\frac{dC^i}{dt} &= (-m_C + e_{RC}a_{RC}R^i - a_{CP}P^i)C^i - d_C(C^i - C^j), \\
\frac{dP^i}{dt} &= (-m_P + e_{RP}a_{RP}R^i + e_{CP}a_{CP}C^i)P^i - d_P(P^i - P^j),
\end{aligned}$$

$(i, j) = (1.2)$ or $(2, 1)$. r's are intrinsic growth rates, m's are mortalities, a's are interaction coefficients, e's are conversion efficiencies, and m's are diffusion rates. The subscripts express species identity and the superscripts denote patch number.

I study conditions for coexistence and competitive exclusion in the following four cases; (1) when the intraguild prey is inferior in both patches, (2) when the intraguild predator is inferior in both patches, and (3) when the local interactions are bistable and either of the intraguild prey and predator can dominate each patch if it is initially abundant, (4) when the intraguild prey is inferior in one patch (a sink) and superior in another patch (a source). I will show that the intraguild prey and predator can coexist regionally in a habitat with a source–sink structure even if one of them becomes competitively excluded in isolated patches in the absence of dispersal. When the habitat is in a true source–sink structure and each species dominates one of the two patches, both patches may become sinks for the intratuild prey when the dispersal rate of the intraguild predator is intermediate. I will also show the stabilizing role of diffusion when the local dynamics are oscillatory. In summary, dispersal between patches in different environmental conditions may either promote or demote coexistence depending on the precise habitat conditions and interaction strengths.

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Statistical methods in computational neuroscience II; Wednesday, June 29, 17:00

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Exploring the Relation of Interval and Count Variability in Neural Spike Trains

Understanding the nature and origin of neural variability at the level of single neurons and neural networks is fundamental to our understanding of how neural systems can reliably process information. At the level of single neuron spike trains we discern two aspects of variability. The variance of inter-spike intervals (ISIs) reflects intra-trial variability on a relatively fast time scale of tens to hundreds of milliseconds. In contrast, the variance of the number of action potentials counted during repeated experimental observations reflects a variability on a comparably slow time scale of seconds or even minutes. On theoretical grounds, interval and count statistics of stochastic point processes are fundamentally related. Analyzing their empirical relation in neural spike trains thus allows to better characterize the observed neural spiking processes [1].

To estimate inter-spike interval variability I employ the empirical coefficient of variation (CV) defined as the standard deviation of ISIs normalized by the average ISI. The empirical count variability is measured by the Fano factor (FF) defined by the ratio of count variance and mean count as estimated during repeated observations. For general stationary non-renewal processes we obtain the relation

$$\lim_{T\to\infty} \mathsf{FF} = \mathsf{CV}^2\Big(1 + 2\,\xi\Big) \qquad \text{with} \quad \xi = \sum_{i=1}^{\infty} \xi_i\,, \tag{1}$$

where ξ_i denotes the ith-order serial interval correlation coefficient. In the case of a renewal process Eq.(1) simplifies to $\mathsf{FF} = \mathsf{CV}^2$. I will discuss how deviations from this equality can be interpreted with respect to non-renewal properties and non-stationarity of the observed spiking processes [1].

The relation Eq.(1) transfers to the population activity of superimposed point processes, which allows to deduce the average CV^2 and serial correlation ξ of single neuron spike trains from the so-called multi unit activity obtained in extracellular recordings [2].

References.

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Poster Session; Friday, July 1, 20:00

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Analysis of pine lopper population dynamics with discrete mathematical models

The well-known discrete time mathematical models (Moran Ricker model, modified discrete logistic model, Kostitzin model, Skellam model, and Varley Gradwell Morris model) were used for analysis of pine lopper (Bupalus piniarius L.) population dynamics in national park De Hoge Veluwe (Klomp, 1966 The Global Population Dynamics Database, N 2727, N 2728 and N 2729). Analysis of three correlated time series (for larva, pupae, and eggs) showed, that good approximation (global fitting) can be obtained with discrete logistic model trajectories. It means that in considering location population cannot realize its eruptive properties (Isaev et al., 1984, 2001), population dynamics can be explained as a result of influence of intra-population self-regulative mechanisms, and its dynamics can be characterized by the narrow phase portrait with unique stationary state.

Poster Session; Friday, July 1, 20:00

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Structural Sources of Robustness in Biochemical Reaction Networks Using a Simplified Analytical Method

Robustness is a property of a biological system which enables maintenance of systemic functionality in presence of external and internal perturbations. Here, we investigate the concept of robustness for the metabolite concentration profiles and its effects on the robustness of the system as a whole: Given a metabolic network operating in steady state, we are interested in characterizing and identifying those metabolites whose concentration assumes only one value under the given internal conditions (specified by the reaction rates). This concept has recently been termed absolute concentration robustness (ACR) [**1**], since the metabolite with such property has the same concentration in every positive steady state the system might admit. Note that a metabolic network in which some metabolites have the ACR property requires smaller extent of regulation to maintain a given steady state, rendering the entire system more robust. Moreover, Shinar and Feinberg have shown that metabolites endowed with ACR can be elegantly determined with the apparatus of the Chemical Reaction Network Theory (CRNT) [**1**].

Metabolic networks often show switching behavior related to multistationarity of metabolite concentrations [**2**]. Moreover, metabolic network states, characterized by the distribution of fluxes and metabolite concentrations, may exhibit intrinsic flux and concentration couplings. Therefore, for metabolic networks, the study of robustness should encompass the interplay between reaction fluxes and the resulting metabolite concentration profiles. To capture the interplay between multistationarity and couplings in the metabolic state, we generalize the concept of ACR to a family of robustness types for the concentration of metabolites. Unlike the CRNT-based approach, we present an analysis based on commutative algebra and algebraic geometry that helps to understand the qualitative properties of metabolic networks that included elements endowed with the proposed robustness types. The concepts are illustrated on paradigmatic network models as well as existing metabolic pathways.

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Cellular Systems Biology; Tuesday, June 28, 17:00

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Integrating multiple signals into cell decisions by a network of protein modification cycles

Cell responses to internal and external stimuli are governed by protein interactions. The enzymatic activity and biological function of proteins is modulated by reversible post-translational modifications such as phosphorylation, acetylation, methylation, ubiquitination, sumoylation, etc. Here we present a general model of reversible protein modifications and show that such system can integrate multiple input signals into digital-like responses, representing robust cellular decisions. Consequently, proteins modified by multiple enzymes can function as complex switches, playing a similar role in cellular information processing as neurons in the brain. We develop an analytical approach for constructing the phase diagram of such systems from the structure of the protein modification network, determining how switching between distinct responses take place. This method can be applied to a broad class of protein modification systems and provides an alternative to numerical approaches that give limited insight when the number of unknown parameters is large.

Undergraduate Biomathematics Education Beyond BIO 2010 (Part I);
Wednesday, June 29, 14:30

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Mathematics, Statistics, and Biology: An Integrative Approach

Over the past five years, with funding from the Howard Hughes Medical Institute, we have developed courses and shorter teaching units to enhance the quantitative education of life science majors. We will present examples that illustrate how biological applications can enhance mathematics and statistics courses at the lower division and how mathematics and statistics can be integrated into biology courses, in particular into labs. We will report on the implementation of the curricula at the University of Minnesota Rochester and the dissemination strategy through the Numbers Count website and workshops held in collaboration with BioQUEST.

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents I; Tuesday, June 28, 17:00

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Deterministic and Stochastic Multi-level Modeling of Hepatitis C Viral Kinetics and Resistance Evolution

Mathematical models of viral dynamics and resistance evolution have brought important insights for understanding the treatment of HIV, HBV and HCV viral infections. However, current models of in vivo anti-viral therapy (CI models) consider only cell to cell infection dynamics, disregarding the impact of intra-cellular replication dynamics. This class of models shows either viral decline with non-resistant viral strains or a permanent viral rebound once a phenotypically resistant strain evolves. Indeed, these are the patterns observed for HIV, where intra-cellular replication has less of an impact because integrated viral DNA is a static replication unit and the various resistance events occur at the time scale of cell infection. However, other patterns of viral evolution kinetics, which are contradictory to the current models, were observed during direct anti-viral therapy against HCV, where intra-cellular dynamics play an important role.

We have therefore developed a novel model (Guedj and Neumann, 2010) for resistance evolution, which includes viral dynamics and evolution in both the intra-cellular replication level and the cell-infection level (ICCI model). As a consequence of the complex interaction between the two levels of viral dynamics, the ICCI model predicts a rich repertoire of viral kinetics and resistance evolution patterns. In particular, we predict that continuous viral decline is possible even if a phenotypically resistant strain has emerged. Furthermore, we show that a resistance related viral breakthrough could be merely transient and nevertheless resolved. In both cases, counter-intuitively to our experience with HIV, viral eradication may be achieved even with a phenotypically resistant virus.

In addition, the ICCI model allows for rapid emergence of resistance evolution without the need for rapid turnover of infected cells, i.e. new cells are not needed to be available for infection by resistance virus. This is due to the fact that the intra-cellular replication space can be freed for evolution to resistant virus within the cells that are already infected. This theoretical possibility was verified also by stochastic modeling of the intra-cellular resistance evolution with a fixed population of infected cells. Furthermore, stochastic simulation of the ICCI model shows how different patterns of resistance evolution occur as function of the intra-cellular parameters. These results elucidate what the important parameters to measure empirically in order to understand what kind of resistance patterns will occur during treatment.

Developmental Biology; Friday, July 1, 14:30

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Spatial Distributed Genetic Mechanism for Stem Cell Niche Structure Control in the Shoot Apical Meristem

There is a qualitative hypothesis of interplay between CLV and WUS genes as a mechanism for the SAM compartmentalization into central zone (CZ stem cells), organizing center (OC), and peripheral zone (PZ). The following is an important moment of the hypothesis: CLV3 expression occurs in the central cells of 3 upper layers (CZ), while WUS expression occurs in the cells of OC, just below CZ; and CLV3 by means of binding with putative receptor CLV1/CLV2 inhibits WUS expression, while WUS activates CLV3 expression. This interplay is believed to be able to regulate stem cell niche structure in the SAM.

We developed a mathematical model of spatial distributed molecular-genetic mechanism of such a compartmentalization of the SAM to test the above hypothesis. We added a hypothetical gene expressing in the uppermost cells. And we supposed regulatory molecules propagate across the SAM by diffusion. A resulting system of differential equations was numerically solved to obtain a stationary solution on a 2D domain representing vertical cut of the SAM.

Obtained model parameters supply a stationary solution for spatial distribution of the modeled genes expression in qualitative accordance with experimentally observed data on vertical cuts of the SAM.

The hypothesized mechanism for stem cell niche structure control in the SAM grasps main features of interaction between the compartments experimentally observed.

Epidemics; Thursday, June 30, 11:30

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Chase and Escape in Groups: Vampire Problem

One of the most important issues in our society is how to understand and deal with the spread of infectious diseases. This is important not only in physical space but in cyberspace as well. There have been numerical and theoretical models used to understand the phenomena of infectious spreads. SIR models such as the Kermack-McKendrick model are based on the population dynamics of "susceptible," "infected," and "recovered" populations. The contact process is another representative theoretical model.

The main purpose of this paper is to introduce the element of "chase and escape" into the above phenomena of infectious spreads. The problems of "chase and escape," also referred to as "pursuit and evasion," have a long history in mathematical literature [1]. They produce rather complex and elegant trajectories out of simple problem settings. Traditionally, the main interest has been the problems in which a single chaser try to catch a single evader. Recently, we introduced the paradigm "group chase and escape," in which one group chases another group [2]. It was motivated by recent research interests in the study of groups, or swarms, such as those of humans, animals, insects, and cars [3]. We have found that a rather complex behavior arises from the models for "group chase and escape."

Here, we will modify our original models for "group chase and escape" to better fit the models for infectious spread. Previously, when a chaser caught an evader, the evader perished. Therefore, the number of evaders decreased monotonically as the process continued. We will modify the process so that the evaders do not become extinct as they are caught but are instead converted or infected to become chasers. Heuristically, this is like vampires trying to increase their numbers by attacking people. In reality, a similar situation is the spread of rabies, in which the infection is transmitted through the bites of the infected.There are studies of models of the spatial spread of rabies. We will show that the element of "chase and escape" will bring in a new phase to the behaviors of the models.

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Epidemics; Tuesday, June 28, 17:00

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Validating early estimation of the transmission potential of pandemic influenza (H1N1-2009): Sample size estimation for post-epidemic seroepidemiological studies

Seroepidemiological studies before and after the epidemic wave of influenza (H1N1-2009) are useful for estimating final size with a potential to validate early estimates of the reproduction number, R, in modeling studies. Nevertheless, a glance at the literature shows that various seroepidemiological studies published so far have adopted a binomial sampling process to quantify the uncertainty of the *proportion* of infected individuals. In the present study, the use of an asymptotic distribution of the final epidemic size that allows for the computation of approximate 95% confidence intervals of the proportion of individuals in a population infected during an epidemic, is proposed since infection events are not independent. Let $\hat{\rho}$ be an observed final size, v be the coefficient of variation of the generation time distribution, and q be the proportion of initially immune individuals. Assuming that v and q are known, we propose the Wald approximation by which the $100(1-2\alpha)\%$ confidence interval for ρ is calculated as

$$\hat{\rho} \pm z_\alpha \sqrt{\frac{\hat{\rho}^3(1-\hat{\rho}) + v^2\hat{\rho}(1-\hat{\rho})^2 \ln^2(1-\hat{\rho}/(1-q))}{n\left[\hat{\rho} + (1-\hat{\rho})\ln(1-\hat{\rho}/(1-q))\right]}} \quad (1)$$

where n is the sample size and z_α denotes $1-\alpha$ quantile of the standard normal distribution. This approach allows the comparison of observed final sizes against model studies based predictions ($R = 1.15, 1.40$ and 1.90) while yielding simple formulae for determining acceptable sample sizes for future seroepidemiological studies. Eleven published seroepidemiological studies of H1N1-2009, which took place after observing the peak incidence in a number of countries, are used in the testing of the methodology. Observed seropositive proportions in six studies appear to be significantly smaller than those predicted from $R = 1.40$; four of the six studies sampled serum less than one month after the reported peak incidence. Comparisons of observed final sizes against $R = 1.15$ provide evidence that all eleven studies do not significantly deviate from the prediction with $R = 1.15$ while comparisons with $R = 1.90$ suggest that the final sizes in nine studies would be overestimated. Sample sizes of published seroepidemiological studies were too small to assess the validity of model predictions except when $R = 1.90$ was used. We recommend the use of the proposed approach in determining the sample size of post-epidemic

seroepidemiological studies, calculating the 95% confidence interval of observed final size, and conducting relevant hypothesis testing instead of the use of methods that rely on a binomial proportion,

Regulatory Networks; Tuesday, June 28, 17:00

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Using iterative methods to determine an antigenic switching network in Plasmodium falciparum

Background: The malaria parasite Plasmodium falciparum evades host protective antibody responses by transcriptional switching between members of the var gene family, which encode the immunodominant surface proteins and virulence factors PfEMP1. This process of antigenic variation must be coordinated across a whole population of parasites during infection to minimise exposure of the parasites limited antigenic repertoire. Analysis of in vitro transcription data has previously suggested that this process underlies a non-random pattern of transcriptional change in which activation and silencing not only differs significantly between individual var genes but may also be biased [1,2].

Methods: To elucidate whether switching between var genes is predominantly governed by local switch hierarchies, whereby activation of var genes is dominated by switch biases between different genes, or by a more global hierarchy in which the rate of activation is independent of the previously active gene, we analysed in vitro expression data from eleven clones of the HB3 isolate together with the parent culture. We used simulated annealing and a Markov Chain Monte Carlo method to determine the off-rates and switch biases that best fitted the data, enabling us to construct a global gene switching network of the var gene repertoire of HB3. Tests using artificial data confirmed that these algorithms can recover reliable estimates despite the large parameter space.

Principle findings: Our results suggest that the course of antigenic variation in P. falciparum can be described by a fixed network of transition rates. Consistent with previous studies we found that activated var genes switch off at fixed rates which range between 0.3% and 5.2% per generation. Our results further show that the likelihood of a particular var being activated depends on which var is switching off, with biases towards one dominant gene found to vary from less than 25% to more than 75%. This indicates that var gene switching in P. falciparum is a combination of local switch biases and global activation hierarchies.

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Poster Session; Friday, July 1, 20:00

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Renal ammonia handling in cirrhosis

Background The kidney plays a dual role in the ammonia metabolism by producing ammonia and controlling the amount of ammonia reabsorbed into the renal vein or excreted into the urine. In advanced stages of liver cirrhosis, renal reabsorption of ammonia seems to diminish in favour of urinary excretion ([**1**]). The underlying mechanisms are not fully understood, but it is likely that the decrease is triggered by an elevated arterial concentration of ammonia and by functional alteration of the ammonia transporter system along the renal tubule. We developed a mathematical model of renal ammonia handling to explore the parameters associated with an increased urinary excretion.
Methods The model is an adaptation of a model by Hervy and Thomas ([**2**]) and was initially designed to study the formation of the osmotic gradient in the medullary interstitium. It simulates the reabsorption and secretion of solutes (NaCl, KCl, urea, ammonia) and water along the renal tubules. Each idealized tubule is composed of a loop of Henle and a collecting duct, and is supplied by a vasa recta. The tubes are bathed and exchange solutes with in an interstitium, which is lumped with the ascending portion of the vasa recta. The equations describe the transmural fluxes between the tubes and interstitium due to osmosis, convection, diffusion and active transport. Baseline parameters values were taken from the rat literature.
Results We compare the outputs of the model obtained with parameters mimicking the healthy and diseased states.

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Plants, growth and transport processes II; Tuesday, June 28, 14:30

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Existence of solutions for the diffusive VSC model.

The concept of a vesicle supply center (VSC), first proposed by Bartnicki-Garcia *et al* lies at the basis for a whole hierarchy of mathematical models which attempt to explain tip growth in fungal hyphae. It assumes that there is a point source in the tip which distributes cell wall material for the tip. Vesicles diffuse out from the VSC to the cell wall, producing growth of the cell wall orthogonal to the wall surface. This yields a geometric evolution equation for the surface of the hypha, in which the normal velocity of the surface is proportional to the flux of new material arriving at the cell wall and the inverse of the mean curvature. In this talk, we shall assume the VSC is given a fixed velocity, we will then show how to prove the existence of surfaces which stay stationary in a coordinate frame moving along with the supply center.

Population Dynamics; Wednesday, June 29, 11:00

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Adaptive advantage of aggregation in a population with Allee effects

Aggregation is often believed to be advantageous in populations with positive density dependence at small population size (i.e., Allee effects). Many species of non-social animals aggregate to acquire resources for survival and reproduction. By aggregating, organisms may create a more favorable environment, reduce per capita predation risk, or procure resources, none of which is likely attainable for individuals acting alone. However, when resources are scarce or population density is high, aggregation likely results in overcrowding and severe competition. Moreover, aggregation behavior can affect the collective reproductive success of the population and thus can alter population dynamics and population density. Because benefits to aggregation behavior may be density dependent, its adaptive advantage can be more properly examined by explicitly accounting for the feedback loop between behavior and population dynamics. The objective of this project is to investigate the conditions under which aggregation is advantageous. We constructed a minimal model that incorporates aggregation, Allee effects, and scramble competition. The part of the model describing the dynamics of group formation by preferential attachment is based on analytical solutions of the stochastic birth and death processes of groups of different sizes. We then used the methods from adaptive dynamics and performed invasion analysis to examine the invasion fitness of various aggregation tendencies. We found that, although a strong tendency to join larger groups is advantageous for establishing a population from a small size, it is generally not advantageous. This is due to high population density produced by effective aggregation. A strategy where individuals pick a group randomly is overall more advantageous and able to invade populations with a stronger aggregation tendency. In some regions of parameter space, we observe evolutionary suicide where invaders go extinct after successfully invading the resident population. Strong tendencies for aggregation become advantageous enough to persist when some mechanisms regulating group size are included or when the population frequently experiences a low density (e.g, dispersal, stochastic high mortality events). We conclude that aggregation alone is mostly not advantageous and needs some additional mechanisms to either regulate group size or suppress population density.

Epidemics; Wednesday, June 29, 08:30

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Equilibrium in model of HIV dynamics with transitions between risk group

It is well known that features of transmission for human immunodeficiency virus allow control the infection process by behavior change. Population heterogeneity in propensity to risky behavior leads to the possibility of separating the phase transitions in epidemic dynamics. These phase transitions distinguish between low-level, concentrated and generalized epidemics. Data analysis[1] shows that an important role in spreading HIV on the territory of Russia is played by processes of social maladjustment: drug abuse, alcoholism and the formation of an increased risk of substance abuse pathology. However, the models have been applied before to explain the situation in the territory of the former Soviet Union, including Russia, show that the formation mechanism of these risk-groups and its influence on HIV epidemics is more complicated than it was represented[2,3]. In this paper we formulated a deterministic model of HIV spread in a heterogeneous population, where dynamics of risk groups is presented as a consequence of social maladjustment. In this model an individual from general population can increase or decrease the level of his/her social maladjustment being susceptible to the virus. In each of these states, one has a certain risk of being infected with HIV. The proposed model in part is similar to the classical model of the spread of STIs in heterogeneous population, as proposed by Cooke and Yorke[4]. Unlike the traditional approach the possibility of transfer individuals between risk groups was taken to account. Thus the formulated model belongs to a broader class of deterministic SI models. This generalization allows obtain new results about the properties of the equilibrium of system and conditions of existence and transition between them. Some of these properties of the model we investigate in this paper.

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Poster Session; Friday, July 1, 20:00

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Modelling auxin transport in root provascular tissues

All vascular plants are called so because they have special vascular or conductive tissues providing effective transport of water, dissolved minerals and organic substances, including phytohormones. Root apical meristem (RAM) contains vascular initials from which protoxylem and protophloem differentiate further producing xylem and phloem, respectively. Acropetal flow of auxin along root provascular tissues is required for normal functioning of the RAM. Auxin distributes in plant tissue by means of diffusion and active transport through the number of membrane transporters (PINs, AUX/LAX etc). In protoxylem, auxin active transport is mediated by PIN efflux transporters that are polarly localized at the basal side of cell membranes. In protophloem, additionally to PINs efflux transporters, AUX1 influx carriers are localized at the apical side of the membranes provide for auxin transport. Thus, protoxylem and protophloem differ in the mechanisms of auxin active transport. To study how these differences in transporters affect the auxin distribution in these tissues we have created mathematical models of auxin transport in root protophloem and protoxylem. Both models use as a prototype the published model of auxin transport along the central axis of the root [Mironova et al., 2010]. In the protoxylem model, the active auxin efflux is determined by PIN transporters, where auxin influx from the intercellular space is provided only by diffusion. In the protophloem model, both PIN and AUX1 transport systems are active. Initially, in both protoxylem and protophloem simulations we used the same set of parameters. Parameter values were (1) taken from the prototype model [Mironova et al., 2010], (2) adjusted using the experimental data on the comparative efficiency of auxin active transport and diffusion [Yang and Murphy, 2009] and (3) estimated using the microarray data [Paponov et al., 2008]. The protoxylem model solutions represented the experimentally observed auxin distribution along the central axis of the root tip. The protophloem model provided these solutions only if the values of some parameters were significantly changed. Based on this, we proposed the following hypotheses about the differences in the mechanisms of auxin transport in protophloem and protoxylem: 1. Auxin-depended PINs degradation in protophloem occurs at higher levels of auxin concentrations; 2. Auxin-dependent activation of PINs synthesis in protophloem occurs at lower auxin concentrations; 3. Auxin transport via PINs in protophloem is more efficient than in protoxylem. The latter hypothesis was indirectly confirmed by the recently published experimental data [Scacchi et al., 2010], where expression of protophloem marker gene BRX was shown to be activated by ARF5, the transcription factor of the primary

auxin response. In its turn, BRX activates the PIN3 expression. One may assume that BRX-mediated PIN3 expression provides the additional facility that makes protophloem auxin transport more effective. On the basis of the numerical simulations we conclude that the same pattern of auxin distribution in provascular tissues provides for by the quite different mechanisms.

The work is partially supported by the RAS programs A.II.5.26, A.II.6.8, B.27.29, SB RAS 107, 119, and RFBR 10-01-00717-,11-04-01254-.

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Epidemics; Wednesday, June 29, 11:00

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On the spread of epidemics in a closed heterogeneous population: Stochastic aspects

In [1,2] we presented an attempt to formulate a general deterministic theory of the spread of an infectious disease in a closed heterogeneous population. Specifically, we looked into heterogeneity in disease parameters (such as susceptibility to a disease); disease parameters were considered as an inherent and invariant property of individuals, whereas the parameter values could vary between individuals. The two major findings for a heterogeneous SIR model were: 1) we derived the equation for the final size of an epidemic for an arbitrary initial distribution of susceptibility, which shows that the initial susceptibility distribution is crucial in determining the part of the population that escapes infection; 2) the widely used power transmission function was deduced from the model with distributed susceptibility and infectivity with the initial gamma-distribution of the disease parameters, therefore, a mechanistic derivation of the phenomenological model, which is believed to mimic reality with high accuracy, was provided.

Here we additionally discuss stochastic aspects of the model, which are impossible to study within the framework of deterministic models, namely:

- In which way the parametric heterogeneity changes the probability of a major outbreak;
- What are the consequences of the parametric heterogeneity on the mean duration of an epidemic;
- What are the mean and variance of the distribution of the final epidemic size for different initial susceptibility distributions.

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Analysis of mathematical models for cancer growth and treatment, Part V; Wednesday, June 29, 11:00

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Hamilton-Jacobi analysis for cancer treatment

Tumor anti-angiogenesis is a cancer therapy approach that targets the vasculature of a growing tumor. In the last fifteen years tumor anti-angiogenesis became an active area of research not only in medicine (see e.g. **[2]**, **[3]**) but also in mathematical biology (see e.g. **[1]**, **[6]**, **[7]**) and several models of dynamics of angiogenesis have been described e.g. by Hahnfeldt et all **[1]**, d'Onofrio **[6]**, **[7]**. In a sequence of papers **[4]**, **[5]** Ledzewicz and Schaettler completely decribed and solved from optimal control theory point of view the following or similar free terminal time T problem (P): minimize

$$J(p,q,u) = p(T) + \kappa \int_0^T u(t)dt \tag{1}$$

over all Lebesgue measurable functions $u : [0,T] \to [0,a] = U$ subject to

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_{0,} \tag{2}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq, \qquad q(0) = q_0. \tag{3}$$

The term $\int_0^T u(t)dt$ is viewed as a measure for the cost of the treatment or related to side effects. The upper limit a in the definition of the control set $U = [0,a]$ is a maximum dose at which inhibitors can be given. The time T is the time when the maximum tumor reduction achievable with the given overall amount A of inhibitors is being realized. The state variables p and q are, respectively, the primary tumor volume and the carrying capacity of the vasculature. Tumor growth is modelled by a Gompertzian growth function with carrying capacity q, by equation (2), where ξ denotes a tumor growth parameter. The dynamics for the endothelial support is described by (3), where bp models the stimulation of endothelial cells by the tumor and the term $dp^{\frac{2}{3}}q$ models endogenous inhibition of the tumor. The coefficients b and d are growth constants. The terms μq and Guq describe, respectively, loss to the carrying capacity through natural causes (death of endothelial cells etc.), and loss due to extra outside inhibition. The variable u represents the control in the system and corresponds to the angiogenic dose rate while G is a constant that represents the anti-angiogenic killing parameter. Ledzewicz and Schaettler analysed the above problem using first-order necessary conditions for optimality of a control u given by the Pontryagin Maximum Principle, the second order: the so-called strengthened Legendre-Clebsch condition and geometric methods of optimal control theory.

In most of the mentioned papers the numerical calculations of approximated solutions are presented. However in any of them there are not proved assertions that calculated numerically solutions are really near the optimal one.

The aim of this paper is an analysis of the porblem (1)-(3) from Hamilton-Jacobi-Bellman point of view i.e. using dynamic programming approach and to

prove that for calculated numerically solutions the fuctional (1) takes an approximate value with a given accuracy $\varepsilon > 0$.

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Evolutionary Ecology; Thursday, June 30, 11:30

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Joint evolution of specialization and dispersal in structured metapopulations

I propose a metapopulation model [1] that is mechanistically based on individual level processes and thus suitable for evolutionary analysis. I use adaptive dynamics [2] to study the joint evolution of dispersal and specialization in resource utilization in the case with consumers facing a trade-off between abilities to consume two different but nutritionally equivalent resources. I illustrate the evolutionary scenarios that are possible in this model. Moreover, I illustrate how different ecological parameters affect evolutionary dynamics. As the main result [3], I show that joint evolution may result in evolutionarily stable coexistence of three phenotypes, two specialists and a generalist, in a metapopulation comprising several patch types.

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Analysis and Understanding of Fungal Tip Growth

Fungi cause devastating plant and human diseases. There is considerable evidence that much of the cellular machinery driving growth of invasive fungal hyphae is common across all fungi, including plant and mammalian pathogens, and involves localized tip growth. Furthermore, successful fungal infection is critically dependent on accurate perception of the host surface at the tip to control morphogenesis and trigger host invasion. This suggests that detailed investigation of these early morphogenetic and signalling events is crucial to a thorough understanding of virulence.

We are therefore developing high-throughput automated microscope-based multi-dimensional image analysis systems to segment and characterize fungal growth, and characterize the patterns of protein localization within the tip that control development. We propose a curvature-based approach to identify fungal cell tip and determine the growth direction, based on segmentation using local thresholding and mathematical morphology methods. The curvature of cell boundary is calculated and the boundary point with the highest curvature value defines the tip cell position. For cell expressing key GFP-tagged regulatory proteins, the image intensity profiles on the left and right side of the tip position are recorded to provide a map of the plasmamembrane protein distribution, and to determine the relationship between growth vector and asymmetric localization. This procedure is repeated for all images in the time-lapse.

We tested the performance of the proposed concept on fluorescence images of Neurospora crassa germlings expressing GFP-CRIB and GFP-tagged MAK2 kinase during hyphal avoidance responses and conidial anastomosis tube fusion, respectively.

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Regulatory Networks; Saturday, July 2, 11:00

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How stochasticity in gene expression differentiates phenotypes without changing genotypes

Bimodal gene expression (the statistical distribution of gene products that has two maxima), as an effect contributing to phenotypic diversity in genetically identical cell populations, enhances the survival of cells in a fluctuating environment. We study a theoretical model of gene expression in a minimal gene cascade, in which the regulatory gene produces transcription factors that have a nonlinear effect on the activity of the target gene. We show that a unimodal distribution of transcription factors over the cell population can generate a bimodal steady-state output without cooperative transcription factor binding and without feedback loops. We introduce a simple method of geometric construction that allows one to predict the onset of bimodality. A. Ochab-Marcinek, M. Tabaka, Bimodal gene expression in noncooperative regulatory systems , PNAS 107(51) (2010) 22096-22101

Fractals and Complexity II; Wednesday, June 29, 17:00

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Fractal analysis in irregular regions of interest

Fractals have been successfully applied in many areas of science and technology. One of the most prominent applications is fractal analysis in medicine, especially in analyses of different kinds of images. For medical images diagnostically important information often lies in the texture. Fractal dimension may be used as an index of irregularity. In this paper we describe the application of the intensity difference scaling method for assessment of the fractal dimension in the irregular regions of interest (irregular ROI-s). Near boundary between different tissues or structures the values of fractal dimensions changed significantly. The values of fractal dimensions were calculated on synthetic fractal textures which ranged in fractal dimension from 2.05 to 2.95 (2.05, 2.10, 2.20, 2.30, 2.40, 2.50, 2.60, 2.70, 2.80, 2.90, 2.95). For each value of fractal dimension thirty 64-by-64 images were obtained. The mean squared error (MSE) for the 330 samples for each algorithm was assessed. We tested 7 methods of computing of fractal dimension of surfaces: rectangular prism surface area method (MSE = 0.0054), triangular prism surface area method (MSE = 0.0098), power spectral density method (MSE = 0.0241), method based on mathematical morphology (MSE = 0.0093), variogram analysis (MSE = 0.0054), intensity difference scaling method (MSE = 0.0020), and our adaptation of intensity difference scaling method in irregular ROI-s (MSE = 0,0017). Our experiments for dental radiovisiographic images, pantomograms and nuclear medicine scans showed that it is difficult to fit the entire regular region of interest within the examined organ with simultaneous inclusion of the relevant fragment avoiding the influence of boundaries and other kinds of unnecessary structures at the same time. Our method of assessment of fractal dimension in irregular regions of interest solves these difficulties.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits I; Wednesday, June 29, 14:30

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Multiscale analysis of pattern formation and wave propagation in a discrete cell signalling model

It is well known that cell-scale interactions can have profound effects on macroscale tissue growth. I will discuss two approaches to analysing such phenomena within a continuum framework, allowing their inclusion within macroscale models of tissue growth.

Firstly, a multiscale asymptotic method with which to analyse fine-grained patterning patterning in cellular differentiation within a continuum framework is introduced, based on a generic discrete signalling model. Most applications of such methods are to continuous systems, while here discreteness on the short lengthscale must be taken into account.

An important feature of such systems is the progression of pattern-forming modulated travelling waves across the discrete lattice. Such phenomena have been widely studied within discrete diffusion equations for monotone waves; employing a WKBJ technique in place of the standard travelling wave ansatz, I show how analysis of such waves is greatly simplified and highlight the crucial dependence of wave propagation on the underlying lattice geometry. In addition, I extend this analysis to the modulated travelling waves exhibited in cell signalling models.

Poster Session; Friday, July 1, 20:00

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Modelling Aquatic Viral Dynamics

Viral haemorrhagic septicaemia (VHS) and infectious haematopoietic necrosis (IHN) are two important viruses of rainbow trout (*Oncorhynchus mykiss*). Both viruses have a significant impact on the trout industry worldwide, with VHS costing an estimated £10.3-31 million per year in Europe [1] and IHN costing the US economy £22.2 million per year (data up to 2005) [2]. Currently the UK is free of both of viruses, but should one or the other enter the UK, knowledge of how they may spread is vital to reducing the overall impact. Methods of introduction are limited to either importation of infected livestock or wild fish movements. Using deterministic models, we can investigate how the viruses would spread geographically over time and predict the effects of different control measures to aid in minimising the overall impact an outbreak of either virus would cause.

This poster will present some initial findings regarding stocking density and an outline of a preliminary first model, looking at viral movements within a single tank of fish.

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Genetics and Genomics; Wednesday, June 29, 08:30

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Mathematical model of tandem repeat evolution based on comparisons of Homo sapiens and Homo neanderthalensis genomes

Tandem repeats are genomic markers well suited for studying evolutionary scenarios for closely related species, due to their high mutation rates. There are many studies concerned with fitting evolutionary models to data on short tandem repeats with conclusions leading to estimates of parameters of tandem repeats mutation process, evolutionary and demographic scenarios of different species and populations etc.

In this talk we present coalescence based mathematical model of evolution of tandem repeats based on comparison of genomes of homo sapiens and Homo neanderthalensis. In the coalescence model we assume the deterministic moment of speciation event leading to Homo sapiens and Homo neanderthalensis species. The results of the coalescence model of evolution are probability distributions of differences between numbers of repeats in two species. These probability distributions depend on parameters, mutation intensities, different for models for evolution of loci with different motif length.

The obtained models are then fitted to data on locations and structures of tandem repeat loci of homo sapiens and Homo neanderthalensis genomes obtained by using the recently developed genome browsing tool BWtrs and the appropriately designed alignment algorithm. Due to imperfections of the assembly process for Homo neaderthalensis genome the model with censored observations is applied and the appropriate EM procedure is designed.

Estimates of mutations rates for different sizes of repeat motifs are compared to results of other population dynamics studies. Possible sources of biases in different approaches are highlighted and possible future improvements of the developed model are presented.

Poster Session; Friday, July 1, 20:00

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Understanding disease control: influence of epidemiological and economic factors

The goal of our work is to find optimal control strategy of epidemics. We have considered extended SIR model including pre- and symptomatic cases for a disease spreading on regular network.

The effective treatment strategies for a disease control are expected to minimize the total cost of an epidemic. In designing control strategies, however, we have to consider both epidemiology and economics. The most optimal control is determined by the relative costs of treatment and infection, as well as the initial distribution of infectious cases and kinetics of its spread and transformation. It has been shown that the knowledge of pathogen may be unknown and we are able to make prediction based on economics analysis only. Although economics determines control strategies, the range of applicability of scenarios depends on epidemiological factors such as infectiousness, detectability, recovery, removal and map of contacts in population. Some of that factors such as contagion or mortality are strongly connected with particular disease and we can hardly change their properties. However on the rest of parameters we have an influence. So the quicker the symptoms occur or the higher recovery level, the smaller control radius. Moreover, the relationship between control and infected neighbourhood size has been studied and an influence of epidemiological parameters on that relation has been discussed.

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Fluid-structure interaction problems in biomechanics; Saturday, July 2, 08:30

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Coupling biochemistry, mechanics, and hydrodynamics to model sperm motility

Calcium (Ca2+) dynamics in mammalian sperm are directly linked to motility. These dynamics depend on diffusion, nonlinear fluxes, Ca2+ channels specific to the sperm flagellum, and other signaling molecules. The goal of this work is to couple Ca2+ dynamics to a mechanical model of a motile sperm within a viscous, incompressible fluid. We will first discuss a model of the CatSper mediated Ca2+ dynamics relevant to hyperactivated motility. The method of regularized Stokeslets is used to investigate the hydrodynamics of swimming sperm. Results showing emergent waveforms, swimming speeds, and trajectories will be compared to experimental data.

Modeling physiological systems: model validation and experimental design issues; Wednesday, June 29, 11:00

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Modeling and parameter estimation in cardiovascular dynamics

The main role of the cardiovascular system is to maintain adequate oxygenation of all tissues. This is accomplished by maintaining blood flow and pressure at a fairly constant level and transporting blood from the heart to the periphery with a minimal loss of energy. In addition, a number of control mechanisms are imposed regulating vascular resistance, compliance, pumping efficiency and frequency. In cardiovascular diseases, both the transport system and its regulation may be compromised, and for a number of diseases it is either not known or difficult to study what mechanism that lead to the breakdown of homeostasis. Typically, some general observations can be made, but these vary significant between individuals. Furthermore, for most patients only a few quantities can be measured, making it difficult to assess essential quantities such as cerebral vascular resistance, cardiac contractility, or the gain and time constants associated with the regulation. This presentation will discuss development of patient specific models obtained by combining models predicting control of blood flow and pressure with parameter estimation techniques. Models analyzed are composed of systems of nonlinear equations each specified via a set of model parameters. Nominal parameter values are obtained from analysis of populations and data available. Subsequently, sensitivity analysis, correlation analysis, and subset selection, are combined with parameter estimation techniques to obtain a subset of patient specific parameters.

Mechanical Models of Movement and Growth of Cells and Tissues II;
Wednesday, June 29, 17:00

A model linking the lamellipodial actin cytoskeleton to cell shape and movement.

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In this talk I will give an overview on a recent modelling effort concerning the lamellipodial Actin-cytoskeleton. In more detail I will outline the mechanical description of protein linkages and compare two different scaling aproaches that apply to either cross-linking proteins or adhesion complexes. The results are macroscopic, possibly nonlinear, friction coefficients. I wil also shortly mention analytic results that concern the interpretation these mathematical models.

Poster Session; Friday, July 1, 20:00

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Ben Adams
Bath University

The effect of disrupting seasonality to dynamics of epidemics: the case of KHV

Koi herpesvirus (KHV), a highly virulent disease affecting carp (fish in freshwater) that emerged in the late 1990s, is a serious threat to aquaculture industry. After a fish is infected with KHV, there is a temperature dependent delay before it becomes infectious, and a further delay before mortality. Consequently KHV epidemiology is driven by seasonal changes in water temperature. It has also been proposed that outbreaks could be controlled by responsive management of water temperature in aquaculture setups. We use a mathematical model to analyse the effect of seasonal temperature cycles on KHV epidemiology, and the impact of attempting to control outbreaks by disrupting this cycle. We show that, although disease progression is fast in summer and slow in winter, total mortality over a two year period is similar for outbreaks that start in either season. However, for outbreaks that start in late autumn, mortality may be low and immunity high. A single bout of water temperature management can be an effective outbreak control strategy if it is started as soon as dead fish are detected and maintained for a long time. It can also be effective if the frequency of infectious fish is used as an indicator for the beginning of treatment. In this case, however, there is a risk that starting the treatment too soon will increase mortality relative to the case when no treatment is used. This counterproductive effect can be avoided if multiple bouts of temperature management are used. We conclude that disrupting normal seasonal patterns in water temperature can be an effective strategy for controlling koi herpesvirus. Exploiting the seasonal patterns, possibly in combination with temperature management, can also induce widespread immunity to KHV in a cohort of fish. However, employing these methods successfully requires careful assessment to ensure that the treatment is started, and finished, at the correct time.

Poster Session; Friday, July 1, 20:00

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PageRank-based identification of signaling crosstalk from transcriptomics data in Arabidopsis thaliana

The levels of cellular organization, from gene transcription to translation to protein-protein interaction and metabolism, operate via tightly regulated mutual interactions facilitating organismal adaptability and various stress responses. Characterizing the mutual interactions between genes, transcription factors, and proteins involved in signalling, termed crosstalk, is therefore crucial for understanding and controlling cell's functionality. Based on the type of data used in the analysis, the existing methods for identifying crosstalk can be divided into two groups: (1) proteomics-based, relying on integration of protein-protein interaction data with existing pathway information and (2) transcriptomics-based, employing high-throughput transcriptomics data sets from different conditions.

Here we propose and analyze a novel method for crosstalk identification which relies on transcriptomics data and overcomes the lack of available information for the signalling pathways in Arabidopsis thaliana. Our method employs a network-based transformation of the results from the statistical analysis of differential gene expression in carefully constructed groups of experiments (conditions). Modification of the PageRank algorithm is then used on the network constructed in the previous step to determine the putative transcripts interrelating different signalling pathways. With the help of the proposed method, we analyze a transcriptomics data set incorporating experiments on four different stresses/signals: nitrate, sulfur, iron, and hormone and identified a promising gene candidates involved in crosstalk.

In addition, we conduct a comparative analysis with the state-of-the art methods in this field which used a biclustering-based approach [**1**]. Unlike approaches based biclustering, our approach does not rely on any hidden parameters. To compare the two approaches, we use transcriptomics data sets from Arabidopsis thaliana under 31 different experimental conditions: 5 nitrate, 4 sulfur, 2 iron and 20 hormone experiments. Surprisingly, the biclustering-based approach fails to identify any candidate genes involved in the crosstalk of the analyzed signals. On the other hand, with the proposed method, we find a small set of interesting genes putatively involved in crosstalk (verified by literature search). The small number of genes involved in crosstalk of these signals could be attributed to: (1) the heterogeneity of the analyzed data and (2) the lack of raw data for all experiments, resulting in a non-uniform normalization. Consequently, we demonstrate that our proposed method is more efficient for species for which large transcriptomics data sets, normalized with same techniques, are available.

References.

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Poster Session; Friday, July 1, 20:00

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Individual-based modeling of spatial population dynamics

In last decades, a variety of mathematical approaches have been explored and they have contributed much to better understand population dynamics in general. Mathematical models have been accumulating. Many of them, however , remain qualitative description of population dynamics focused at "population level" where analytical tractability is prioritized and mechanistic process of individual birth and death are ignored.

$$N_{t+1} = \exp\left[r\left(1 - \frac{N_t}{K}\right)\right] N_t \tag{1}$$

For example, the assumption that per capita growth rate linearly or exponentially decreases with population size as assumed in the Ricker logistic model (1) is completely descriptive one without any mechanistic process explicitly considered at individual level; we just assume it and start from such a descriptive model.
In order to understand population dynamics in general, we think it is necessary to link population dynamics, a phenomenon at population level, with mechanistic processes of birth and death that occur at individual level. In this paper, we aim to reconstruct a population dynamics in terms of individual birth and death and try to derive a dynamical system based on mechanistic interactions between individuals. We first construct a spatial population dynamics where an individual is a point located in a continuous two dimensional space and a population is represented as a point pattern. Each individual has a territory with radius σ_c and consumes renewable resource to reproduce. Interaction between individuals occurs when territories overlap and overlapped area is handled according to a certain rule each individual adopts. These algorithmic rule constitutes a point process and we have built a flexible framework to implement these rules as individual-based simulation model. We analyze how the point pattern changes temporarily in terms of population size and pair correlation function. And we derive a dynamical system to explain behaviors of the individual-based simulation.

$$N_{t+1} = \left\{ \sum_{k=0}^{\infty} {}_{N_t-1}C_k (4\pi\sigma_c^2)^k (1 - 4\pi\sigma_c^2)^{N_t-1-k} e^r \times \mathrm{Max}\left[1 - \frac{\alpha k}{2}, 0\right] \right\} N_t \tag{2}$$

where α is the interaction coefficient.
Our final goal is to understand phenomena at population level based on mechanistic interactions of individual level and how such interactions can be described as a mathematical form. Our individual-based framework also allows to explore evolution of parameters such as territory size and dispersal range. We discuss an

individual-based approach to better understand population dynamics as well as evolutionary dynamics.

Multiscale modelling of biological systems: the Chaste framework;
Tuesday, June 28, 11:00

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A multiscale computational framework for modelling biological systems: Chaste

The Chaste framework (http://web.comlab.ox.ac.uk/chaste) in an Open Source numerical library which enables multicellular and multiscale simulations of biological processes. In this, the first talk of the mini-symposium, we introduce the multiscale framework on which Chaste is based on, discuss the development of the framework, and provide a demonstration of how to set up a simulation.

The mathematical framework is based upon the observation that the natural structural unit of biology is the cell, and it consists of three main scales: the tissue level (macro-scale); the cell level (meso-scale); and the sub-cellular level (micro-scale), with interactions occurring between all scales. The cell level is central to the framework and cells are modelled as discrete interacting entities using one of a number of possible modelling paradigms, including lattice based models (cellular automata and cellular Potts) and off-lattice models (cell centre and vertex based representations). The sub-cellular level concerns numerous metabolic and biochemical processes represented by interaction networks rendered stochastically or into ODEs. The outputs from such systems influence the behaviour of the cell level affecting properties such as adhesion and also influencing cell mitosis and apoptosis. Tissue level behaviour is represented by field equations for nutrient or messenger concentration, with cells functioning as sinks and sources. This modular approach enables multiple models to be simulated and is easily extensible allowing more realistic behaviour to be considered at each scale.

Chaste is comprised of libraries of object orientated C++, developed using an agile development approach. All software is tested, robust, reliable and extensible. The library enables general simulations to be undertaken and includes tools to automatically curate and store simulation results expediting model development. One key aspect of such a framework is the ability to model specific biological systems using multiple modelling paradigms, as a case study we present a simple model of the colorectal crypt using four different cell level models and illustrate the similarities and differences.

Population Dynamics; Saturday, July 2, 14:30

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Convergence properties of the law of reproduction by the first principle derivation in population dynamics

We want to relate the law of reproduction with interaction between individuals. For this purpose, we use the form of infinite series, which is called "first principle derivation" [**5**, chapter 4]. By this method, we can derive the population reproduction function from the relationships of individuals (the distribution function of individuals and the interaction function between individuals). Previous research[**1, 5**] has derived a few concave functions, which are Ricker model and Skellam model. We extended previous research in economical viewpoint. As a result, we could derive new types of function like Holling's type III functional response [**2**], so we could represent bistability in population dynamics[**3**]. The reason comes from the fact that the derived function has convexity in case that population is small. Previous research did not have this property. Our model, in other hand, contains both density dependent effect and Allee effect. In order to clarify the mathematical properties of the law of reproduction from "first principle derivation", we analysed the stability and bifurcation structure of fixed points of our infinite series function[**4**, chapter 2].

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Mechanical Models of Movement and Growth of Cells and Tissues I;
Wednesday, June 29, 14:30

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From Crawlers to Swimmers — Mathematical and Computational Problems in Cell Motility

Cell locomotion is essential for early development, angiogenesis, tissue regeneration, the immune response, and wound healing in multicellular organisms, and plays a very deleterious role in cancer metastasis in humans. Locomotion involves the detection and transduction of extracellular chemical and mechanical signals, integration of the signals into an intracellular signal, and the spatio-temporal control of the intracellular biochemical and mechanical responses that lead to force generation, morphological changes and directed movement. While many single-celled organisms use flagella or cilia to swim, there are two basic modes of movement used by eukaryotic cells that lack such structures – mesenchymal and amoeboid. The former, which can be characterized as 'crawling' in fibroblasts or 'gliding' in keratocytes, involves the extension of finger-like filopodia or pseudopodia and/or broad flat lamellipodia, whose protrusion is driven by actin polymerization at the leading edge. This mode dominates in cells such as fibroblasts when moving on a 2D substrate. In the amoeboid mode, which does not rely on strong adhesion, cells are more rounded and employ shape changes to move – in effect 'jostling through the crowd' or 'swimming'. Here force generation relies more heavily on actin bundles and on the control of myosin contractility. Leukocytes use this mode for movement through the extracellular matrix in the absence of adhesion sites, as does Dictyostelium discoideum when cells sort in the slug. However, recent experiments have shown that numerous cell types display enormous plasticity in locomotion in that they sense the mechanical properties of their environment and adjust the balance between the modes accordingly by altering the balance between parallel signal transduction pathways. Thus pure crawling and pure swimming are the extremes on a continuum of locomotion strategies, but many cells can sense their environment and use the most efficient strategy in a given context. We will discuss some of the mathematical and computational challenges that this diversity poses.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -II; Tuesday, June 28, 14:30

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Multiscale Modeling in Biology — The Mathematical and Computational Challenges

New techniques in cell and molecular biology have produced a better understanding of cell-level processes that has in turn led to better cell-level models for problems ranging from biofilm formation to embryonic development and cancer. However this raises the problem of how to incorporate detailed descriptions of individual-level behavior, be it at the cell, tissue or organ level, into population level descriptions. We will illustrate the mathematical and computational challenges involved with an f example from pattern formation in bacteria, and will discuss some of the open problems in this area.

Modeling physiological systems: model validation and experimental design issues; Wednesday, June 29, 11:00

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Patient specific modeling of the heart as a tool for early diagnoses and treatment planning.

The perspective for Patient Specific Modeling (PSM) is to create and develop medical decision system based mathematical modeling of the underlying mechanisms and statistics. We will give an example of PSM of the function of the heart including a discussion of patient specific parameter estimation based on the model in combination with new individual patient data obtained from MR measurements of various relevant blood volumes (and flows). Such parameters will characterize the state of the patients in far more details than clinical investigations unveil today. Thus these parameters will define diagnosed heart illnesses in a refined manner and pinpoint exactly where in the physiological system malfunctioning appears. This opens up for early diagnoses and individual treatments targeting the actual malfunctioning part of the physiological system.

Recently precise and detailed volume data have become assessable by help of MR scanning and imaging technologies. The associated finding confirm earlier results except that atria volumes may show one hump or two hump and all intermediate configurations in between during one heart cycle. These findings are reflected in the corresponding ventricle volume curves but are not so pronounced. In addition, these curves vary very much with the condition of the contractile strength of the atria and ventricles and thus it become reduced in cicatrical myocardial tissue (after an infarction) and with the condition of the heart valves.

Data from 40 subjects encompass left atria volume, left ventricle volume, right atria volume, right ventricle volume, flow from left ventricle into aorta, and flow from right ventricle into pulmonary aorta versus time during one heart cycle. Data was recorded for objects at rest and for objects given dobutrex and robinul as well.

Our model describe preload to atria, atria itself, ventricle, and afterload for left heart using ordinary differential equations. Based on data, sensitivities on and correlation between the model parameters will be investigated and parameter estimation on a meaningful subset will be performed. Thus various pathologies, including decreased contractile capacities and stenosis, will be categorizes in terms of the model parameters.

Epidemics; Saturday, July 2, 08:30

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Epidemiological Models with Prevalence Dependent Endogenous Self-Protection Measure

A simple mathematical model for human disease epidemics that takes the human learning behaviour and self-protective measures into account is proposed. We analyse the effect of endogenous self-protective measures with respect to the prevalence level of the disease and conversely. In the model it is assumed that people start reacting against contracting a disease with self protective measures whenever they are informed about the disease and when the burden of the disease is in a recognizable stage. We show how suppressing the prevalence of the disease is more sensitive to the average effectiveness of self-protective measures than increasing the proportion of individuals in a population into which awareness is created.

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Modelling biofilms: from gene regulation to large-scale structure and function; Wednesday, June 29, 17:00

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A new necessary condition for coexistence of species in equilibrium states of the Wanner-Gujer-Kissel biofilm model

We consider the classical Wanner-Gujer-Kissel 1D-model [1,2] in the case of two bacterial species competing for space and a single limiting substrate in a biofilm of a given fixed thickness. We focus on the model's ability to describe equilibrium states in which the two species coexist. If we let $f(z,t) = (f_1(z,t), f_2(z,t))$, $0 \le z \le L$, $t \ge 0$, denote the volume fractions of the two species and $S(z,t)$ the concentration of the limiting substrate, then the model consistes of the following system of non-linear PDEs:

$$f_t + (vf)_z = A(S)f, \quad f_1(z,t) + f_2(z,t) = 1, \quad v(0,t) = 0, \tag{1}$$

and

$$S_t - DS_{zz} + \lambda^T A(S)f = 0, \quad S_z(0) = 0, \quad S(L) = S^0, \tag{2}$$

along with appropriate initial data. Here $v = v(z,t)$ is a (scalar) velocity field, $A(S) = \mathrm{diag}(a_1(S), a_2(S))$ the growth matrix, and S^0 the bulk concentration of the substrate at the biofilm-water interface $z = L$. Moreover, D denotes diffusivity and λ is a vector containing reciprocal yield coefficients. More about mathematical biofilm modelling can be found in a recent overview by Klapper and Dockery [3]

In this work we derive a new necessary condition, in the form of an inequality, for the existence of coexistence equilibrium states to the model (1) and (2). This condition is used in numerical experiments to locate model parameters which exibit coexistence states, something which would be difficult otherwise. The equilibrium is computed using a robust numerical method developed by the author and presented at the ECMTB 2008 in Edinburgh. It is hoped that our necessary condition could be a stepping stone in the search for a mathematically rigorous proof of the existence of coexcistence equilibrium states for biofilm models of this class.

A motivation for this work is a recent article by Klapper and Szomolay [4], where an exclusion principle for ruling out occurence of certain coexistence equilibrium states is presented. While this principle is correct, it is exemplified with a biofilm system, of the kind studied here, for which the authors seem to imply that a coexistence equilibrium may occur only for one special value of the applied substrate bulk concentration S^0. Our investigations indicate that the situation is far more favorable, and that coexistence equilibria actually exists for a whole range of values of S^0, and that for each such value, the system is actually attracted to a coexistence equilibrium state.

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Poster Session; Friday, July 1, 20:00

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Analysis of protein - small molecule interactions using probilistic approach

Analysis of protein - small molecule interactions is crucial in the discovery of new drug candidates and lead structure optimization. Small biomolecules (ligands) are highly flexible and may adopt numerous conformations upon binding to the protein. Using computer simulations instead of sophisticated laboratory procedures may significantly reduce cost of some stages of drug development. Inspired by probabilistic path planning in robotics, stochastic roadmap methodology can be regarded as a very interesting approach to effective sampling of ligand conformational space around a protein molecule. Protein - ligand interactions are divided into two parts electrostatics, modeled by the Poisson-Boltzmann equation, and van der Waals interactions represented by the Lennard-Jones potential. The results are promising since it can be shown that locations of binding sites predicted by the simulation are in agreement with those revealed by experimental x-ray crystallography of protein-ligand complexes. We would like to extend our knowledge beyond scope available to most of the current molecular modeling tools toward better understanding of the ligand binding process. We try to accomplish this goal using two-level model of protein-ligand interaction and sampling of ligand conformational space covering the entire surface of protein target.

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Cell migration during development: modelling and experiment; Saturday, July 2, 08:30

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An integrated experimental/theoretical approach to explore cell migration during embryonic development

Cell migration is critical to multiple developmental processes, from early embryonic reorganisation to the intricate wiring of the nervous system. Neural crest cells (NCCs) form a highly motile population characterised by an epithelial to mesenchymal transformation that allows their migration to various remote target tissues, where they differentiate into multiple cell types. Failure to migrate, proliferate or differentiate leads to a plethora of birth defects. Melanoblasts, a subtype of NCC and the embryonic precursors of melanocytes, serve as a model system for cell migration during development and in pathologies such as cancer cell metastasis. Melanoblasts migrate out of the neural crest into the developing skin before localising into the developing embryonic hair follicles. A variety of factors may contribute to their colonisation of the embryonic skin, including tissue growth, melanoblast motility, melanoblast proliferation and extracellular signaling factors. In this talk I will discuss our integrated experimental/theoretical approach to understanding melanoblast invasion, in which data obtained in an ex vivo system for live imaging of melanoblast migration in embryonic skin is incorporated into mathematical models which, in turn, are used to test distinct hypotheses for colonisation and formulate experimentally testable predictions.

Modeling and analysis of tumor invasion II; Tuesday, June 28, 14:30

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The impact of a heterogeneous environment on invasive processes

The invasion or migration of cells in tissues, either during embryonic development, normal physiological processes such as tissue repair or as a result of pathologies such as cancer, can be highly variable according to cellular and tissue type. In this talk I will present a variety of results, based on both indivudual and continuous level models, that examine the impact of the extracellular matrix environment on invasion. Specifically, I will examine the impact of both a heterogeneous adhesive environment surrounding cells and varying degrees of anisotropy resulting from the oriented structure of matrix fibres.

Poster Session; Friday, July 1, 20:00

Laurence Palk
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A mathematical model of fluid secretion and calcium dynamics in the salivary gland.

It is estimated that 20% of adults in the US will suffer xerostomia, a condition whereby a lack of saliva production causes issues with dental cavities, oral pain and infection. We construct a mathematical model of the parotid acinar cell with the aim of investigating how the distribution of K+ channels and Ca2+ wave speed affects saliva production. Secretion of fluid is initiated by Ca2+ signals acting the Ca2+ dependent K+ and Cl- channels. The opening of these channels facilitates the movement of Cl- ions into the lumen which water follows by osmosis. We use recent results into both the release of Ca2+ from internal stores via the inositol (1,4,5)-trisphosphate receptor (IP3R) and IP3 dynamics to create a physiologically realistic Ca2+ model which is able to recreate important experimentally observed behaviours seen in parotid acinar cells. We show that maximum saliva production occurs when a small amount of K+ conductance is located at the apical membrane, with the majority in the basal membrane. We simulate Ca2+ waves as periodic functions of time at both the apical and basal membranes. This enables us in investigate how the phase difference of apical and basal Ca2+ signals affects fluid flow. We find maximum fluid flow when Ca2+ signals are in-sync, predicting increased cell efficiency with faster Ca2+ waves.

Systems Biology of Development; Saturday, July 2, 14:30

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Cell elongation and cell adhesion suffice for vascular network formation

The formation of blood vessels is crucial in many biological processes including embryonic development, wound healing and cancer. Vascular networks form by migration of endothelial cells and their interaction with the ECM. A multitude of computational models explain vascular network formation by means of chemotaxis driven aggregation. However, experiments suggest that vascular networks may form also without secreted chemoattractants [1].

Previously, we have highlighted cell length as a key property for vascular-like network formation [2]: a cell-based, Cellular Potts model indicated that chemotaxis and cell elongation, together, suffice for forming stable, regular networks. We have now analyzed the dynamics of this model in absence of chemotaxis, and find that cell elongation and cell adhesion alone suffice for forming network-like structures.

The deformability of cells and their adhesion to the ECM turn out to be key to network formation. Flexible, adherent cells form blobs with individual cells packed closely together. More rigid, elongated cells cannot assume their ideal shape inside a blob, making network-like structures the preferred configuration. Without chemotaxis, network-like patterns form in a narrow region of parameter space; chemotaxis dramatically widens this region and sharpens the phase transitions between blobs and networks. Concluding, vascular network formation does not necessarily require chemotaxis or similar, midrange attractive forces between cells, although such forces make network-like patterning more robust.

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Population Dynamics; Thursday, June 30, 11:30

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Mathematical modeling of an ecosystem with three-level trophic interactions

In this talk, the speaker will discuss the mathematical modeling of the spatio-temporal dynamics of an ecosystem with three-level trophic interactions. In this model, a general trophic function based on the ratio between the prey and a linear function of the predator is used at each level. At the two limits of this trophic function, one recovers the classical prey-dependent (Lotka-Volterra type) predation model and the ratio-dependent predation model, respectively.

The model results in a strongly-coupled system of parabolic partial differential equations. The speaker will analyze the existence, uniqueness, stability and bifurcation of equilibrium (steady state) solutions using the upper-lower solutions method and the topological degree method. He will also interpret some of these results in the context of different predation behaviors (prey-dependent vs ratio-dependent).

The speaker also points out that he and his co-authors have used similar methods to study ecosystems with different predation behaviors and strategies, different spatial features, as well as different species growth patterns. This talk will include a brief survey of some of these results (which have been published in a series of papers in Proc Roy Soc Edinburgh, Proc London Math Soc, J Differential Equations, IMA J Appl Math, SIAM J Appl Math etc).

Statistical Analysis of Biological Signals II; Saturday, July 2, 11:00

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The joint distribution of the sum and maximum of exponential random variables with applications to biology

We consider the joint distribution of the maximum Y and sum X of n iid exponential random variables. We present the exact joint distribution of the vector (X, Y) together with its marginals and conditionals. Further, we extend our result to stochastic number of terms, and present the exact joint distribution of the random vector (N, X, Y), when N has a geometric distribution. Then, X is the random sum and Y is the random maximum of N iid exponential random variables. We illustrate the modeling potential of these distributions using applications in biology.

Structure and Dynamics of Biochemical Reaction Networks I; Tuesday, June 28, 14:30

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Persistence and the Global Attractor Conjecture: Recent Approaches

We describe recent approaches to proving the Persistence Conjecture (which describes a class of mass-action systems for which variables do not approach zero) and the Global Attractor Conjecture (which describes a class of mass-action systems for which trajectories converge to a single positive equilibrium). We introduce the class of "endotactic" networks (which contains the class of weakly reversible networks), and formulate the Extended Persistence Conjecture, which says that endotactic mass-action systems are persistent, even if the reaction rate parameters are allowed to vary in time (to incorporate the effects of external signals). We describe a proof of the Extended Persistence Conjecture for systems that have two-dimensional stoichiometric subspace. In particular, we show that in weakly reversible mass-action systems with two-dimensional stoichiometric subspace all bounded trajectories are persistent. These ideas also apply to power-law systems and other nonlinear dynamical systems. Moreover, we use these results to prove the Global Attractor Conjecture for systems with three-dimensional stoichiometric subspace. This is joint work with Gheorghe Craciun and Fedor Nazarov.

Poster Session; Friday, July 1, 20:00

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Spin coherent state representation of the Crow-Kimura and Eigen models of quasispecies theory

We present a spin coherent state representation of the Crow-Kimura and Eigen models of biological evolution. We deal with quasispecies models where the fitness is a function of Hamming distances from one or more reference sequences. In the limit of large sequence length N, we find exact expressions for the mean fitness and magnetization of the asymptotic quasispecies distribution in symmetric fitness landscapes. The results are obtained by constructing a path integral for the propagator on the coset $SU(2)/U(1)$ and taking the classical limit. The classical limit gives a Hamiltonian function on a circle for one reference sequence, and on the product of $2m-1$ circles for m reference sequences. We apply our representation to study the Schuster-Swetina phenomena, where a wide lower peak is selected over a narrow higher peak. The quadratic landscape with two reference sequences is also analyzed specifically and we present the phase diagram on the mutation-fitness parameter phase space. Furthermore, we use our method to investigate more biologically relevant system, a model of escape from adaptive conflict through gene duplication, and find three different phases for the asymptotic population distribution.

Population Genetics; Wednesday, June 29, 17:00

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Evolutionary advantage of small populations on complex fitness landscapes

Recent experimental (Rozen et al. 2008) and theoretical (Handel and Rozen, 2009) studies have shown that small asexual populations evolving on complex fitness landscapes may achieve a higher fitness than large ones due to the increased heterogeneity of adaptive trajectories. Here we introduce a class of haploid three-locus fitness landscapes that allow the investigation of this scenario in a precise and quantitative way. Our main result derived analytically shows how the probability of choosing the path of the largest initial fitness increase grows with the population size. This makes large populations more likely to get trapped at local fitness peaks and implies an advantage of small populations at intermediate time scales. The range of population sizes where this effect is operative coincides with the onset of clonal interference. Additional studies using ensembles of random fitness landscapes show that the results achieved for a particular choice of three-locus landscape parameters are robust and also persist as the number of loci increases. Our study indicates that an advantage for small populations is likely whenever the fitness landscape contains local maxima. The advantage appears at intermediate time scales, which are long enough for trapping at local fitness maxima to have occurred but too short for peak escape by the creation of multiple mutants. This presentation is based on the paper (Jain et al. 2011).

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Evolutionary Ecology; Thursday, June 30, 11:30

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Joint evolution of dispersal and cooperation in a locally stochastic metapopulation model

In this talk I will investigate a structured metapopulation model [2], consisting of small local populations. Local population dynamics (birth, death, emigration and immigration) is thus stochastic. The evolution of dispersal in this model has been earlier studied [3]: the dispersal rate evolves, because catastrophes and demographic stochasticity result in sparsely populated patches, into which immigration is beneficial. In addition, dispersal reduces kin competition.

Recently, the evolution of public goods cooperation in this model has also been studied [4]. In each habitat patch, individuals can contribute to a common resource, which benefits the reproduction of all individuals of the patch. Contribution is costly, and increases the death rate of the contributor. I assume that cooperation is altruistic, thus the direct benefits from the own action of a focal individual will never exceed their direct costs. Nevertheless cooperation can evolve, because of benefits to own kin.

It is obvious that dispersal affects the evolution of cooperation: for low dispersal rates relatedness is high, and cooperation can evolve. Increasing the dispersal rate is expected to decrease relatedness, and thus make cooperation less favorable. This is, however, not always the case, and even evolutionary suicide can be observed [4]. Cooperation will also affect the evolution of dispersal: a highly cooperating individual is expected to disperse less than an individual, which cooperates only little or not at all. These effects give motivation for the study of the joint evolution of dispersal and cooperation using the methods of adaptive dynamics [1]. In this talk I will present various evolutionary outcomes possible in the model, including evolutionary branching and evolutionary suicide. I will also discuss the effect of essential parameters.

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Ecosystems Dynamics; Tuesday, June 28, 14:30

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Influence of Macrophytes on Biological Residence Time in a Flow-Through System

While plankton have often been thought to behave as passive tracers, completely at the mercy of the hydrodynamic flow, the commonness of plankton patches, as well as field studies showing evidence of microorganism movement against the bulk (or mean) flow, suggests that individual plankton behavior such as vertical/horizontal migration may dominate at smaller scales. In natural water bodies such as embayments and estuaries, macrophytes can have a significant and complex effect on water flow and can greatly complicate physical/biological interactions. Using a two-dimensional hydrodynamic model to create flows in an idealized channel with macrophytes modeled as a porous layer, we first model the channel under a number of different macrophyte regimes, varying the number of patches and height and density of the macrophytes. We next model plankton behavior under these different flow regimes with an individual-based model and explore the extent to which vertical migration in the presence of macrophytes affects plankton trajectories. In particular, we are interested in studying how the interaction of plankton migration behaviors and macrophyte structures affect biological retention and whether a set of migration regimes exists for a given hydrodynamic forcing that will allow the plankton to stay within the study system (avoid washout) 'forever.'

Modeling of immune responses and calcium signaling I; Tuesday, June 28, 17:00

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Oscillations and feedback regulation in the NF-B signalling

Time-lapse cell imaging showed that in response to Tumour Necrosis Factor alpha (TNF) Nuclear Factor kappa B (NF-B) transcription factor oscillates between the cytoplasm and nucleus (Nelson et al., (2004) Science 306: 704). Treatment with repeat pulses of TNF at different intervals enabled frequency-dependent encoding of target gene expression (Ashall et al., (2009) Science 324: 242). Development of a highly constrained mathematical model suggested that cellular variation in NF-B dynamics arises from a dual-delayed negative feedback motif (involving stochastic transcription of IB and IB). We suggest that this feedback motif enables NF-B signalling to generate robust single cell oscillations by reducing sensitivity to key parameter perturbations. Enhanced cell heterogeneity may represent a mechanism that controls the overall coordination and stability of cell population responses by decreasing temporal fluctuations of paracrine signalling (Paszek et al., (2010) PNAS 107: 11644). We have also shown that the cell to cell heterogeneity is profoundly increased following low-dose stimulation. Low doses of TNF resulted in stochastic delays in single cells, but once the first translocation occurs the typical 100 min period was maintained (Turner, et al., (2010) J. Cell Sci. 15: 2834). Our analyses demonstrate a fundamental role of oscillatory dynamics in control of inflammatory signalling at different levels of cellular organisation.

Recent advances in infectious disease modelling I; Saturday, July 2, 11:00

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Modeling within-host dynamics of influenza virus infection including kinetics of innate and adaptive immune responses

Despite vaccines and antiviral agents, influenza infection remains a major public health problem worldwide. It is of great importance to study the biological events underlying virus replication and host immune response in order to develop more effective vaccines, treatments, and other prevention strategies. Here, we develop a new mathematical model to study the within-host dynamics of influenza infection. By comparing modeling predictions with both interferon and virus kinetic data, we examine the relative roles of target cell availability, innate and adaptive immune response in controlling the virus. This work provides a detailed and quantitative understanding of the biological factors that can explain the virus kinetics during a typical influenza infection.

Modeling of immune responses and calcium signaling IV; Saturday, July 2, 08:30

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Positive feedback in NF-κB signaling

NF-κB is a key transcription factor controlling immune responses, such as inflammation, proliferation and apoptosis. Its regulatory system is tightly controlled by several feedback loops. The two negative loops mediated by NF-κB inducible inhibitors, IκBα and A20, provide the oscillatory responses to the tonic TNFα stimulation, in which NF-κB translocates in and out of the nucleus with period of about 100 min. These oscillations maintain NF-κB phosphorylation, and are indispensable for NF-κB dependent signalling. Here, we explore the role of the feedback loop mediated by the NF-κB inducible cytokine TNFα, which is secreted by the activated cells and can bind TNFα membrane receptors of the neighboring cells, or of the same cell that give rise to the positive feedback regulation. This positive feedback is negligible in most of cell lines, but may become, as suggested by our study, dominant in immune cells like monocytes or macrophages that have a high level of TNFα expression.

The proposed stochastic model pursues our earlier studies [1-2], by including the positive feedback loop regulation. The bifurcation analysis performed for the deterministic approximation of the stochastic model, revealed that for a broad range of the bifurcation parameter (rate of TNFα synthesis) the limit cycle and stable steady state coexist. As a result single cells stochastic trajectories may jump between these two attractors. Such jumps correspond to the spontaneous activatory – inactivatory transitions. In the stochastic model the bifurcation parameter controls the *on* and *off* rates and the probability that cell is in the oscillatory state. Interestingly, even in the parameter range in which the limit cycle oscillations of the deterministic approximation are not present, the spontaneous activation probability is not zero. The model satisfactorily reproduces single cell kinetic of SK-N-AS cell [3], which exhibit spontaneous activation in the absence of TNF stimulation.

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936 and Foundation for Polish Science grant TEAM/2009-3/6.

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Modeling of immune responses and calcium signaling V; Saturday, July 2, 11:00

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On mechanical effects accompanying and influencing the diffusion of calcium.

We discuss the coupling between chemical and mechanical processes which are accompanying and influencing the diffusion of calcium in biological tissues. The tissue as a whole, similarly as a single cell, is treated as a visco-elastic medium. The diffusion of calcium is enhanced by the autocatalytic release of calcium, and modified by reaction with diffusing buffers. In addition, the mechanical strain can also influence the release of the cytosolic calcium. As a result, the waves of calcium concentration can be excited by the mechanical as well as by the chemical means. Developing certain asymptotic procedures with respect to the viscosity of the medium as well as with respect to its size (a thin cylinder as a model of a cell and a thin layer of tissue), and finally assuming the fast reaction terms in equations for buffers, we reduce the full system of equations to a single nonlinear reaction diffusion equation. The dimensionality of this equation corresponds to the dimensionality of the problem (a single space variable for the cell, two space variables for a thin layer of tissue, and three space variables in case of a bulk medium).

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936.

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Cancer; Tuesday, June 28, 11:00

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Bright solitons in malignant gliomas

Malignant gliomas are the most common and deadly brain tumors. Survival for patients with glioblastoma multiforme (GBM), the most aggressive glioma, although individually variable, is in the range of 10 months to 14 months after diagnosis, using standard treatments which include surgery, radiotherapy, chemotherapy (temozolamide and antiangiogenic drugs such as bevacizumab) [1]. GBM is a rapidly evolving astrocytoma that is distinguished pathologically from lower grade gliomas by the presence of necrosis and microvascular hyperplasia.

Many mathematical models have been proposed to describe specific aspects of GBM cell lines in vitro [2,3] and the tumor growth in vivo even under the action of radiotherapy [4-6]. Recently some applications of these models have been used to predict the survival of patients after surgical resection of GBMs [7].

Most of the mathematical models in use for GBM are based on a simple reaction-diffusion equation: the Fischer equation [8]. This equation in one spatial dimensions has travelling wave solutions of kink type but has no travelling wave solutions in higher dimensions [9].

In this communication we will first describe two extensions of the Fischer equation, the first one accounting for the necrotic core and the normal tissue and the second one incorporating the vasculature. We will then show how bright tumor solitons arise spontaneously separating a kink of normal tissue from a kink of growing necrotic tissue. We will relate the soliton parameters (corresponding to the active tumor area) to the clinically relevant parameters. The effect of surgical resection on the nonlinear dynamics of the system will be discussed. In our analysis we will resort to different tools of the theory of nonlinear waves: time-dependent variational methods [10], moment methods [11], Lie group theory methods [12], similarity transformations [13], and numerical simulations. We will also discuss the existence of multidimensional travelling waves employing analytical methods and advanced numerical methods incorporating the system's geometry [14].

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Modelling biofilms: from gene regulation to large-scale structure and function; Wednesday, June 29, 17:00

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Early stages of biofilm formation of Pseudomona syringae on leaves surfaces

Bacterial aggregates observed on leaf surfaces can be compared to biofilms in aquatic and medical environments due to their nutrient heterogeneity, and constantly changing water conditions. Bacteria on leaves surface are found forming aggregates of a wide range of sizes. A localized high level of density of cells may foster genetic and metabolic exchange; furthermore epiphytic survival of bacteria during desiccation is likely enhanced when they are aggregated. Aggregates may also locally facilitate coordinated bacterial population responses for traits expressed in a density-dependent manner through quorum sensing. We developed a stochastic model to describe the frequency, size, and spatial distribution of the gram-negative bacterium Pseudomonas syringae aggregates on bean leaf surfaces. Our model, a logistic birth-death model with migration (time-homogeneous Markov process), is able to elucidate two factors fostering aggregate formation: migration and variability of the leaf surface environment. Our results successfully explain quantitative experimental data available. We discuss how to analyse the joint distribution of the numbers of aggregates of different sizes at a given time and explore how to account for new aggregates being created, that is, the joint distribution of the family size statistics conditional on the total number of aggregates. Through simulations we examine several migration regimes in order to find out how this affects the aggregates size distribution. We discuss the ecological significance of the large aggregates formed on leaves as early stages of biofilm formation. Aggregation formation is thought to be the first step towards pathogenic behaviour of this bacterium; understanding aggregate size distribution would prove useful to understand the switch from epiphytic to pathogenic behaviour.

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From one to many: Cell-based modeling of collective, emergent behaviors in biology -II; Tuesday, June 28, 14:30

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Multiscale modelling of vascular tumour growth and angiogenesis

A three-dimensional multiscale model of vascular tumour growth is presented. In our model, cells are modelled as individual entities (agent-based approach) each with their own cell cycle and subcellular-signalling machinery. Nutrients are supplied by a dynamic vascular network, which is subject to remodelling and angiogenesis.

The model is formulated on a regular grid that subdivides the simulation domain into lattice sites. Each lattice site can be occupied by several biological cells whose movement on the lattice is governed by reinforced random walks, and whose proliferation is controlled by a subcellular cell cycle model. The vascular network consists of vessel segments connecting adjacent nodes on the lattice, with defined inflow and outflow nodes with prescribed pressures. We also specify the amount of haematocrit entering the system through the inlets. The vessel network evolves via sprouting of tip cells with a probability that increases with the local VEGF concentration, tip cell movement is described by a reinforced random walk, and new connections forming via anastomosis. In addition, vessel segments with low

wall shear stress may be pruned away. Elliptic reaction-diffusion equations for the distributions of oxygen and VEGF are implemented on the same spatial lattice using finite difference approximations, and include source and sink terms based on the location of vessels (which act as sources of oxygen and sinks of VEGF) and the different cell types (e.g. cells act as sinks for oxygen and hypoxic cells as sources of VEGF).

In our simulations we demonstrate how our model may be combined with experimental data, to predict the spatio-temporal evolution of a vascular tumour together with angiogenesis.

Bridging the Divide: Cancer Models in Clinical Practice; Thursday, June 30, 11:30

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Modelling the Spatio-Temporal Distribution of Drugs in Tumours

The distribution of drugs in tumours is studied in a multiscale modelling framework. On the molecular scale we analyse the random walk of drug molecules through subsystems of the vascular network, from which molecules extravasate into the tissue, diffuse in the interstitial space, bind to receptors on the surfaces of tumour cells and finally induce apoptosis. Knowledge gained on the molecular scale, like diffusion coefficients and reaction rates, is then incorporated in a multiscale model of vascular tumour growth and angiogenesis. The model combines blood flow, angiogenesis, vascular remodelling, interactions between normal and tumour cells and diffusive nutrient / VEGF transport as well as cell-cycle dynamics within each cell. To study the effects of therapies, the model enables us to include a drug specific intracellular response (modelled by ordinary differential equations) and link it to an extracellular drug concentration that is described by reaction-diffusion equations. Drugs are supplied by the vascular system and adsorbed by normal and cancer cells, as well as decomposed by natural decay.

The numerical simulations let us analyse how the heterogeneity of the tumour structure influences the drug distribution and lead to predictions of therapeutic efficacy.

Epidemics; Thursday, June 30, 11:30

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On the reproduction number in different infectious diseases models

The classical Kermack-McKendrick homogeneous SIR (susceptible, infected and removed) model is well known. Its general solution is a function of the unique parameter (the reproduction number) that is equal to a mean number of secondary cases produced by a typical infected individual in a completely susceptible population. If the reproduction number is more than one (the threshold value) its value describes an epidemic level larger values correspond to stronger epidemics. This model bases on two assumptions 1) all members of the population have the equal probability to get infected and 2) mixing in the population is uniform. It is clear that both of these assumptions are nonrealistic for any large human population. In the more complex compartment SIR models the population is divided into several non-overlapping groups. It allows us to partly remove assumptions of the classical model. Twenty years ago Diekmann et al 1 showed that for this kind of models, just as for the classical model there is the threshold parameter R0. Usually it is called by the same name the reproduction number though the physical meaning of this parameter has changed. However, this new parameter is a not unique measure of an epidemic severity (it will be proven during my talk). In particular it means that for such models comparison of the severity of two epidemics by simple comparing values of their reproduction numbers is incorrect. Since the more realistic model has to contain much more parameters for more detailed descriptions of the population and epidemic itself, we can be sure that the last conclusion is valid for the real epidemics too. Individual-based models (IBMs) are more complex in comparison with the compartment ones since they use overlapping groups (school children are members of a family also, for example). This peculiarity of IBMs makes Diekmanns calculation method of the reproduction number inapplicable. Moreover there is no usual mathematical formulation for the IBMs (by differential equations, for example). It means that we may not use analytic methods of research and therefore, an existence of any similarity parameter in the solution (for example, a threshold condition or some analog of the reproduction number) has to be proved numerically. Unfortunately, papers with misunderstandings of the IBMs peculiarities continue to appear.

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The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits II; Wednesday, June 29, 17:00

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Understanding the spatial organization of bacteria

The spatial self-organization of bacteria can be understood by thinking of bacteria as self-propelled rods that interact by pushing each other. Despite the simplicity of the model, it is possible to show that the combination of these two ingredients, self-propulsion and volume exclusion, is enough to reproduce the phenomena observed in experiments: collective motion, clustering, and aggregation. Interestingly, the combination of self-propulsion and volume exclusion can induced a surprisingly rich variety of self-organized patterns which is not limited to the above mentioned patterns. As a proof of principles, it will be shown that when volume exclusion induces stagnation of cells, a new phenomenology driven by the jamming of cells emerges.

Heart rate dynamics: models and measures of complexity (part II);
Wednesday, June 29, 17:00

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Correlation in human heart rate variability from a stochastic model

The extraction of Kramers-Moyal coefficients [1] from measurement data was applied to human heart rate variability. The expansion truncated at the second element is known as the Fokker-Planck equation. The Langevin equation is equivalent to a model of the system dynamics consisting of two parts: a deterministic one and a stochastic term. The necessary assumption is that the noise term be due to δ-correlated noise [2,3]. For heart rate variability, we found that such a description is valid only for daytime recordings of heart rate variability. Nighttime heart rate variability is characterised by non-negligible higher order Kramers-Moyal coefficients [4]. This effect can be explained by the correlation properties of heart rate variability. Correlations may be related to both deterministic and stochastic components of the heart rate. Using Kramers-Moyal expansion the drift (deterministic) and diffusion (stochastic) terms are calculated. Deterministic term coresponds to regulatory processes in the cardiorespiratory coupling. The stochastic one is a measure of the noise amplitude.
We will present the analysis of shortterm correlations. Especially a particular, asymmetric form of the dependence of the diffusion coefficient on the heart rate will be discussed. This is a measure of the ability of the system to lengthen and shorten the RR intervals [5]. Moreover, for different recordings we obtained a different ranges and shapes of the slow-varing diffusion term as a function of the heart rate close to its minimum. This property can be related to arrhytmic RR intervals. To ilustrate this, several recordings from patients with hypertrophic cardiomyopathy will be compared with time series from healthy men.
We will also focus on the occurence of higher order Kramers-Moyal coefficients and their meaning in terms of correlations [4]. We will discuss the variability of heart rate (mechanisms of increasing and of decreasing of the heart rate) including the effect of recorded pathology on the obtained Kramers-Moyal expansion.

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Poster Session; Friday, July 1, 20:00

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Sources of variability in the gene expression profile of follicular thyroid tumours: SVD analysis of microarray data

Many attempts have been performed by microarray gene expression profiling of thyroid follicular tumours in order to find genes that distinguish adenomas and carcinomas. The two types of thyroid follicular tumours: adenomas (benign) and carcinomas (malignant) are indistinguishable before surgical procedure by classical pathology. A hypothesis that gene expression profiling by microarray test may aid in the diagnosis has not been fully verified. The aim of our study was to apply unsupervised methods of gene expression analysis to identify the main sources of variability in follicular tumors which may influence the feasibility of genetic testing in this disease. We performed microarray gene expression profiling in 45 follicular tumours by Affymetrix hgu133plus2 microarray. We performed Singular Value Decomposition (SVD) analysis of the whole dataset to identify the supergenes (modes) that characterise the main sources of variation and are more representative/stable than single transcripts. Next we analysed the biological meaning of the variability related to each supergene. We selected genes that contribute most to each of the supergenes and analysed them with different biological mining methods: gene ontology analysis, gene groups analysis and hierarchical clustering of samples. We revealed that the main sources of variance in the analysed dataset are related to the immune response (1st, 3rd and 6th supergenes), cell proliferation (2nd and 5th supergenes) and differentiation (2nd supergene). Among genes that contribute most to the 1st, 3rd and 4th supergene, many are related to the difference between thyroid carcinoma and normal thyroid tissue. As in the analysis we noted certain arbitrary steps, we also performed SVD analysis on the artificial microarray dataset to assess the influence of these parameters on the results. Comparison of SVD to other unsupervised methods will also be presented.

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The interaction of leaves with the environment

Plant leaves are highly specialized organs to facilitate gas exchange, carbon uptake and water loss usually upon illumination. Leaf internal structures have an enormous influence on these processes. For example, heterobaric leaves have bundle sheaths with extensions which reach from the upper to the lower epidermis and create closed compartments. Homobaric leaves, on the other hand lack these extensions and have large interconnected intercellular spaces so that lateral diffusion of CO2 can substantially support photosynthesis in particular, when one part of the leaf is shaded being a CO2 source while the adjacent leaf area is illuminated and a CO2 sink. Light environment also plays a key role for a range of plant processes. A light beam interacting with a leaf penetrates the epidermis with little interaction and the largest part of the energy is absorbed bythe pigments in the mesophyll cells driving off water vapor which in turn affects the epidermis with stomata. This interaction feeds back on stomata and provides a control mechanism for the interaction of stomata with the environment. These processes aim at a mechanistic description of the interaction of plants with the environment. Comprehensive understanding of plant interaction with the environment for a prediction of plant performance requires a measurement of phenotyping variation with a range of genotypes. This approach called plant phenotyping is a rapidly evolving concept that links genomics with ecophysiology and agronomy. The basis of this concept is that the functional plant body (phenotype) originates during plant growth and development from the dynamic interaction between the plant genetic background and the environment in which the plant develops.

Delay Differential Equations and Applications II; Saturday, July 2, 08:30

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Gompertz model with time delays

We study the influence of time delays on the dynamics of the classical Gompertz model. First we consider the models with one discrete delay introduced in two different ways and next the models with two delays. We present the basic properties of investigated models including the asymptotic behaviour of solutions, the examination of Hopf bifurcation occurrence and stability switches. We also show results for the types of occurring bifurcations. The analytical results are illustrated and completed by numerical simulations.

Heart rate dynamics: models and measures of complexity (part II);
Wednesday, June 29, 17:00

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Structure of heart rate asymmetry

Heart rate asymmetry (HRA) is a physiological phenomenon reflecting the fact that heart rate decelerations contribute more to short-term HRV than accelerations, and accelerations contribute more to long-term and total HRV than decelerations. These HRA methods are variance-based, and can be called macrostructural. Recently, a methods based on a counting statistics which depends on fast- and slow- changing rate of microstructure of the RR intervals time series was defined. In this study we show that the related entropic parameters H_{AR} (dependent on accelerations) and H_{DR} (dependent on decelerations) are asymmetric. The nature of this asymmetry is exactly the same as with the variance-based descriptors: it is unidirectional and consistent.

Materials and methods: 24-hour Holter ECG recordings were obtained from 50 healthy subjects, including 27 women. The microstructure related to decelerations and accelerations was calculated from the resulting RR time series and the H_{AR} and H_{DR} were computed. This was repeated for the same recordings in shuffled order, for which the shuffling distribution of microstructure is known for theoretical considerations. The H_{AR} and H_{DR} were compared with the t-test after establishing normal distribution with the Shapiro-Wilk test. The presence of asymmetry in the studied group was established with the binomial test.

Results: The value of H_{AR} was 1.08 ± 0.021 and H_{DR} 1.01 ± 0.18. This difference is statistically significant with $p<0.001$. There were 43 cases with $H_{AR} > H_{DR}$, and the binomial test for equality of both of proportions being equal gives a statistically significant result $p<0.001$. No differences were observed for shuffled data.

Discussion: Heart rate asymmetry understood as a consistent and unidirectional difference between patterns of accelerations and decelerations is an inherent property of the RR intervals time series. It is visible both in macrostructural, variance-based descriptors and microstructural counting based entropic parameters.

Mathematical modeling of biomechanical regulation in bone tissue (Session I); Wednesday, June 29, 08:30

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A coupled systems biology-micromechanical model for mechanostat-type regulation of bone remodeling

The capacity of bone tissue to alter its mass and structure in response to mechanical demands was recognized more than a century ago and Frost formulated the so-called mechanostat theory for capturing this phenomenon mathematically. This theory proposes that bone responds to changes from a loading relating to an equilibrated bone turnover by triggering either increased bone resorption or formation as response to decreased or increased loading. While this conceptual theory is useful for a qualitative understanding of bone tissue level responses to mechanical loading no quantitative estimates of bone volume/mass changes can be made. Also incorporation of the underlying cellular mechanisms is still outstanding. Over the last several years significant progress has been made to identify the cells and signaling molecules involved in the mechanical adaptation of bone. It is now well accepted that osteocytes act as mechanosensory cells in bone which express several signaling molecules able to trigger bone adaptation responses. Here we present an extended bone cell population model incorporating a simplified osteocyte-feedback to simulate bone remodeling events corresponding to the actual mechanical loading. The mechanical feedback to bone biology is achieved by employing continuum micromechanics-based homogenization of bone stiffness, allowing for estimation of the deformation osteocytes are subjected to. This methodology allows for monitoring effects of mechanical load changes on the composition, and thus on the load-carrying capacity of bone. To the authors knowledge, this is the first model which incorporates the mechanostat theory based on cellular feedback mechanisms.

Epidemics; Tuesday, June 28, 11:00

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Human social network structure is reflected in sequence data for commensal bacteria

DNA sequence data has traditionally been used to infer transmission networks only in the context of epidemics and outbreaks of pathogens, but it can analogously be applied to cases of ubiquitous commensal bacteria in order to infer information about host contact networks. Here, we show that multilocus DNA sequence data, based on multilocus sequence typing schemes (MLST), from isolates of commensal bacteria circulating in an endemic equilibrium can be used to infer both the local and global properties of the contact networks of the populations being sampled. Indeed, we show that MLST data obtained from simulations of spread on a small-world network can be used to robustly estimate the small world parameter controlling the degree of structure in the contact network. Moreover, the pairwise distances in the network — degrees of separation — correlate with genetic distances between isolates meaning that how far apart two individuals in the network are can be inferred from MLST analysis of their commensal bacteria. This result has important consequences, and we show an example from epidemiology — how this result could be used to test for infectious origins of diseases of unknown etiology. We also extend our previous work to include the study of the spread of commensal bacteria on scale-free networks; in particular, we examine the role of highly connected individuals in determining the overall distribution of sequence types.

Heart rate dynamics: models and measures of complexity (part II);
Wednesday, June 29, 17:00

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Modeling of the human atrium using Liénard equations

Liénard systems can be used for modeling oscillatory behaviour of many phenomena - starting from chemical reactions, through neuron excitability [1], up to the action potential in the heart muscle. The universality of the Liénard systems and the rather well-established mathematical knowledge about them creates a flexible framework for designing simple models. Such models are very robust and computationally efficient. On the contrary, the existing physiological ionic channel models of cardiac cells are too complex to allow an investigation of long time dynamical properties of the heart. As a consequence, very rarely do they address the problem of heart rate variability comparable with portable ECG recordings.

We focus on the simulation of human atria, where the dynamics of action potential propagation affects the sinus rythm the most. In the model of the right atrium proposed here, we describe the various anatomical parts of the atrium by means of different equations but all of the same class of Liénard equations. The two nodes - the sinoatrial and the atrioventricular node are modeled by diffusively coupled modified van der Pol-Duffing oscillators while the atrial muscle tissue is currently represented by a diffusively coupled modified FitzHugh-Nagumo system.

Models of the sinoatrial and atrio-ventricular nodes were developed taking into account physiologically important properties such as the phase response curve, the refraction period and threshold potential. Several modifications of the models presented in [2] allowed to achieve a more physiological behaviour of the model. The effect of the autonomous nervous system activity is incorporated into the model in a simple way.

We performed a series of simulations of the atrium, with differing anatomical simplifications varying from a simple 1 dimensional chain of oscillators to a two-dimensional mapping of the atrium with chosen anatomical details included. The simulations allowed to reconstruct such effects as the AV node reentry tachycardia - both in an extended one dimensional model and in the 2D simulation, the phase relations between sinus rhythm and the location and properties of an ectopic source and their effects on the resultant rhythm.

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Mathematical Models in Eco-epidemiology I; Wednesday, June 29, 08:30

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A spatially extended trophic chain model with recycling : how spatial structure determines the matter cycle?

In this work, we study spatially extended trophic chain models. We focus on the role of nutrient recycling on the food chain dynamics. Top predators recycling is known to have some positive effects on the primary producers and that the importance of these effects can be compared to the role that top predators have on primary producers by regulation of herbivores. The role of recycling is here investigated by means of two models with different levels of details. Then these models are spatially extended to understand how the spatial structure affects the trophic chain dynamics. The spatial scales are assumed to be small enough to allow individuals to move fast with respect to local population dynamics. We aim to provide a mathematical formulation of the functional responses at the global scale, which can be suggested as the functional responses to use at larger scales. The global functional responses integrate the spatial effect and the recycling effects.

Poster Session; Friday, July 1, 20:00

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Estimation of individual firing frequencies from superposed spike train

When monitoring neurons with single extracellular electrode the action potentials from different neurons are commonly recorded. One of the problems is to identify the active neurons. The analysis of the pooled record of several independent spike trains with refractory period leads to identification of specific groups of the spikes appearing in time intervals shorter than the refractory period (these are usually called doublets, triplets, etc.). In (Meunier et al., 2003), this problem was solved for two independent spike trains and the result is generalized for any number of independent records here.

How the firing frequencies of individual neurons are related to the relative frequencies of occurrence of doublets, triplets, etc. in the superposed spike train is shown. The closed form-relations between the respective firing frequencies and properties of the superposed record are derived. A method for estimation of respective firing frequencies of any number of neurons, producing indistinguishable spikes, from the knowledge of the superposed record, number of recorded neurons and the refractory period is presented. The task is similar to the problem of coincidence detection (Grün et al., 1999; Krips & Furst, 2009).

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Computational toxicology and pharmacology - in silico drug activity and safety assessment; Saturday, July 2, 11:00

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Systems Biology in drug development - cardiotoxicity prediction

Cardiac liability testing of the drugs candidates during development process has gained increased regulatory and public attention due to a growing awareness of the cardiac risks across a variety of marketed products. Nowadays, cardiac safety assessment in pre-approval clinical trials is obligatory and possible failure at this late stage of the R&D pipeline has tremendous impact on pay-off of the whole process. Thus it is desirable to screen compounds as early as possible, before large amounts of time and money have been spent. Traditional pre-clinical in vivo and ex vivo animal studies employed in risk assessment are criticised due to the ethical and meritorious reasons and in vitro cell lines based studies are currently effectively utilized. Results extrapolation from the in vitro tests to in vivo human risk became an issue and systems biology approach is proposed to derive appropriate conclusions from in vitro lab observations. Developed system is hybrid in nature and combines mathematical model of the human left ventricle cardiomyocyte with in vitro assessed drug induced ionic channels inhibition. The third main element is a virtual population generator. Based on the data derived from available scientific literature dynamic database of the population was developed. Randomly chosen virtual individuals are described by physiological and genetic parameters, namely cardiomyocyte volume, sarcoplasmic reticulum volume, cell electric capacitance, potassium channels genetic polymorphism, which are used as simulation parameters. Therefore the system allows for the inter-individual variability assessment which is a fundamental advantage comparing with animal in vivo and other available muli-scale models. Combination of above-described approach with physiology based pharmacokinetic models (PBPK) used for plasma and tissues drug concentration changes prediction can be used for concentration dependent in vitro - in vivo extrapolation of the cardiotoxic effect for new chemical entities.

Analysis of mathematical models for cancer growth and treatment, Part II; Tuesday, June 28, 14:30

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Optimal and suboptimal treatment protocols for anti-angiogenic therapy

In 1971 Judah Folman discovered that growth of any tumour is strongly dependent on the amount of blood vessels that it induces to grow. He surmised that, if a tumour could be stopped from growing its own blood supply, it would wither and die. Anti-angiogenic therapy is a novel treatment approach that aims at preventing a tumour from developing its own blood supply system.

On the basis of the biologically validated model proposed by Hahnfeldt, Panigrahy, Folkman and Hlatky in 1999, with the usage of the optimal control theory, some protocols of anti-angiogenic treatment were proposed. However, in our opinion the formulation of that model is valid only for the anti-vascular treatment, that is treatment that is focused on destroying endothelial cells. Therefore, we propose a modification of the original model which is valid in the case of treatment which is focused on blocking angiogenic signaling.

We propose also a new mathematical description of the anti-angiogenic treatment goal. In current studies it is assumed that the main goal of anti-angiogenic treatment is to minimize the tumor volume at the end of treatment. On the other hand, chemotherapy is still the main kind of cancer treatment, while anti-angiogenic treatment is only a supplement. The efficient treatment with chemotherapy is possible only when the drug can be distributed evenly, that is when vessels penetrate most of the tumour regions.

Therefore, we assume that the main goal of anti-angiogenic treatment, despite the minimization of the tumour volume, is to maintain high ratio of vessels volume that support the tumour to the actual tumour volume. We analyze it as an optimal control problem and a solution of the problem is given in some cases.

Developmental Biology; Friday, July 1, 14:30

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Mechanisms of pattern formation in biological systems caused by diffusion instability

Pattern formation in living systems including morphogenesis is one of the most challenging problems of theoretical biology. Starting from early seventies a number of models based on the idea of the so-called Turing instability [1] were suggested (one can find some examples in [2]). Turing instability is a type of diffusion instability when one of the eigenvalues of the linearized problem becomes positive in a certain non-zero range of wave vectors. This instability may be responsible for stationary nonhomogeneous pattern formation.

Another type of diffusion instability is the wave instability when a pair of complex conjugate eigenvalues acquires a positive real part in a certain range of wave vectors. Wave instability may be responsible for a lot of spatial-temporal patterns observed both in biological (for example, in bacterial colonies) and in chemical systems (Belousov-Zhabotinsky reaction in microemulsion [3]). While Turing instability can arise in a two-variable reaction-diffusion model, not less than three equations are necessary for the wave instability.

We obtain the conditions for both Turing and wave instabilities in a three-variable reaction diffusion model which follow from linear analysis and formulate qualitative properties of the system for each of the instabilities to occur. While for the Turing bifurcation the system should possess an autocatalytic variable which has a sufficiently small diffusion coefficient compared with the two others (it coincides with the condition for this bifurcation in a two-variable model), the conditions for the wave bifurcation are somewhat different. Autocatalysis is necessary but not sufficient. Namely, the sum of two terms on the main diagonal of the linearization matrix should be positive and the diffusion coefficient of the third variable should be sufficiently large. It is essential that the conditions for these two bifurcations do not contradict and both instabilities can take place simultaneously.

Numerical simulations of the modified Brusselator model support analytic results and demonstrate a variety of spatial-temporal patterns for different regions of the parametric space. Finally we discuss biological systems in which pattern formation may be caused by the above mechanisms.

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Epidemics; Tuesday, June 28, 14:30

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Modelling the role of acaricide in preventing tick borne disease in a wild game bird.

The incidence of tick borne diseases is increasing which has the potential to impact on humans, live stock and wildlife. Ticks feed on a number of different host species which can play different roles in disease transmission acting i) as a disease host which cannot sustain the ticks, ii)a tick and disease host, iii) a tick host which does not transmit the disease but does increase the tick population. Here we will use mathematical models to consider the role that acaricide can play in reducing the tick population, preventing tick bites and reducing disease incidence.

We consider in particular the dynamics of louping ill virus (LIV) a potentially fatal tick borne disease affecting red grouse, an important economic game bird in upland Britain. In this case sheep and red deer both play a crucial role in maintaining the tick population. In theory any efforts made to reduce the tick population should reduce the opportunity for ticks to bite grouse and hence lower virus incidence. Here we discuss SIR type models considering multiple hosts and including management strategies that use acaricide to achieve the reduction in virus incidence. We also discuss whether the treatment of individual grouse broods can provide protection for the rest of the grouse population.

Poster Session; Friday, July 1, 20:00

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Disease-free survival – (non-)parametric estimation

Treatment efficacy in patients with a disease is usually expressed using the disease-free survival, i.e. the probability of staying in a remission after its achievement or after a therapeutic intervention. However, this concept does not allow to evaluate the proportion of disease-free patients in subsequent remission after further possible relapses. The method proposed by Klein et al. enables to estimate the probability of being in first and second remissions.

The contribution presents two new methods of estimation the probability of being in any of remissions. The first one extends the non-parametric estimation proposed by Klein et al. that is based on Kaplan-Meier estimators of survival functions. The second one utilizes a multistate model and it adopts the method for matrix model parameters identification based on quadratic programming (the idea originally elaborated by Wood) to estimate probabilities of remissions and relapses of any rank. The methods are illustrated on data of chronic myeloid leukaemia patients.

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Cellular Systems Biology; Saturday, July 2, 11:00

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Dynamics of synthetic genetic repressilators with phase-repulsive coupling

Oscillatory processes have been discovered in various biological contexts. Circadian clock [1], biochemical oscillations [2] and cell cycle [3] are the well-known examples.

Recently, there were constructed genetic networks exhibiting a specific type of dynamical behavior [4, 5, 6]. A prominent example of synthetic genetic circuit is the repressilator constructed of three transcription factors inhibiting each other in cyclic way. The obvious output of such interaction is oscillations in protein concentrations [4].

Synthetic genetic circuits are organized simpler than natural ones and can evince important details of dynamical properties of the latter.

Given that cells interact with each other it would be of particular interest to investigate dynamics of such integrated population. Quorum sensing is the coupling mechanism found in many bacteria and utilizes a small molecule, autoinducer, which diffuses through cell membrane and activates some target gene [7].

Two theoretical schemes of the repressilator with the quorum sensing coupling mechanism were proposed earlier: phase-attractive [8] and phase-repulsive [9]. The latter one utilizes a negative feedback loop in the autoinducer production module in addition to the average negative feedback loop of the repressilator core. The following system of dimensionless equations describes the behavior of coupled repressilators with phase-repulsive coupling [9]:

$$\begin{aligned}
\frac{\mathrm{da_i}}{\mathrm{dt}} &= -a_i + \frac{\alpha}{1+C_i^n}; & \frac{\mathrm{dA_i}}{\mathrm{dt}} &= -\beta(A_i - a_i)\\
\frac{\mathrm{db_i}}{\mathrm{dt}} &= -b_i + \frac{\alpha}{1+A_i^n}; & \frac{\mathrm{dB_i}}{\mathrm{dt}} &= -\beta(B_i - b_i)\\
\frac{\mathrm{dc_i}}{\mathrm{dt}} &= -c_i + \frac{\alpha}{1+B_i^n} + \kappa\frac{S_i}{1+S_i}; & \frac{\mathrm{dC_i}}{\mathrm{dt}} &= -\beta(C_i - c_i)\\
\frac{\mathrm{dS_i}}{\mathrm{dt}} &= -k_{s0}S_i + k_{s1}B_i - \eta(S_i - Q\bar{S})
\end{aligned}$$

The uppercase letters A_i, B_i and C_i denote protein concentrations, while lowercase a_i, b_i and c_i are proportional to the concentrations of mRNA corresponding to those proteins, S_i denotes AI concentration, where i is a cell index. $\bar{S} = \frac{1}{N}\sum_{i=1}^{N} S_i$,

where N is the total number of cells. α is a maximal transcription rate. n is Hill coefficient or cooperativity. Q is proportional to population density. β is the ratio between mRNA and protein lifetimes.

We have investigated dynamics of synthetic genetic oscillators — repressilators — coupled through autoinducer diffusion in phase-repulsive manner. We have examined emergence of periodic regimes, stable inhomogeneous steady states depending on the main systems' parameters: coupling strength and maximal transcription rate. However, these regimes were shown to exist in [9].

It has been found that the autoinducer production module added to the isolated repressilator causes the limit cycle to disappear through infinite period bifurcation for sufficiently large transcription rate (α). We have found hysteresis of limit cycle and stable steady state, the size of which is determined by ratio between mRNA and protein lifetimes.

Two coupled oscillators system demonstrates stable anti-phase oscillations which can become a chaotic regime through invariant torus emergence, that was investigated in [10], or via Feigenbaum period doubling bifurcation cascade [11], which is alternative way to chaos found by us in the system.

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Cancer; Tuesday, June 28, 14:30

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Modelling the effects of cell-cycle heterogeneity on tumour response to chemotherapy: Biological insights from a hybrid multi-scale cellular automaton model

The therapeutic control of a solid tumour depends critically on the responses of the individual cells that constitute the entire tumour mass. A particular cells spatial location within the tumour and intracellular interactions, including the evolution of the cell cycle within each cell, has an impact on their decision to grow and divide. They are also influenced by external signals from other cells, and oxygen and nutrient concentrations. Hence, it is important to take these into account when modelling tumour growth and the response to various cell-kill therapies, including chemotherapy.

In order to address this multi-scale nature of tumour growth, we propose a hybrid, individual-based approach that analyses spatio-temporal dynamics at the level of cells, linking individual cell behaviour with the macroscopic behaviour of cell organisation and the microenvironment. The individual tumour cells are modelled by using a cellular automaton (CA) approach, where each cell has its own internal cell cycle, modelled using a system of ODEs. The internal cell-cycle dynamics determine the growth strategy in the CA model, making it more predictive and biologically relevant. It also helps to classify the cells according to their cell-cycle states and to analyse the effect of various cell-cycle dependent cytotoxic drugs. Moreover, we have incorporated the evolution of oxygen dynamics within this hybrid model in order to study the effects of the microenvironment in cell-cycle regulation and tumour treatments. An important factor from the treatment point of view is that the low concentration of oxygen can result in a hypoxia-induced quiescence (G0/G1 arrest) of the cancer cells, making them resistant to key cytotoxic drugs. Using this multi-scale model, we investigate the impact of oxygen heterogeneity on the spatio-temporal patterning of the cell distribution and their cell-cycle status. We demonstrate that oxygen transport limitations result in significant heterogeneity in HIF-1 alpha signalling and cell-cycle status, and when these are combined with drug transport limitations, the efficacy of the therapy is significantly impaired.

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling II; Saturday, July 2, 11:00

Applications of phase field models in biological systems

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Shapes of complex geometry are ubiquitous in our natural environment. A few examples are snow flakes, crack patterns, microstructures in materials or th evein network in plant leaves. These shapes have in common that they are created by out-of-equilibrium phenomena and thus evolve in time. The understanding of a diverse array of phenomena involving complex time-dependent shapes in the physical and biological sciences has been greatly enhanced by a theoretical/computational framework rooted in statistical physics, that is commonly refered to as phase-field modeling. The main challenge in this field is to construct models which encompass the complexity of practically relevant materials or biological systems, are capable of making quantitatively accurate predictions and are mathematically simple enough to be solved on physically realistic time and length scales.

We present various applications in biological systems, including cell dynamics, viral capsides and bone remodeling.

Epidemics; Tuesday, June 28, 14:30

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The Perturbation Effect in wildlife diseases: An emergent behaviour of simple models

Population reduction is often used as a disease control strategy when dealing with wildlife hosts; however, in some systems it has been associated with an increase in disease (including bovine tuberculosis in badgers and classical swine fever virus in wild boar). This increase in disease following population reduction is often referred to as the perturbation effect. Several possible reasons for the perturbation effect have been suggested, including increased movement and contact rates, and compensatory reproduction following population reduction.

We use mathematical epidemiological SI models containing key processes, to investigate properties of the perturbation effect and study how it arises as an emergent property of the underlying population and disease dynamic.

In a non-spatial context, we investigate how a change in host behaviour (as a consequence of population reduction) leading to an increase in horizontal disease transmission, can give rise to the perturbation effect. We also investigate how characteristics of demography and disease affect the magnitude of this increase.

In a stochastic spatial context, we investigate the role of density dependent movement between multiple sub populations, and how the horizontal disease transmission between groups can affect the increase. Finally we investigate how different population reduction strategies can maximise the perturbation effect.

We find that the perturbation effect is most likely to occur in disease systems with low disease prevalence, where populations are close to the carrying capacity and the disease is spatially heterogeneous in nature.

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling I; Saturday, July 2, 08:30

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Cell Adhesion and Re-organisation in a Multiphase Model Describing Tumour and Tissue Growth

The main aim of the talk is to describe how to embed the experimental results recently obtained studying the detachment force of single adhesion bonds in a multiphase model developed to describe the growth of tumours and tissues in general. In order to do that the microscopic infomation is upscaled to the macroscopic level to describe the dependence of some crucial terms appearing in the PDE model on the sub-cellular dynamics involving, for instance, the density of bonds on the membrane, the probability of bond rupture and the rate of bond formation. In fact, adhesion phenomena influence both the interaction forces among the constituents of the mixtures and the constitutive equation for the stress of the cellular components.

Studying the former terms a relationship between interaction forces and relative velocity is found. The dynamics presents a behaviour resembling the transition from epithelial to mesenhymal cells or from mesenchymal to ameboid motion though the chemical cues triggering such transitions are not considered here.

The latter terms are dealt with using the concept of evolving natural configurations consisting in decomposing in a multiplicative way the deformation gradient of the cellular constituent distinguishing the contributions due to growth, to cell rearrangement and to elastic deformation. This allows to describe situations in which if in some points the ensemble of cells is subject to a stress above a threshold, then locally some bonds may break and some others may form, giving rise to an internal re-organisation of the tissue that allows to relax exceedingly high stresses.

Speciation; Wednesday, June 29, 08:30

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Magic traits, mate choice and speciation

Many theoretical models on sympatric speciation rely on assortative mating functions, in which the probability that two individuals mate decreases with increasing phenotypic difference. We give results on the effect of assortative mating functions in models, where the trait that controls mate choice also determines fitness in ecological selection (so called magic traits). In particular, we concentrate on the deficiencies of these mating functions and contrast the results with mate choice which is also based on indicators of adaptedness. Further, we introduce mate choice that is based on a strategy of sequential search, where the decision to mate depends on the density distribution of the population and the fitness returns to the searcher.

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Speciation; Wednesday, June 29, 08:30

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Evolutionary responses to migration load: A tall fence or a melting pot?

Gene flow between populations in different ecological conditions can reduce fitness in both populations. This can be due to immigration of alleles that are not adapted to local ecological condition or because hybrids between populations have lower fitness. But this reduction in fitness, or genetic load, is also a potential engine to drive evolution: The magnitude of the genetic load sets an upper bound to the strength of selection to compensate for the cost of migration. This load can be reduced through mating preferences for high quality mates, mating preferences for local genotypes, or by changes in the genetic architecture. Preferences for local mates would lead to reinforcement of low hybrid fitness and potentially speciation. Alternatively, preferences for high quality mates or changes to the genetic architecture might allow incipient species to continue to transfer genetic information without population collapse. I will discuss the relative strength of each pathway and the implications for local adaptation and speciation.

Poster Session; Friday, July 1, 20:00

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Towards a whole-tissue model of the intestine.

The intestinal epithelium is a paradigmatic system to study regenerative tissues. In this tissue the stem cells are confined to a well-defined niche at the bottom of invaginations called crypts. The progeny of these stem cells specify into different functional lineages and regenerate the entire tissue within a few days.
A multitude of genetically altered mouse stems show not only changes in this turnover but also clear morphological changes of the entire intestine. In order to explain these phenotypes a whole-tissue approach is required.
Recently, we introduced an off-lattice model of single crypt dynamics [1]. This model explains crypt dynamics in steady state and after perturbations in agreement with experimental data. We here present a modelling framework that allows extending this model to multi-crypt systems representing a first step towards a whole-tissue model.
We implemented a Cellular Potts Model on a curved surface representing multiple crypts and applied the regulatory mechanisms and organisation concepts of our off-lattice model. This enables us to cover the self-organisation of cell production and loss in the tissue, which is assumed as fixed in the former model. We provide first simulation results applying this model to circadian rhythms of intestinal turnover and compare the results to experimental data [2].

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Poster Session; Friday, July 1, 20:00

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Recurrence plot analysis of time series derived from observations of *Dreissena polymorpha*

Biological Early Warning Systems provide a rapid warning of the occurrence of contaminants in water at concentrations which could be immediate threat to living organisms. In our work we use long-term observations of freshwater mussels for monitoring water contamination. This paper presents a recurrence plot (RP) based approach to analyse data derived from the observations of *Dreissena polymorpha*. Studying the non-linear characteristics of data sequences can assist in understanding the relationships between measured mussel activities and actual state in surrounding environment. Data sequences are extended to m-dimensional phase space and then we use recurrence plots to visualize recurrences of trajectories of dynamical systems. Finally, the recurrence quantification analysis (RQA) is used to quantify the structures found in RPs and to classify them. In order to check the effectiveness of this approach, we need to examine the adequacy of the methods used at various stages of analysis. Therefore, we will discuss usage of various parameters for RP and RQA and classification methods (SVM, KNN, FDA,SRDA, PDA, DLDA). Preliminary experiments and previous results of work show that such formulation of the problem allows to extract relevant information from signal and lead to effective solutions to considered problem. It is found, for example, that RQA may support identification of the effects of pollution in the water.

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Cancer; Tuesday, June 28, 17:00

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Computational study of vascular tumour growth in response to combined therapies

The microvascular network plays crucial role in development of the solid tumours. It constitutes a source of the nutrient for the tumour and enables its continuous growth. However, due to fast metabolism of the tumour cells hypoxic regions may occur. Such regions are then cause of the angiogenesis. This study is intended to analyse computationally interplay between the tumour cells and vascular network, and additionally to find optimal scheduling for the combined chemotherapy and anti-angiogenic therapy [1].

The deterministic model is represented by a system of non-linear partial differential equations and enables to simulate growth of the solid tumour in its vascular phase as well as a process of the angiogenesis. In contrast to other models (*e.g.* [2]) the microvascular network is modelled *explicite*, not as a density of blood vessels. It enables to capture the heterogeneity of the tumour tissue, not only its averaged picture. In order to find optimal parameters for the combined chemotherapy and anti-angiogenic therapy a few heuristic algorithms are employed, including simulated annealing [3] and evolutionary algorithm.

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Plants, growth and transport processes I; Tuesday, June 28, 11:00

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Transport of metal and water in plant roots: Modelling and Analysis

We study the problem of metal and water transport through plant roots. The model equations reflect the complex microscopic structure of a root tissue. We distinguish between apoplastic and symplastic pathways for metal and water transport. The active water transport is modelled by Stokes equations and is defined by the pressure difference between roots and atmosphere and by the osmotic pressure in cells. The transport of metal molecules is specified by reaction-diffusion-convection equations. The ordinary differential equations describe the dynamic of metal transporter concentrations on cell membranes. Using multiscale analysis we derive a macroscopic model for transport processes defined on the scale of a whole root branch. The convergence of nonlinear terms is shown applying the unfolding method.

Population Genetics; Friday, July 1, 14:30

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Development of distinct colonies of genotype in a sympatric model of diploid entities

As part of an investigation of sympatric speciation this study used a computer model of a population of diploid entities to investigate the development of stable colonies of genotypes. The investigation tested development in variously shaped spaces where, in order to maintain a sympatric environment, uniform developmental characteristics were applied in all areas.

The objective of this work is to establish whether species can separate in a uniform environment simply by random genetic development. The study's demonstration of stable 'colonies' within a uniform space seems to imply that sympatric speciation is possible.

The computer model represented chromosomes as binary numbers, with each digit equivalent to a gene: being either 'wild' or mutated. Processes of inheritance were modelled using probabilistic rates of mutation and cross-over. The population was subject to a randomly-applied death-rate and off-spring competed for the resulting space. A key characteristic of this model was the limited range for selecting a mate and placing offspring. This places the model between models which allow panmictic mating and those which employ sexual selection mechanisms.

In a ring-shaped corridor, starting with uniform or random populations, four or five distinct colonies of genotypes developed and remained stable for several thousand generations. These colonies were similar to biological 'ring-species' but in the model all the neighbouring colonies become equally incompatible with each other. The development of these colonies was found to be related to the width of the corridor, as well as to the rates of recombination and mutation which were applied. In a narrow corridor several distinct colonies persisted whereas in a wide corridor one dominant type quickly developed.

Further study is required to establish whether these colonies can be considered as proper examples of sympatric speciation.

Epidemics; Tuesday, June 28, 11:00

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Approximation of infection spread in multigroup SIR models through homogeneous models

In recent years there has been a tremendous increase in the complexity of epidemic models developed for the spread of infection in humans; often models include households and other types of mixing groups, as well as heterogeneities due to age, behaviour, etc. In another direction, a great number of data on infection spread have been analysed with the use of mathematical models, which often are based on homogeneous mixing, or simple variants of that. Aim of this work is starting to understand why, while definitely mixing patterns and individual behaviour are complicated, simple homogeneous models may still reproduce adequately the overall epidemic spread. Our prototype of complex models is relatively simple, namely a stochastic SIR model for a closed population divided in groups, with uniform global transmission and heterogeneous local transmission; simulations show that this type of models can be approximated adequately by a homogeneous model, as long as the number of groups is sufficiently large. Heuristic methods suggest the relations of the synthetic parameters of the homogeneous model with the original parameters. Extensions to models with differential transmission routes are being examined.

Population Genetics; Wednesday, June 29, 14:30

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Nonhomogeneous Markov chains and quadratic stochastic processes in biology

Nonlinear mappings appear in many branches of mathematics and its applications. In mathematical biology, so-called quadratic stochastic processes (QSP) are used to describe the evolution of biological systems. We examine the limit behavior of such processes as well as the relationship between the asymptotic properties of nonhomogeneous Markov chain and asymptotic properties of QSP. Moreover, we study the geometric structure of the set of Markov chains with a particular limit bahavior.

Neurosciences; Wednesday, June 29, 08:30

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A dynamical model of epilepsy in a plastic neuronal network

In this work we explore the parameter dependence of self-organization scenarios taking place in a neuronal network model equipped with activity-dependent synaptic plasticity [1]. We identify several distinct stationary states as well as parameter regions in which two or more states are unstable and the system displays spontaneous dynamic transitions between them. Such transitions take place recurrently, in various patterns, and involve abrupt reorganization of functional connectivity with simultaneous appearance of new oscillatory behavior. For selected parameter regions the pattern of transitions suggestively resembles stereotypical seizure-like events that reproduce some important pathophysiological features of epilepsy. These include: a pronounced peak in neuronal activity accompanied by hypersynchronization during the events and long, irregular inter-event intervals. We also demonstrate transient "pre-seizure states", a feature which has been recently identified by nonlinear EEG analysis in some forms of epilepsy [2]. Our model suggests a novel hypothesis for the still poorly understood basic mechanisms of epilepsy and seizure generation. We discuss the biological plausibility and bio-medical implications of our findings and outline some possible interpretations in the context of phase transitions and complex systems theory.

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Mathematical modeling and simulations of angiogenesis I; Wednesday, June 29, 08:30

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Characterizing Endothelial Cell Behavior and Adaptation During Brain Capillary Regeneration by Rule Oriented Modeling

Cell-cell communication defines how blood vessels regenerate through a process called angiogenesis. Growth factors like vascular endothelial growth factor (VEGF) and brain-derived growth factor (BDNF) guide angiogenic sprouting in the brain, in conditions of hypoxia, such as during a stroke or in brain cancer. Here, we present a computational strategy to characterize the sequence and magnitude of cell-cell interactions, allowing us to quantify how each endothelial cell behavior inhibits or augments each other. We introduce a novel rule-oriented agent-based programming method to allow rapid testing and comparison of multiple hypotheses in silico to in vitro angiogenic experiments. Results show the interaction of tip and stalk endothelial cells, and predict how migration, proliferation, branching, elongation and quiescence states inhibit or enhance one another to form capillary structures within an in vitro 3D matrix, leading to distinct capillary phenotypes in the presence of VEGF and BDNF. This quantitative understanding of how cells move as a function of molecular stimuli, and form vessels, will be used to help guide small molecule drugs and tissue engineering therapies targeting the brain microvasculature.

Multiscale modelling of reaction kinetics in biology; Tuesday, June 28, 14:30

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Timescales of stochastic gene expression

Gene expression exhibits a high degree of stochasticity when studied at the level of individual cells. Even in genetically identical cell populations exposed to a uniform environment, gene activity levels and their phenotypic consequences are subject to random fluctuations that generate cell-to-cell variations and eventually lead to alternative cell fates. This stochastic noise in gene expression is a critical, biologically relevant property of genetic circuits in both microbial and eukaryotic cells.

Many studies underlined the importance of network architecture and of feedback loops for shaping and controlling the gene expression noise. Here we defend a different point of view, according to which in many situations the order relations between different timescales of the biochemical processes are determinant of the expression fluctuations.

In order to cope with network multi-scaleness we developed hybrid stochastic approaches (Crudu et al 2009). These methods distinguish between molecular species according to their abundances. Species in small amounts can be treated as discrete variables, whereas species in large amounts can be considered continuous. For computational ends, hybrid approaches can be used to simplify biochemical mechanisms, accelerate simulation and facilitate model analysis.

Hybrid stochastic approaches can also be used to understand the impact of multi-scaleness on the expression noise in gene networks. We distinguish between two situations referred to as normal and inverted time hierarchies. The noise can be buffered by network feed-back in the first situation, whereas can have rich, often counterintuitive behaviour in the latter.

The theoretical results are supported by recent experimental findings concerning stochastic noise in the bacterium catabolite repression (Ferguson et al).

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Population Genetics; Friday, July 1, 14:30

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Linkage disequilibrium in populations of variable size

We consider neutral evolution of a large population subject to changes in its population size to understand how the covariance of gene-histories and linkage disequilibrium are influenced by such population-size fluctuations. Within the coalescent approximation, using the approach employed by [2] and the result of [3], we have obtained an exact expression (see [1]) for the covariance of gene-histories in a population with a population size that randomly jumps between two values. We show under which circumstances an effective-population-size approximation is appropriate, and when it fails. In addition, we identify a parameter regime where two-locus gene-history correlations are well described by a coalescent process with multiple mergers.

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Poster Session; Friday, July 1, 20:00

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Flagellar dependence of the directional persistence for bacterial run and tumble chemotaxis

Motivated by experimental data, we extend an existing individual based model for bacterial run and tumble chemotaxis to include the dependence of the directional persistence on the fraction of CW-rotating flagella. The model is built in two dimensional space for a fixed source of nutrient. We assume that the nutrient concentration has a Gaussian distribution profile. We measure the effect of flagellar cooperativeness on the chemotactic performance by the ability of the bacterium to reach a favourable region and to stay in that zone. Furthermore we analyse the effect of varying the directional persistence on the optimality of run and tumble chemotaxis and compare the obtained results with those found in other works.

Ecosystems Dynamics; Tuesday, June 28, 17:00

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A density-dependent diffusion model for a two-phase invasion

A break of the slope between the range expansion in the initial years of invasion and the later years has been observed for different species. We present an approach to explain this two-phase invasion using a model with non-linear density-dependent diffusion. We establish the condition for the existence of a travelling wave solution of the model. We investigate also the effects of the density-dependent diffusion on the speed of species expansion during the two phases of the invasion, and study the duration of each phase.

Applications of nonnegative Radon measure spaces with metric structure to population dynamic models; Wednesday, June 29, 17:00

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Structured population models for evolution

We are interested in an integro-differential model that describe the evolution of a population structured with respect to a continuous trait. Those model are able to capture various biological phenomena, and in particular the speciation process, that is the concentration of the population around a finite number of traits. We analyse this property, and relate it to other theoretical tool used by theoretical biologists. We are also able to analyse some cases pointed out by biologists, where the concentration phenomena does not occur.

Population Dynamics; Saturday, July 2, 11:00

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Equilibria and stability results for some zooplankton size-structured models

Structured models are increasingly used in biological modelling, particularly to describe marine ecosystems, where the behaviour of individuals is strongly dependant of their size. To modelize zooplankton community, we first have to describe how an individual of some size feeds, and then how it uses the acquired food to grow and reproduce (according to some dynamic energy budget in order to guarantee mass conservation). Since the model includes cannibalism throughout zooplankton population, we obtain a variant of the well-known McKendrick-von Foerster equation with integral terms which appear in growth, mortality and reproduction.

Such models are often hard to analyse mathematically. Nevertheless, with some more hypotheses on the cannibalism behavior, we can find equilibria of the model as fixed points of a function in a finite dimensional space. The linearized system around the equilibrium provides us, thanks to the use of linear semigroup theory, some local (un)stability results about these equilibria.

Results obtained will be applied to a simple version of the model, which allows us to go further into the mathematical analysis.

Keywords : Size-structured models, Zooplankton ecosystem, Cannibalism, Strongly continuous semigroups.

References.

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Vector-borne diseases; Tuesday, June 28, 14:30

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Evolutionary determinants of antigenic variation in malaria

Many pathogenic bacteria, fungi, and protozoa achieve chronic infection through an immune evasion strategy known as antigenic variation. In the human malaria parasite Plasmodium falciparum, this involves transcriptional switching among members of the var gene family, causing parasites with different antigenic and phenotypic characteristics to appear at different times within a population. Here we use a genome-wide approach to explore this process in vitro within a set of cloned parasite populations. Our analyses reveal a non-random, highly structured switch pathway where an initially dominant transcript switches via a set of switch-intermediates either to a new dominant transcript, or back to the original. We show that this specific pathway can arise through an evolutionary conflict in which the pathogen has to optimise between safeguarding its limited antigenic repertoire and remaining capable of establishing infections in non-naïve individuals. Our results thus demonstrate a crucial role for structured switching during the early phases of infections and provide a unifying theory of antigenic variation in P. falciparum malaria as a balanced process of parasite-intrinsic switching and immune-mediated selection.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -II; Tuesday, June 28, 14:30

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Guided Motion of Individual and Collective Swimmers in Funnel Arrays

We generalize a model of swimming bacteria in asymmetric arrays of obstacles [1] to include different rules of motion, including various rules for collective behvaiors. For individual noninteracting swimmers, we observe guided motion and rectification by the asymmetric barriers when the particles align with the walls they contact, but we find no rectification if the particles are reflected by the walls or bounce off the walls. For collectively interacting swimmers, it is possible for the particles to form large swimming clumps that can move against the normal rectification direction of the asymmetric barrier array. In general, the rectification by the barriers is lost when the length scale of the swarms of collectively moving particles is significantly larger than the length scale of the funnel shaped barriers. A particle swarm can become trapped inside a funnel; however, individual strings of particles that follow each other can escape from the trap and move against the funnel direction. [1] M.B. Wan, C.J. Olson Reichhardt, Z. Nussinov, and C. Reichhardt, Phys. Rev. Lett. 101, 018102 (2008).

Mechanical Models of Movement and Growth of Cells and Tissues I;
Wednesday, June 29, 14:30

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Forcing the way to metastasis: mechanical interactions between endothelial and circulating tumor cells

Metastasis to distant organs is an ominous feature of most malignant tumors, and it is the major cause of mortality. However, no more than 0.01% of circulating tumor cells is able to withstand all steps of a metastatic cascade, such as an escape from primary tumor mass into the blood stream, circulation with the blood flow and extravasation into the new site that can be subsequently colonized. The process of tumor cells extravasation, i.e., their ability to leave the circulation system under the physiological blood flow is still poorly understood. I will present a biomechanical model of circulating tumor cells and their interactions with endothelial cells forming the vascular wall. This model will be subsequently used to analyze various modes of tumor cell translocation under the blood flow: from circulation to rolling, to crawling, to transmigration.

Fluid-structure interaction problems in biomechanics; Saturday, July 2, 08:30

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Interactions between interstitial fluid and tumor microenvironment in chemotherapy

Interstitial fluid, a solution filling the space between stromal cells, provides a means of delivering various molecules (such as nutrients, oxygen or drugs) to the cells, as well as removal of metabolic waste. In tumorous tissues, the transport of anticancer drugs is moderated by differences in interstitial fluid pressure that varies in different tumors and at different tumor sides, as well as by changes in stromal tissue structure. I will discuss computational simulations showing how tumor tissue metabolic state (its oxygenation and acidity) become modified due to actions of chemotherapeutic drugs leading to the emergence of tumor zones with potentially drug-resistant cells and/or to tumor areas that are not exposed to drugs at all. Both of these phenomena can contribute to the moderate clinical success of many anticancer drugs.

From one to many: Cell-based modeling of collective, emergent behaviors in biology -I; Tuesday, June 28, 11:00

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Contribution of Individual cells to homeostatic balance and imbalance in epithelia

Epithelial tissues (simple or stratified) form multicellular systems of well defined topology and function. In order to maintain such a fine tissue microarchitecture individual cells must act collectively and respond to signals from their neighbors and from the environment. I will present a mathematical model and computational simulations addressing the questions of individual contributions of epithelial cells to tissue homeostatic balance during its development and turnover. In contrast, the disruption of tissue structure is often associated with the initiation and progression of abnormal tissue states, such as tumors. Specific local cell-cell interactions that can lead to the emergence of abnormalities on tissue scale will be also discussed.

Information, human behaviour and infection control; Saturday, July 2, 08:30

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Mathematical Epidemiology and the Economics of Social Planning

Over the last 50 years, mathematical biologists have developed a deep theory of infectious disease dynamics. Today, management problems are as much economic and social as biological. We face a variety of social, behavioral, and political challenges today in the public-health management of infectious diseases. In the last few years, a variety of new modelling approaches including social networks, game theory, information propagation and explicit-behavioral models have been proposed as descriptions of how these economic influences interact with the biology of disease transmission. In this talk, I will review some of recent work I've been involved with in game-theoretic economics models of infectious disease management, and mentioning some open problems in the field.

Structure and Dynamics of Biochemical Reaction Networks II; Tuesday, June 28, 17:00

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Statistical inference for reaction constants in stochastic biochemical networks

The problem of estimating values of reaction constants in biochemical networks if fundamental for any network reconstruction from the trajectory data. The talk will outline some recent developments in statistical inferential procedures for reaction constants in stochastic biochemical network models. We will especially focus on some newly proposed dynamical programming methods, which are similar to the Viterbi-type imputation algorithms for hidden Markov chain and are especially suitable when observed trajectories contain missing data for some species. It will be shown how the use of dynamic programming principles allows for efficient inference via either the Gibbs sampler or the EM algorithm and g the so-called uniformization representation of a Markov jump process. The applicability of the inferential procedures will be illustrated with data from the longitudinal mamalian genetic studies as well as the US CDC data from the onset of the 2009 H1N1 flu pandemic in the US

Epidemics; Wednesday, June 29, 11:00

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A brood-parasites dynamics model

We consider a Common Cuckoo dynamics deterministic model. It is a brood-parasite which lays its egg in the nest of other bird species and use host individuals to raise its young. We present a Common Cuckoo and a host species dynamics deterministic model taking into account a discrete set of offsprings and their care. All individuals have pre-reproductive, reproductive, and post-reproductive age intervals. Individuals of reproductive age are divided into single and those who care of young offsprings. All individuals of pre-reproductive age are divided into young (under maternal care) and juvenile classes. Juveniles can live without maternal care but cannot produce their offsprings. It is assumed that after the death of mother all her young offsprings die. The model consists of integro-partial differential equations subject to the conditions of the integral type. Number of these equations depends on a biologically possible maximal number of eggs laid by a hen of host species in a nest. Separable solutions and numerical results will be discussed.

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Population Dynamics; Friday, July 1, 14:30

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The role of silica defences in driving vole population cycles

As with many small mammals, vole populations are commonly characterized by multi-year cycles of abundance. Uncertainty remains over the mechanisms underpinning these population cycles. One possible factor is the interaction between the voles and their food.

Some grass species mount a delayed defensive response to grazing by increasing their rate of uptake and deposition of silica. This induced response occurs when herbivore populations are high. Elevated silica levels make the grass a lower quality food for herbivores, leading to a reduction in herbivore performance. When grazing impact is lessened, silica defences relax and plant quality recovers. This inducible defence may have an important role in driving cycles in some populations of voles.

We have developed a delay differential equation model to represent this herbivore-plant interaction. This has been parameterized using empirical data from a particular system, namely field voles (Microtus agrestis) and their principal food species, the grass Deschampsia caespitosa, in Kielder Forest in Northern England. I will discuss the predictions of this model, and their implications for the hypothesis that silica defences shape the dynamics of cyclic vole populations.

Cancer; Tuesday, June 28, 17:00

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Evaluation of the antitumor effect of PCV chemotherapy on diffuse low-grade gliomas with a longitudinal tumor growth inhibition model

Objective: To develop a tumor growth inhibition (TGI) model able to describe the evolution of diffuse low-grade gliomas (LGGs) growth dynamics after first-line PCV chemotherapy and to use this model as a theoretical tool to suggest potential improvements of the PCV chemotherapy regimen.

Methods: The model was formulated as systems of ordinary differential equations distinguishing between two cell populations: one proliferative treatment-sensitive cell population and one quiescent treatment-resistant cell population that spontaneously undergoes apoptosis. Model evaluation was performed in a series of 21 patients treated with first-line PCV chemotherapy in which the evolution of the mean tumor diameter had been previously assessed.

Results: Consistent with LGGs biology, the model estimated that LGGs consist mostly of quiescent cells. Despite large inter-individual variability the model correctly predicted individual tumor response profiles in the 21 patients. Unexpectedly, model simulations suggested that the 6 weeks interval between PCV cycles might be suboptimal and that lengthening the time interval between cycles might significantly improve treatment efficacy.

Interpretation: Based on the hypothesis that LGGs consist of proliferative treatment-sensitive cells and quiescent treatment-resistant cells that spontaneously undergo apoptosis we propose a mixed-effect model that accurately describes the evolution of these tumors during and after PCV chemotherapy. Model simulations of different PCV schedules illustrate how this approach could possibly help designing more effective chemotherapy regimens for LGGs.

Multiscale mathematics of liver: bridging molecular systems biology to virtual physiological human scale; Wednesday, June 29, 11:00

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A biphasic Finitee-Element-Model for Sinusoidal Liver Perfusion Remodeling

Liver resection can lead to focal outflow obstruction due to transection of hepatic veins. Outflow obstruction may cause additional damage to the small remnant liver. Drainage of the obstructed territories is reestablished via dilatation of sinusoids. Subsequently sinusoidal canals are formed draining the blood from the obstructed territory to the neighboring unobstructed territories. We raised the phenomenological hypothesis that the blood pressure gradient is the main driving force for the formation of sinusoidal vascular canals. Based on the theory of porous media we generated a biphasic mechanical model to describe this vascular remodeling process in relation to the variable pressure gradient. Therefore, we introduced a transverse isotropic permeability relation as well as an evolutional optimization rule to describe the relationship between pressure gradient and the direction of the sinusoidal blood flow in the fluid phase. As a next step, we developed a framework for the calculation concept including the representation of the governing weak formulations. The governing equations of the model are developed on the basis of a consistent thermo-mechanical approach including the momentum and mass balances of both solid and fluid phases. The mathematical concept describes the motion of the solid phases coupled by the fluid transport due to pressure development. The theoretical formulations are implemented into the finite element code FEAP. Then, we examined a representative numerical example with simulation of the blood flow under both conditions, the physiological situation as well as after outflow obstruction. We based our simulation on the concept of mechanical-induced remodeling. We incorporated the fluid directly into the model as a mixture together with the solid. We hypothesized that the reorientation of the sinusoidal flow and the remodeling of the sinusoidal structure depends mainly on the fluid pressure and the fluid pressure gradient caused by the outflow obstruction. We tested this hypothesis with a numerical simulation and compared the results to the experimental findings. As we did not implement liver resection in the mathematical model presented here, but concentrated on focal outflow obstruction only, liver growth (=regeneration) was not addressed. Doing so, we were able to reproduce numerically the experimentally observed process of reestablishing hepatic venous drainage via redirection of blood flow and formation of new vascular structures in respect to the fluid flow. The calculated results support the hypothesis that the reorientation of blood flow mainly depends on the pressure gradient. Further investigations are needed to determine the micromechanical influences on the reorientation of the sinusoids.

Poster Session; Friday, July 1, 20:00

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Optimal Control of Disease in Multihost System

The majority of the world's pathogens are generalist with approximately 80% of livestock diseases able to transmit between different species [1]. It is therefore essential that any control strategy takes into account the dynamics of this interaction to consider the full impact of the disease. The two species apparent competition model has been widely studied and well understood. Using the methods developed by Greenman and Hoyle [2] this model has been extended to include the interactions of distinct spatial groups. This metapopulation-type approach allows us to consider the impacts of disease spread over a much wider scale and to account for changes in spatial distribution of infected individuals due to control. An increase in ranging behaviour has been observed in the European Badger (*Meles meles*) in response to culling as a method of bovine TB (*Mycobacterium bovis*) control in England [3]. This model may be employed to provide a long term prediction of the effect of badger culling on a large scale and to optimise control strategies to reduce the impact of bovine TB from England.

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Mathematical modeling and simulations of angiogenesis I; Wednesday, June 29, 08:30

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Blood vessel network remodeling during tumor growth

With the help of a theoretical model the process in which a growing tumor transforms a hierarchically organized arterio-venous blood vessel network into a tumor specific vasculature is analyzed. The determinants of this remodeling process involve the morphological and hydrodynamic properties of the initial network, generation of new vessels (sprouting angiogenesis), vessel dilation (circumferential growth), blood flow correlated vessel regression, tumor cell proliferation and death, and the interdependence of these processes via spatio-temporal changes of blood flow parameters, oxygen / nutrient supply and growth factor concentration fields. The emerging tumor vasculature is non-hierarchical and compartmentalized into different zones. It displays a complex geometry with necrotic zones and "hot spots" of increased vascular density and blood flow of varying size. The origin of these hot spots is discussed. The blood vessel network transports drug injections efficiently, but the computation of the interstitial fluid flow shows that most of the drug is quickly washed out from the tumor after extravasation.

Epidemiology, Eco-Epidemiology and Evolution; Saturday, July 2, 11:00

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An epidemic model on computer networks

We study failure spread scenarios in computer/communication networks. A general epidemic model of type *Susceptible-Infected-Disabled* is analyzed and takes into account two levels of failure caused by the attack of a virus or a worm for instance. The first level takes place when the failure can be repaired without disconnecting the node, preserving the connections passing through this node. The second failure level involves that the node must be replaced and, consequently, the connections are dropped.

The dynamic process is given by a Markov chain in continuous time according to the transmission and recovery processes. Several results on both types of steady states, disease-free and endemic, are given and an epidemic threshold is stated. Here the network features are summarized by the largest eigenvalue of the weighted adjacency matrix of the network.

On the other hand, a second model is presented according to the heterogeneous mean-field approach. In this case, the network features are given by both the node degree distribution and the conditional probabilities (i.e. the connections of the neighbours of each node).

We have carried out several stochastic simulations using different network topologies (e.g. *scale-free* generated via Barabási-Albert, *random* generated via Erdős-Rényi, *homogeneous*, ...). Finally, a complete-parameter comparison is performed in order to evaluate the theoretical approaches presented.

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Regulatory Networks; Tuesday, June 28, 17:00

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Tailored graph ensembles as proxies or null models for real networks

There is a great demand, especially in cellular biology, for precise mathematical approaches to studying the observed topology of networks. We generate new tools with which to quantify the macroscopic topological structure of large directed networks, via a statistical mechanical analysis of constrained maximum entropy ensembles of directed random graphs. We look at prescribed joint distributions for in- and out-degrees and prescribed degree-degree correlation functions. We follow the approach pioneered in [1] for undirected networks. Applications of these tools include: comparing networks; distinguishing between meaningful and random structural features; and, defining and generating tailored random graphs as null models. We calculate exact and explicit formulae for the leading orders in the system size of the Shannon entropies and complexities of these ensembles. The results are applied to data on gene regulation networks.

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Epidemics; Tuesday, June 28, 14:30

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Epidemic models with uncertainty

One of the first quantities to be estimated at the start of an epidemic is the basic reproduction number, $\mathcal{R}_0$. The progress of an epidemic is sensitive to the value of $\mathcal{R}_0$, hence we need methods for exploring the consequences of uncertainty in the estimate. I will analyse the Kermack-McKendrick model, and its special case the *SIR* model, by expanding the state variable in orthogonal polynomials in uncertainty space. The resulting dynamical systems need only be solved once to produce a deterministic stochastic solution. The method will be applied to data from the New Zealand epidemic of H1N1 influenza in 2009, to demonstrate the level of uncertainty when making projections based on a limited amount of data.

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Metabolism: Integrating cellular and microenvironmental heterogeneity to drive tumor progression

Clinical and experimental evidence increasingly suggests that cellular and microenvironmental heterogeneity plays a significant role in tumor progression and response to treatment. Zones of hypoxia, acidosis, and necrosis in the tumor and surrounding tissue can exert selection pressure on a dynamic heterogeneous tumor population, driving the emergence of increasingly aggressive phenotypes. Critically, cellular metabolism acts as a key integrator between these cellular and microenvironmental components. In order to understand the complex interplay between these elements, we have developed a hybrid multi-scale mathematical model of tumor growth in a vascularized tissue. Cellular behavior, including proliferation, migration, death and signaling, are driven by microenvironmental conditions, mediated through cellular metabolism. A range of tumor phenotypes emerges due to selection by the heterogeneous microenvironment. The response of a tumor to treatment depends on the presence of different tumor phenotypes, as well as the local conditions. By tracking the multiple routes of tumor progression, we use the model to predict optimal treatment strategies that can block the most malignant routes.

Undergraduate Biomathematics Education Beyond BIO 2010 (Part I);
Wednesday, June 29, 14:30

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Modeling of the Growth Hormone Network

Hormone secretion patterns are determined by the frequency of secretion events, the amount secreted, and the length of time the secretion event lasts. They encode messages for the target cells that control vital physiological processes, and an alteration of a secretion pattern may impede one or more of these processes. Understanding hormone secretion and developing the capability to recognize both normal and pathological patterns of hormone production is of utmost importance for establishing medical diagnoses, initiating treatment, and assessing the effects of treatment. It is generally impossible to collect data directly from the endocrine glands, where the hormones are secreted. Secretion patterns have to be inferred from hormone concentration in the blood where distortions, due to binding, excretion and/or biotransformation, begin immediately after the hormones enter the bloodstream. Thus, mathematical models of the hormone network interactions and control mechanisms play a critical role in the understanding of endocrine osciallations. The talk will outline a model of the growth hormone network and a related undergraduate project appropriate for use in calculus-based courses.

Bridging Time Scales in Biological Sciences; Saturday, July 2, 14:30

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Rare events in chemical reaction systems

Chemical kinetics can usually be described by a deterministic system of ordinary differential equations. However, when the concentrations of certain species become small, stochastic fluctuations play an important role, which can be modeled by the chemical master equation (CME). For some systems, the steady state solution of the CME is a multimodal distribution with small transition rates (rare events), a situation comparable to metastable molecular conformations. In this talk we will present a mesh-free discrete Galerkin method for the solution of the CME, which allows for an efficient computation of transition rates. In particular, we will discuss the future potential of this method for the simulation of endocrinological networks.

Cancer; Tuesday, June 28, 14:30

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Response to anti-angiogenic therapy in human brain tumors: the role of the microenvironment and heterogeneity

Background: Gliomas are diffuse and invasive primary brain tumors that are notoriously difficult to treat and uniformly fatal. Angiogenesis is the process of neovascularization and is a hall mark of glioblastoma, which are considered amongst the most angiogenic of tumors. This suggests that interactions between glioma cells and the cascade of biological events leading to tumor-induced neoangiogenesis play an important role in aggressive tumor formation and progression.

Anti-angiogenic therapies have been used in the treatment of gliomas with spurious results ranging from no apparent response to significant imaging improvement with extremely diffuse patterns of tumor recurrence. The clinical task of assessing a patients response to brain tumor therapy is difficult, and the topic of much current debate. Paradoxically, anti-angiogenic therapies likely increase the efficiency of tumor vasculature through normalization, leading to a resolution of abnormality on imaging, while at the same time increasing the tumors invasive phenotype and actually promote rather than hinder tumor growth. As a result, response to anti-angiogenic therapies is inadequately assessed by current imaging techniques but may be interpretable by multi-modality approaches combined with mathematical modeling.

Methods: Much of the difficulty in improving the outcomes of patients with gliomas lies with the extensive invasive potential and incredible phenotypic heterogeneity of these tumors. To quantitatively explore these tumor-microenvironment interactions, we extend our previous experience with biologically-based mathematical models for glioma growth and invasion to explicitly incorporate the interactions of normoxic glioma cells, hypoxic glioma cells, vascular endothelial cells, diffusible angiogenic factors and the formation of necrosis, hallmarks of the histological diagnosis of glioma and investigate the role and effects of anti-angiogenic therapies in silico.

Results: Using in silico experimentation, we find that anti-angiogenic therapies drastically decrease the hypoxic phenotype and promote the invasive phenotype. However, the degree and characterization of response to anti-angiogenic therapies depends on the relative extent of invasion and proliferation of the tumor, and can

vary from one patient to the next. Moreover, these effects vary across histologic grades and may promote malignant progression from low to higher grades. These results suggest that a combination of therapies must be used if anti-angiogenic therapies are to be effective in human gliomas.

Modelling dengue fever epidemiology; Saturday, July 2, 08:30

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Simulation of a dengue vaccine

Dengue is a vector-borne disease. It is nowadays endemic in more than one hundred countries, predominantly in tropical and subtropical areas. Up to the moment, the effectiveness of the programs for vector control is low and, unfortunately, there is no specific effective treatment for dengue. For recent mathematical investigations on the subject, we refer to [**1, 2**] and references therein.

There are no commercially available dengue clinical cures or vaccine, but efforts are underway to develop one [**3**]. So far, the difficulties in elaborating a vaccine stemmed from the fact that the vaccine must protect simultaneously against the four serotypes of dengue. This is a difficult but crucial constraint, because protection against only one or two dengue viruses could actually increase the risk of Dengue Haemorrhagic Fever. The population effect of a vaccination programme may be thought of as the collective impact of individual vaccination on the transmission of infection in that population. While direct individual protection is the major focus of mass vaccination programmes, population effects also contribute indirectly to individual protection through herd immunity, providing protection for unprotected individuals.

We present a SVIR-ASI epidemiological model for the human and mosquito populations, respectively. It is considered an imperfect vaccine, where a proportion of population is vaccinated. Some simulations, with different levels of vaccine efficacy, are studied. It is shown that the efficacy of the vaccine has a preponderant role in the reduction of the spread of the disease.

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Cancer; Friday, July 1, 14:30

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Mathematical model of lymphoma as a failure in maintanance of naïve T cell repertoire

We introduce a stochastic model of lymphoma based on the model of the competitive exclusion between different clonotypes in the maintenance of the naïve T cell repertoire [1,2]. Two clonotypes of T cells compete with each other and with other clonotypes for survival stimuli provided by professional cells (APCs) [3,4]. We assume that one of the clonotypes is normal and the other is tumorous. We model the competition as a continuous-time bivariate Markov process [5]. To model the evolution of the tumorous clonotype we introduce an augmented rate of influx of new naïve T cells, descendants of mutated stem cells, from the thymus. We obtain a deterministic approximation to the stochastic model using Van Kampen's large N expansion technique [6] and analyse four cases of competition between the two clonotypes of T cells, both analitically and numerically.

We obtain two possible scenarios, depending on the values of parameters: either both clonotypes survive in the repertoire or the clonotype of the normal T cells becomes extinct, meanwhile the clonotype of the tumorous T cells is maintained, after achieving some maximum level of growth. We show that if the income of the new T cells from the thymus is augmented, then the tumorous clonotype, which is very competitive, would never be removed from the repertoire; meanwhile the normal clonotype could become extinct if it was not specialized enough to compete effectively for survival stimuli. This result supports the hypothesis of mutated stem cells as the origin of cancer, in particular lymphoma. Any of these cells might initiate an outbreak of the illness, so as long as we do not entirely get rid of all the mutated stem cells, we can not successfully defeat lymphoma.

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Modelling the impact of helminth parasite on rock partridge population dynamics

The aim of this work was to explore the effect of helminth parasites on rock partridge (*Alectoris graeca saxatilis*) population dynamics in the Dolomitic Alps (northern Italy). Specifically, we investigated the hypothesis that the nematode parasite *Ascaridia compar* can drive population cycles in rock partridge dynamics. In order to support this hypothesis, we compared the predictions obtained from a host-macroparasite interaction model with multi-annual empirical data of *A. compar* infection in natural host populations. We estimated host demographic parameters from rock partridge census data, and the parasitological parameters from a series of experimental infections in a rock partridge captive population. Our model predicts higher levels of *A. compar* infestation for rock partridge population with a cyclic dynamics respect to those with a non-cyclic dynamics. In addition, for populations exhibiting cyclic dynamics, the model predicts a positive correlation between the mean parasite burden and the length of cycle period. Model predictions are well-supported by field data; in fact, a significant differences in parasite infection between cyclic and non cyclic populations and within cyclic populations with different oscillation periods were observed. On the basis of these results, we conclude that helminth parasites can be a possible driver for rock partridge population dynamics and must be considered when planning conservation strategies of this threatened species.

Plants, growth and transport processes I; Tuesday, June 28, 11:00

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Plant gas exchange: Theoretical considerations on the level of single stomata

Plant gas exchange: Theoretical considerations on the level of single stomata Land plants require gas exchange between leaf interior and atmosphere to obtain sufficient amounts of CO2 for photosynthesis. Stomata, micropores on the leaf surface, are the gateways for plant gas exchange. The stomatal pore is formed by two guard cells whose shape change (caused by changing turgor) controls the aperture width. This in turn controls stomatal conductance. Tight control of stomatal conductance is necessary since diffusional CO2 influx through open stomata is accompanied by water vapour loss (= transpiration). Besides stomatal pore area that is controlled by the guard cells, the actual stomatal conductance is dependent on various other anatomical traits, such as stomatal density and depth and shape of the stomatal pore [1, 2].

The entire diffusion pathway is, however, more complex in reality. In most cases, it is still unclear where evaporation inside the leaf occurs. If cutinization does not reach beyond the stomatal channel, i.e. if internal cuticles are absent, then evaporation should occur close to the stomata [3, 4]. If internal cuticles are present, evaporating sites are seated more deeply within the leaves. Shifting evaporation deeper into the mesophyll by cutinization beyond the stomatal channel can lead to a substantial decrease in stomatal conductance for water vapour (with all other parameters constant) [4].

Details of leaf internal diffusion of water vapour and CO2 are of interest, due to different aspects. For example, measurement of stomatal conductance for water vapour is used also for analyses of photosynthesis, implicitly assuming that diffusion pathways of CO2 and water vapour are mostly identical. In ecophysiology, various modifications of stomata are ascribed to adaptations to environmental conditions. For example, arrangement of stomata in stomatal crypts, that are depressions of the leaf surface in which stomata are seated, should restrict water loss. It is, however, questionable whether this really happens, or if other functional benefits may linked to these kind of structures. Furthermore, variations in stomatal structure and/or arrangement add more parameters to the stomatal pathway, thereby altering the contribution of the controllable stomatal channel to overall conductance.

As a whole, important details of stomatal diffusion are still not well understood. Analyzing gas diffusion on the level of single stomata, and within the mesophyll, can contribute substantial information to various topics in ecophysiology and plant physiology.

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Poster Session; Friday, July 1, 20:00

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Unravelling the transmission dynamics of streptococcus pneumoniae with approximate bayesian computation

Approximate Bayesian computation (ABC) provides an appealing method for connecting stochastic models to observed data. With the help of ABC, it is possible to distinguish probabilistically, given the data, between different model candidates, and finally learn the distributions of model parameters. Furthermore, having posterior distributions for models and model parameters, one can calculate posterior means, and perform prediction.

Streprococcus pneumoniae is a bacteria colonizing especially children. After introduction of vaccine against the most common strains, what has been observed is a fast serotype replacement, after which the prevalence of streptococcus pneumonia strains in general remains unchanged. Large carriage studies from children were conducted during these years. To understand the transmission dynamics of streprococcus pneumonia, as well as the observed diversity and fast serotype replacement, we aim to conduct ABC model selection and parameter learning. This could help to say whether there exists fittness differences between different strains, and what the ultimate effects of vaccination will be.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits I; Wednesday, June 29, 14:30

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Periodicity, spatial correlations, and waves in a probabilistic lattice model of the cardiac cell.

Cardiac cells have a surprisingly complex internal architecture, and dynamic instabilities of the calcium signaling within them may lead to ventricular fibrillation, the leading cause of sudden cardiac death. We study a system of locally-coupled stochastically-excitable elements in a 2D automata lattice that replicates physiological features of the cardiac cell, including threshold excitation, refractory period, global periodic forcing signal, and spatial nearest-neighbor interactions. We first derive a simple mean-field difference equation which models the expected excitation rate at each beat, and find conditions under which it can undergo a bifurcation to period-2 behavior (mimicking the pathological condition known as "alternans"). Using a local structure approximation to account for pairwise (and higher-order) correlation, we show these conditions are dependent on the nature of the neighbor-to-neighbor coupling, as well as the geometry of the cell itself. We finally consider the continuous-time case, which allows for cascading spatial interactions, resulting in the formation of excitation waves.

Poster Session; Friday, July 1, 20:00

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Identification and continuity of the distributions of burst-length and inter-spike-intervals in the stochastic Morris-Lecar neuron

Using the Morris-Lecar model neuron with a type II parameter set and K+ channel noise, we investigate the inter-spike interval distribution as increasing levels of applied current drive the model through a sub-critical Hopf bifurcation. Our goal was to provide a quantitative description of the distributions associated with spiking as a function of applied current. The model generates bursty spiking behavior with sequences of random numbers of spikes (bursts) separated by inter-burst intervals of random length. This kind of spiking behavior is found in many places in the nervous system, most notably, perhaps, in stuttering inhibitory interneurons in cortex. Here we show several practical and inviting aspects of this model, combining analysis of the stochastic dynamics of the model with estimation based on simulations. We show that the parameter of the exponential tail of the ISI distribution is in fact continuous over the entire range of plausible applied current, regardless of the bifurcations in the phase-portrait of the model. Further, we show that the spike sequence length, apparently studied for the first time here, has a geometric distribution whose associated parameter is continuous as a function of applied current over the entire input range. Hence this model is applicable over a much wider range of applied current than has been thought.

Poster Session; Friday, July 1, 20:00

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Extraction and detection of freshwater mussels behaviours, using wavelets and kernel methods

Some species of mussels are well-known bioindicators and may be used to create a Biological Early Warning System. Such systems use long-term observations of mussels activity for monitoring purposes. Yet, many of these systems are based on statistical methods and do not use all the potential that stays behind the data derived from the observations. In the paper we propose an algorithm based on wavelets and kernel methods to detect behaviour events in the collected data. It consists of raw data obtaining, pre-processing and feature extraction. In the pre-processing step, a high-pass filters and white de-noising were used. During the recognition of events wavelet packet was applied and then the data was averaged by kernel method. Our motivation was to highlight the multiple time scale properties and to exam the possible connections between behaviour of zebra mussel and water state. Results show that pollution could be characterized by the biological signal generated by *Dreissena polymorpha*. Our study also showed that wavelet transforms could be powerful methods for probing the dynamical relationship between the signal and environment variability.

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Neurosciences; Thursday, June 30, 11:30

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On the Interspike Times of two Coupled Neurons

Stochastic Leaky Integrate and Fire models describe the evolution of the membrane potential $\{X_t\}_{t\geq 0}$ through the Stein equation

$$\begin{cases} dX_t = -\frac{X_t}{\tau}dt + adN_t^+ + idN_t^- \\ X_0 = x_0 \end{cases}.$$

Here, $a > 0, i < 0$ are constants representing excitatory and inhibitory inputs, τ is the membrane time constant and x_0 is the resting potential. Furthermore, $\left\{N_t^+\right\}$ and $\left\{N_t^-\right\}$ are two independent Poisson processes of rates $\lambda > 0$ and $\beta > 0$, respectively. The release of a spike corresponds to the first time when the membrane potential attains a threshold value $S > x_0$. After a spike, the membrane potential is reset to its resting value and the process restarts its evolution until a time t_{max}. The Interspike Intervals (ISI) are modeled through the random variables $T = \inf\{t : X_t > S\}$. In the seventies, the difficulty of the first passage time problem for the Stein process has motivated the introduction of diffusion limits for its equation. As result, an Ornstein-Uhlenbeck process is obtained. It models the sub-threshold membrane potential dynamics and it has developed the study of the input-output relationships of a single neuron.

However, one should consider two or more dependent neurons to study the transmission on information in a network. Here, we extend the Stein process to the case of k neurons, modeling its spiking activity. For this aim, we prove the convergence of a k-dimensional Stein process to a k-dimensional Ornstein-Uhlenbeck one. We also prove the weak convergence of their ISIs.

In the two dimensional case, we numerically determine the joint distribution of the ISIs of the two neurons. Finally, we illustrate some results on the dependencies of these times.

Reports from US - African BioMathematics Initiative: Conservation Biology; Saturday, July 2, 14:30

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Looking to the future: how to progress to success from the US-Africa Biomathematics Initiative

In this session, we have heard reports from the US-Africa Biomathematics Initiative's two Advanced Studies Institutes (ASIs) for Conservation Biology. The question remains, what happens next? The original goals of the initiative were to bring together US and African students to examine questions in conservation biology in Africa, using a combination of mathematical and biological approaches. This goal has been achieved and has produced results beyond original expectations. In this talk, we will address how to progress from here: the process of publication, the potential for future work, communicating results back to conservation biologists. We will also discuss how participants will take this experience back to their home institutions, and avenues for sharing the benefits of the experience. We hope that this will enable us all to distill important lessons in both collaboration and higher education pedagogical and communication abilities.

Bioinformatics and System Biology; Wednesday, June 29, 11:00

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Close order in triplet composition in genomes

We studied a two-particle distribution function $l(\omega_1, \omega_2)$ of a distance defined in the number of nucleotides between two given triplets $\omega_1 = \nu_1\nu_2\nu_3$ and $\omega_2 = \mu_1\mu_2\mu_3$. For each entry of a given triplet ω_1 the distance to the nearest given triplet ω_2 has been determined, thus revealing the distribution function $l(\omega_1, \omega_2)$ of the couples of triplets in a genetic entity. The function is defined in rather multi-dimensional space ($64^2 = 4096$) that makes the problems of its analysis and visualization rather acute.

The distribution function $l(\omega_1, \omega_2)$ was found to be rather complex; it has several maxima, and the number and location (relative distance) of those maxima are specific, for various couples of triplets. For yeast genome of *Pichia stipitis* CBS 6054, typical number of maxima was equal to three, for any chromosome. Intra-genomic variation of the shape of $l(\omega_1, \omega_2)$ is rather significant; at least, different chromosomes have indistinctively discrete types of the function.

Special attention has been paid to the couples of triplets that make so called complementary palindrome. That latter is a couple of triplets read equally in opposite directions with respect to the complimentary rule substitution, say, ATG $\leftrightarrow$ CAT of GCA $\leftrightarrow$ TGC. Such triplets (and longer strings) are well known for a kind of symmetry in genomes: the frequency of each string in a complementary palindrome is pretty close each other. Information charge of the triplets composing a complimentary palindrome is another important issue, for the analysis of the close order in genomes. This former is a ratio of real frequency $f_{\nu_1\nu_2\nu_3}$ to the mostly expected one $\widetilde{f}_{\nu_1\nu_2\nu_3}$, which is defined as

$$\widetilde{f}_{\nu_1\nu_2\nu_3} = \frac{f_{\nu_1\nu_2} \times f_{\nu_2\nu_3}}{f_{\nu_2}} .$$

Information charge $p_{\nu_1\nu_2\nu_3}$ is more sensitive to the biological peculiarities of the genetic entity under consideration.

We have examined more than 20 genomes with as many sequences, as one hundred. All the investigated genetic entities exhibit the close order of triplet composition. The pattern of the order was different for the different species (and higher taxa). Moreover, even an intra-genetic variability of the patterns was high enough to put on the problem of the comprehensive analysis of the pattern itself.

To verify the patterns observed at the real genetic entities, we have carried out several computational experiments. We have generated a surrogate random non-correlated sequence with the same frequencies of nucleotides and the same length, and developed similar patterns to figure out the deviation in the patterns observed over a real sequence from similar observed over a surrogate. Significant difference has been detected.

Some biological issues of the observed order are discussed. The work is a part of a greater project of a study of the distribution of longer strings with increased information charge alongside a genome.

Immunology; Wednesday, June 29, 17:00

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T cell anergy as a strategy to reduce the risk of autoimmunity

Some self-reactive immature T cells escape negative selection in the thymus and may cause autoimmune diseases later. In the periphery, if T cells are stimulated insufficiently by peptide-major histocompatibility complex, they become inactive and their production of cytokines changes, a phenomenon called "T cell anergy". We explore the hypothesis that T cell anergy may function to reduce the risk of autoimmunity. The underlying logic is as follows: Since those self-reactive T cells that receive strong stimuli from self-antigens are eliminated in the thymus, T cells that receive strong stimuli in the periphery are likely to be non-self-reactive. As a consequence, when a T cell receives a weak stimulus, the likelihood that the cell is self-reactive is higher than in the case that it receives a strong stimulus. Therefore, inactivation of the T cell may reduce the danger of autoimmunity. We consider the formalism in which each T cell chooses its response depending on the strength of stimuli in order to reduce the risk of autoimmune diseases while maintaining its ability to attack non-self-antigens effectively. The numerical calculation reveals that T cell anergy is the optimal response when a T cell meets with antigen-presenting cells many times in its lifetime, and when the product of the autoimmunity risk and the number of self-reactive T cells has an intermediate value.

Epidemics; Wednesday, June 29, 08:30

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Quantifying transmission of high- and low-pathogenicity H7N1 avian influenza in turkeys

Outbreaks of avian influenza in poultry can be devastating, and yet many of the basic parameters have not been accurately characterised. In 1999-2000 in Northern Italy, outbreaks of H7N1 low-pathogenicity avian influenza virus (LPAI) preceded the emergence of H7N1 high-pathogenicity avian influenza virus (HPAI). This study investigates the transmission dynamics in turkeys of representative HPAI and LPAI H7N1 virus strains from this outbreak in an experimental setting, allowing direct comparison of the two strains. The fi

tted transmission rates for the two strains are similar: 2.04 (1.5-2.7) for HPAI, 2.01 (1.6-2.5) for LPAI. However, the mean infections period is far shorter for HPAI, due to the rapid death of infected turkeys: 1.48 (1.3-1.7) days for HPAI, 7.65 (7.0-8.4) days for LPAI. Hence the basic reproductive ratio, R0 is significantly lower for HPAI than for LPAI: 3.01 (2.2-4.0) for HPAI, 15.37 (11.8-19.8) for LPAI. To be able to extrapolate experimental results from relatively small numbers of birds to the commercial poultry flock size, two competing hypotheses for how transmission rates vary with population size were investigated. Frequency-dependent transmission was determined to give a better

fit to data from experiments with varying number of birds.

Cellular Systems Biology; Tuesday, June 28, 14:30

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Biochemical reaction networks meet Coalitional Game Theory: The importance of not being single

A fundamental question in the analysis of complex biological networks is how to determine which components (e.g. reactions) are most important regarding specific function. Virtually all existing approaches for establishing the importance of a reaction in a biological network are based on vitality-like indices. The importance of a reaction is then specified by the effect of its removal, emulating single knockout experiments in biology. However, such technique neglects topological features, like bypassing pathways, which are crucial for network robustness. Coalitional game theory provides a framework for extending the vitality-like indices by considering the contribution of single network elements with respect to all of its interactions in the network, based purely on the network topology. Here we propose a method combining cooperative game theory with flux balance analysis, a standard technique in the investigation of metabolic networks. We employ the method to rank reactions in metabolic networks with respect to a biologic function, in particular biomass production. Furthermore, our method is used in the design of a novel approach for determining network robustness to changes imposed by gene knock-outs.

Mechanics of the cytoskeleton and cortical actin at the cellular level;
Saturday, July 2, 08:30

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Role of the polar actin cortex in cytokinesis

During cytokinesis, the process of physical separation of the cell into two daughter cells, actin filaments accumulate at the cleavage furrow, producing the force for the equatorial constriction. A cortical network is however also present at the membrane of the two cellular poles. The actin network is dynamically polymerized and depolymerized, and myosin molecular motors generate internal stresses in the layer, putting the cortex under tension. Here we show that for a sufficiently large value of the polar cortical tension, the symmetric shape of the dividing cell is theoretically unstable, and oscillations of the volume of the cellular poles are expected to occur for a sufficiently slow actin turnover rate. Such oscillations of dividing cells are experimentally observed and are well described by the theoretical framework we propose.

Statistical methods in computational neuroscience II; Wednesday, June 29, 17:00

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Parameter estimation of the stochastic Morris-Lecar model with particle filter methods

Stochastic Morris Lecar model is a well-known two-dimensional stochastic differential equation (SDE) describing neuronal activity by taking into account the random behavior of neurons. Drift and volatility functions of this SDE are non-linear functions of the process and depend on unknown physiological parameters. Statistical estimation of these parameters from neuronal data is very difficult. Indeed, neuronal measurements correspond to discrete observations of only the first coordinate of the system. Furthermore, the SDE has no explicit solution. We propose an estimation method based on a stochastic version of the EM algorithm, the SAEM algorithm, which requires the simulation of the hidden coordinate conditionally to the observations. We propose to perform this simulation step with a Particle Markov Chain Monte Carlo algorithm. We illustrate the performance of our estimation method on simulated and real data.

Poster Session; Friday, July 1, 20:00

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LC-Elliptical Fourier Analysis for quantitative Pavement Cell shape analysis

Although considerable progress has been made in identifying genes that control cell polarity, it is still unclear how they work together to generate cells with particular shapes. Indeed, we have limited understanding on how multicellular dynamics and patterning is linked to cell shape and how cell shape in turn influences intracellular dynamics.

The complex pattern of lobes and indentations of Pavement Cells in the epidermis of the leaf of Arabidopsis thaliana offers an ideal system to address this problem. To quantify cell shape changes in a growing leaf is extremely important to gain insight on the time scale involved in cell morphogenesis and cell polarity coordination. Moreover, how the dynamics of cell morphogenesis is regulated and influenced by the position of the leaf and leaf developmental stage has remained elusive.

Quantitative methods for shape analysis are essential to assess the influence of cell shape on cell intracellular dynamics and to analyse the polarity effects of a given mutation or treatment. We propose a new method to quantify cell shape changes based on Elliptical Fourier Analysis(EFA). Our new method called Lobe-Contribution EFA provide a measurement that directly relates to morphological periodicities and provide a good separation of cells according with their degree of lobbing in analysis of populations of cell after a Principal Component Analysis.

Population Dynamics; Tuesday, June 28, 14:30

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Exponential growth and extinction in age structured populations incorporating environmental stochasticity

We study different strategies to ascertain growth or extinction in Leslie type matrix models for age structured populations subjected to environmental stochasticity [1]. We think of a population described at time n by vector $\mathbf{X}_n = (x_n^1, ..., x_n^N)^T$ and living in an ambient in which there are s different environmental states. The vital rates corresponding to each one of these environments are given by the Leslie matrices $\mathbf{L}_\alpha \in \mathbb{R}^{N\times N}$, $\alpha = 1, ..., s$ in such a way that, for each α, $\mathbf{L}_\alpha$ contains the fertility and survival rates of the population in environment α. The environmental variation is characterized by a sequence of random variables τ_n, that we will consider to be an irreducible and aperiodic Markov chain, with state space $\{1, ..., s\}$ in such a way that τ_{n+1} describes for the environmental condition for the system between times n and $n+1$. Thus, the model reads

$$\mathbf{X}_{n+1} = \mathbf{L}_{\tau_{n+1}} \mathbf{X}_n \tag{1}$$

where $\mathbf{X}_0 \geq \mathbf{0}$ is a fixed (non random) non-zero vector. Moreover, we assume that the set of matrices of vital rates meets a certain technical condition (ergodic set).

The most important parameter concerning the behavior of (1) is the so called stochastic growth rate (s.g.r.) defined as $a := \lim_{n\to\infty} \log \|\mathbf{X}_n\| / n$, with probability one [2]. Therefore, $a > 0$ implies that every realization grows asymptotically with rate e^a, and $a < 0$ implies that the population goes extinct with probability one. However, even in very simple situations, it is not possible to calculate a analytically. In order to find a useful way to study these models, the so called "lognormal approximation" has been proposed [2]. It consists in assuming that the distribution of population size has a lognormal distribution. In this way an approximate s.g.r. $\hat{a}$ can be defined. The validity of this approximation has only been tested numerically and in very specific situations [3]. Moreover, in principle the approximation does not allow one to calculate $\hat{a}$ analytically.

In the first place, this work examines both numerically and theoretically, the validity of the lognormal approximation, finding the range of situations in which it can be considered that it works well. Moreover, we build different bounds for a and for $\hat{a}$, and analyze the conditions under which each bound works best. This is used to give necessary-sufficient conditions for the explosion and the extinction of the population. The results are applied to the case of a population structured in juveniles and adults living in an ambient with a "good" and a "bad" environment.

References.

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Ecology and evolution of infectious diseases; Friday, July 1, 14:30

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Resistance threshold in spatially explicit epidemic model: Finite size scaling applied to dynamic percolation in epidemic processes with mixed cultivar planting

We examine the fraction of resistant cultivars necessary to prevent a global pathogen outbreak (the resistance threshold) using a spatially explicit epidemiological model (SIR model) in a finite, two-dimensional, lattice-structured host population[1]. Threshold behaviour of this spatially explicit SIR model cannot be reduced to that of bond percolation, as was previously noted in the literature, unless extremely unrealistic assumptions are imposed on infection process. The resistance threshold is significantly lower than that of conventional mean-field epidemic models, and is even lower if the spatial configuration of resistant and susceptible crops are negatively correlated. Finite size scaling applied to the resistance threshold reveals that its difference from static percolation threshold (0.41) is inversely proportional to the basic reproductive ratio of pathogen. Estimated value, 4.7, of critical basic reproductive ratio in a universally susceptible population is much larger than the corresponding critical value (1) in the mean-field model and nearly three times larger than that of SIS model.

References.

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Evolutionary Ecology; Wednesday, June 29, 08:30

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A computational model of plant life cycle: genetic mechanism of local adaptation in flowering time

The timing of the transition from vegetative to reproductive development is a critical adaptive trait as it is essential for plants to complete seed production in favorable conditions. Proposed in A. thaliana, the gene regulatory model of floral transition describes the complex interactions between environmental signals (e.g., photoperiod and temperature) and endogenous cues (e.g., size, leaf number, or age). I modeled the interaction between photoperiod and vernalization (low-temperature) pathways, and combined this gene regulation dynamics and growth dynamics in a genetic-physiological model to explore local adaptation to two different environments (Hyogo; the western part of central Honshu, and Hakodate; the southern part of the north island in Japan). Temperature is warmer and seasonal variations in daylength are smaller in Hyogo than Hakodate. For simplicity, I assumed long-day plants that are self-compatible and evergreen. The analysis of the model demonstrated that there is a clear difference in sensitivity to daylength between the two plant populations. It was predicted that a Hakodate population responds to more extreme critical daylength than the one in Hyogo, which enables the plant flower in appropriate season in mid spring in Hakodate. I discuss the validity of the theoretical prediction using the data of Arabidopsis halleri.

Population Dynamics; Tuesday, June 28, 17:00

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Swimming Patterns Of Zoospores

Oomycetes are a group of pathogens that cause many destructive diseases in animals and plants. One species in particular, Phytophthora Infestans, is perhaps the most well known and is responsible for the potato blight disease. This causes severe economic damage estimated at 3 billion per annum. The epidemic spread of the disease is primarily based on rapid dispersal from host to host by free-swimming zoospore cells. These are single-nucleated, wall-less cells that are released only into aqueous environments. Zoospores exhibit a variety of tactic responses to their environment to locate suitable infection sites. We have begun to model this process using a PDE chemotaxis model of Keller-Segel type and in this talk we show that this approach captures some general behaviour seen in experiments. We will also discuss the existence of solutions to these equations and the metastability of such solutions.

Bioengineering; Tuesday, June 28, 14:30

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The anisotropic Bidomain model of electrocardiology: a comparison of coupled and uncoupled parallel preconditioners

The anisotropic Bidomain model describes the bioelectric activity of the cardiac tissue and consists of a system of a parabolic non-linear partial differential equation (PDE) and an elliptic linear PDE. The PDEs are coupled with a system of ordinary differential equations (ODEs), modeling the cellular membrane ionic currents. The discretization of the Bidomain model in three-dimensional (3D) ventricular geometries of realistic size yields the solution of large scale and ill-conditioned linear systems at each time step. The aim of this work is to construct and study parallel multilevel and block preconditioners, in order to strongly reduce the high computational costs of the Bidomain model, allowing the simulation of the whole heart beat in 3D realistic domains. We analyze the scalability of multilevel Schwarz block-diagonal and block-factorized preconditioners for the Bidomain model and compare them with multilevel Schwarz coupled preconditioners. 3D parallel numerical tests show that block preconditioners are scalable, but less efficient than the coupled preconditioners. Finally, we present simulations of the cardiac *virtual electrode* phenomenon, yielding anode make and break mechanisms of excitation, using the developed parallel solver.

Crowd Dynamics: Modeling, Analysis and Simulation (Part 2); Wednesday, June 29, 14:30

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Modeling of pedestrian dynamics – Cellular automata models

In the talk we first give a classification of the different modelling approaches that have been used to describe pedestrian flows and crowd dynamics. The merits and problems of these approaches are discussed [**1, 2**].

Then we focus on cellular automata models. This model class has successfully been applied to a variety of complex systems [**2**]. One main advantage of this approach is its computional efficiency. Large crowds can be simulated faster than real-time. The floor field model [**3, 4, 5, 6**] is introduced which allows to reproduce the empirically observed collective phenomena like lane formation. The interactions between the pedestrians are implemented in the form of virtual chemotaxis [**6**]. Several extensions of the model are discussed which improve its realism in certain situations. We also present a calibration of the model using empirical data from laboratory experiments and an application to the evacuation of a football stadium.

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Analysis of mathematical models for cancer growth and treatment, Part V; Wednesday, June 29, 11:00

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Optimal protocols for chemo- and immunotherapy in a mathematical model of tumor-immune interactions

In this talk, a classical model for the interactions between tumor and the immune system under treatment is considered as an optimal control problem with multiple controls representing actions of cytotoxic drugs as well as of agents that give a boost to the immune system. In the objective, a weighted average of several quantities that describe the effectiveness of treatment is minimized. These terms include (i) the number of cancer cells at the terminal time, (ii) a measure for the immunocompetent cell densities at the terminal point (included as a negative term), (iii) a measure for the side effects and cost of treatment in form of the overall amount of agents given and (iv) a small penalty on the terminal time that limits the overall therapy horizon which is assumed to be free. This last term is essential in obtaining a well-posed problem formulation. The form of the objective is motivated by the dynamics of the system without treatment and models the goal to move the state of the system from a region of malignant cancer growth into a benign region. Employing a Gompertzian growth model for the cancer cells, for various scenarios optimal controls and their corresponding system responses are calculated. Both the cases of mono- and combination therapies will be considered.

Poster Session; Friday, July 1, 20:00

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New developments in the diurnal changes of nitrogen metabolism in *Chlamydomonas reinhardtii*

The capability of plants to assimilate nitrogen plays a crucial role in optimising biomass production. This is of particular interest for maximising crop yields as well as for detoxifying stressed soils.

The green algae *Chlamydomonas reinhardtii* renders a suitable model organism, as it is rather easily accessible compared to higher plants and shows circadian oscillations, which are involved in many metabolic and physiological processes [1]. Furthermore, new findings reveal that several RNAs are alternatively spliced in the green algae [2]. We demonstrate that stoichiometric data are sufficient to provide valuable insight into the nature of the nitrogen uptake system. This is achieved by considering different carbon sources, environmental conditions, the repressive behaviour of the circadian regulated mRNA-binding protein CHLAMY1 [3] and the application of Elementary Flux Mode analysis [4]. We retrieved the most efficient fluxes in regard to the biosynthesis of amino acids that show a high nitrogen to carbon ratio. Moreover, we provide clues for the role of CHLAMY1 in the regulation of nitrogen uptake and show a reasonable time course of nitrogen incorporation throughout the day.

An investigation of the overall distribution of amino acids in *C. reinhardtii* reveals a rather high abundance of simple amino acids in the green algae. Thus, we included these amino acids into our metabolic pathway analysis as they constitute a potential alternative nitrogen deposit.

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Model selection of networks that are robust against kinetic uncertainties

Gene regulatory networks are driving major biological processes, such as cell differentiation. Dynamical models can often be built on a small number of key regulators, but are usually hampered by the lack of quantitative knowledge about the detailed interaction kinetics. Thus, it is desirable to deduce certain system properties already from the qualitative interaction structure.

This study aims at selecting prototypes of minimalistic three-node network motifs, that can serve as a genetic switch model driving cell differentiation. As a selection criterion, we demand that a candidate model must be able to produce the biologically observed three cell states: a progenitor, and two differentiated cell types. The goal is to find necessary conditions on the interaction structure such that a network exhibits the required stable steady states, and to classify the robustness of this capability. For this model selection, we employ a qualitative modeling framework based on ordinary differential equations, but requiring only few qualitative assumptions on the genetic interactions. The robustness of a model is defined as the maximum perturbation on the interaction functions under which the model criteria are still fulfilled, and thus measures the validity of the model if only qualitative knowledge is available.

In particular, we focus on the role of the operator combining the interactions acting on the same node: These can be connected in an OR-fashion (i.e. ingoing activators and inhibitors act independently of each other), or in an AND-fashion (resulting e.g. from complex formations at gene promoters). We show that neither the OR-networks selected as models for the system are a subset of the AND-networks selected as models, nor vice versa; but among them are networks that meet the selection criteria for OR- as well as for AND-kinetics. This nonempty set of models can be regarded as robust not only against quantitative uncertainties, but also against uncertain knowledge about the exact interaction conjunctions. Furthermore, the network connectivity is directly correlated to the robustness of the network capability to meet the model selection criteria. In conclusion, for some specific interaction networks it may be uncritical whether they are modeled with OR- or AND-interaction kinetics, but also in many cases only one of the two options can successfully result in a model that reproduces the system properties.

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The Role of Cell-Cell and Cell-Matrix Adhesion in Cancer Cell Invasion: A Multiscale Individual-Based Modelling Approach

The malignancy of almost all types of solid tumours is determined by the ability of cancer cells to invade the surrounding tissues and then to form secondary tumours (metastases) at distant sites in the body. These metastases are responsible for 90% of cancer deaths. In order to advance and improve cancer treatment strategies, it is therefore of high importance to understand the processes involved in cancer cell invasion.We focus on modelling the first steps driving localised cancer cell invasion and try to identify key processes that lead to observed invasion patterns and that allow collective cell migration and/or the detachment of individual cells or small cell clusters from the main tumour mass.
In order to do this, we use an individual-based, force-based multi-scale approach and model the physical properties of the cells and intra- and inter-cellular protein pathways involved in tumour growth, cell-cell and cell-matrix adhesion. The key pathways include those of E-cadherin and beta-catenin. Our approach also allows us to model the components of the extracellular matrix explicitly (e.g. fibronectin fibres).
Using computational simulations, we consider a growing mass of cells and investigate the spatio-temporal distribution of E-cadherin and beta-catenin levels in individual cancer cells and predict what implications this has for the adhesion of the cancer cells to each other and to the extracellular matrix. By examining the cell-matrix interactions with our model we can furthermore highlight the importance of the microenvironment in tumour progression and how the composition of the matrix together with the E-cadherin/beta-catenin dynamics may lead to different invasion patterns. We also show the influence of matrix realignment caused by cell traction forces on the cells' invasive behaviour and the spatio-temporal patterns that emerge.

Poster Session; Friday, July 1, 20:00

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The network of the RNA-binding protein AtGRP7, a component of a molecular slave oscillator in *Arabidopsis thaliana*

The AtGRP7 autoregulatory circuit is the first identified molecular "slave" oscillator that is coupled to the circadian ("master") oscillator of *Arabidopsis thaliana*. The AtGRP7 protein regulates the accumulation of its own mRNA at the posttranscriptional level via alternative splicing. It was recently shown that there is also a cross regulation with the AtGRP8 autoregulatory circuit. We modeled the system composed of these autoregulatory circuits interconnected with the "master" oscillator via an ordinary differential equation approach. As for many biological systems the parameters of these equations are barely known. We defined a cost function that quantifies the overlap between our model and key experimental features. A search in parameter space should evaluate if our proposed model fits with the given experimental data.

Poster Session; Friday, July 1, 20:00

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Modeling approach to T cell electrophysiology

An effective immune response to invading pathogenic microorganisms requires the regulated interplay of T-lymphocytes and antigen-presenting cells (APC) facilitated by the support of various cytokines. The activation of T helper cells requires the recognition of antigen, which is bound to major histocompatibility complex molecules, type class II, on the APC. For the purpose of activation the T cell receptor (TCR), assisted by coreceptors including CD4, interacts with the bound antigen and builds up the so called immunological synapse. These complex interactions imply sophisticated signaling pathways in the lymphocyte cells and implicates a network of ion channels in T cells for managing signals.

With regard to the complexity of the signaling pathways and corresponding ion fluxes through the T cell membrane, a mathematical modeling approach to T cell electrophysiology, based on experimental data of electrophysiological measurements, is needed for understanding and illustrating this functional network.Technically, the background of the projected simulation of T cell electrophysiology is based on mathematical modeling of the electrophysiology of the pancreatic beta cell [1]. The T cell model is based on single protein conductance data and, in a first step, is focussed on the electrophysiology of a resting T helper cell. In a second step, the simulation of the resting T lymphocyte will be adapted to the activated T cell state. Based on this simulation it is planned to study the effect of inhibiting and exciting drugs onto T cell activation on the level of calcium dynamics.

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Modeling Dynamics of Complex Biological Systems; Tuesday, June 28, 17:00

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Linking network structure and stochastic dynamics to neural activity patterns involved in sleep-wake regulation

Sleep and wake states are each maintained by activity in a corresponding neuronal network, with mutually inhibitory connections between the networks. In infant mammals, the durations of both states are exponentially distributed, whereas in adults, the wake states yield a heavy-tailed distribution. What drives this transformation of the wake distribution? Is it the altered network structure or a change in neuronal dynamics? What properties of the network are necessary for maintenance of neural activity on the network and what mechanisms are involved in transitioning between sleep and wake states? We explore these issues using random graph theory, specifically looking at stochastic processes occurring on random graphs, and also by investigating the accuracy of predictions made by deterministic approximations of stochastic processes on networks.

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Mathematical modelling of physiological processes in patients on dialysis;
Saturday, July 2, 11:00

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Physiology-based approach to modeling of dialysis

Physiologically based pharmacokinetic models attempt to utilize basic physiological, biochemical, biophysical, and physicochemical information to describe the distribution, disposition, conversion, and elimination of a given substance. More specifically, such models require information about organ volumes, physiological blood flow rates, solute generation rates, enzymatic reactions, as well as information on thermodynamic characteristics such as solubilities, dissociation constants, partition coefficients, diffusivities, and membrane permeabilities. Teorell was among the first to present a physiologically based pharmacokinetic model more than 70 years ago [1].

The distribution volume, the number of compartments, and the exchange of solute between compartments are important components of a kinetic model. Models for hemodialysis are characteristic for assuming a change in compartment volume because of ultrafiltration. On the other hand, rate constants describing the exchange between compartments, the generation and the elimination of solute are generally assumed as constant.

Parameters of physiologically based models have an important meaning. For example, transport within and between compartments is described by convection and diffusion through the cardiovascular system. Two limiting cases of transport may be distinguished: Flow-limited transport for solutes with high diffusivity and membrane permeability such as urea, and diffusion-limited transport for solutes with low membrane permeability such as creatinine. Notice that transport of solutes between organs is determined by convection irrespective of solute diffusivity. The importance of organ perfusion for solute kinetics in hemodialysis was first recognized by Dedrick [2]. Thus, even if diffusion across cell membranes is almost instantaneous for substances such as urea, the equilibration throughout the whole body during the typical post-dialysis urea rebound takes about 30 min because of differences in regional perfusion [3]. Surprisingly, a similar time course is observed for other solutes such as creatinine which, unlike urea, have much reduced membrane permeability. The kinetics for both urea and creatinine (and possibly other solutes) can be described by a unified model combining flow-limited transport between organs and diffusion-limited transport within organs [4]. The assumption of constant exchange rates between compartments must be questioned when hemodialysis and ultrafiltration-induced changes in blood volume are known to affect cardiovascular control and regional blood flow distribution [5, 6].

Indicator dilution has a long tradition in physiology to model characteristics of solute transport and to identify important model parameters inaccessible to direct measurement [7, 8]. In hemodialysis, the focus of indicator dilution is on measuring blood flows such as access blood flow and cardiac output, and distribution volumes such as central blood volume and lung water [9, 10]. A variant of indicator dilution

is the modeling of ultrafiltration-induced changes in blood volume and vascular refilling in the microcirculation for the purpose of understanding fluid balance during hemodialysis [11, 12].

Physiologic models are more complex and require more data that usually cannot be obtained in the single experiment. It is often impossible to analyze various tissues relating to specific compartments, especially in man, and one has to rely on in-vitro or animal data. In addition to data acquisition problems, the models are often composed of complex sets of nonlinear differential equations that must be solved numerically. Also, the expansion of compartments has been criticized as an addition of arbitrary parameters to artificially improve the model fit whereas in reality each additional compartment represents a constraint that can be checked against real data should they become available [13].

Physiologically based kinetic models can be used to identify meaningful physiological parameters inaccessible to direct measurements such as volumes, flows, and permeabilities. Unlike statistical models extrapolation of mechanistic models outside the range of data is possible with some confidence. In hemodialysis this is important when scaling the treatment with regard to treatment duration, treatment frequency, and body size [14, 15].

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Speciation; Wednesday, June 29, 08:30

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Can dominance prevent the evolution of assortative mating and sympatric speciation?

Consider a quantitative trait that is under a mixture of frequency-independent stabilizing selection and density- and frequency-dependent selection caused by intraspecific competition for a continuum of resources. The trait is determined by a single (ecological) locus and expresses intermediate dominance, and the population mates assortatively with respect to this trait.

We study weather mutations at modifier loci can invade, which either increase the level of dominance or the level of assortment. From a naïve point of view, complete dominance and complete assortative mating seem to be two alternative mechanisms to eliminate unfit offspring with intermediate traits. However, we will see that the interaction of assortative mating and dominance is rather complex. The two evolutionary responses can promote each other or hinder each other. Overall, we find that dominance might be the more likely evolutionary outcome, and that the evolution of assortative mating in small steps leading to sympatric speciation seems unlikely.

Structure and Dynamics of Biochemical Reaction Networks II; Tuesday, June 28, 17:00

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A model of threshold behavior reveals rescue mechanisms of bystander proteins in conformational diseases

Conformational diseases result from the failure of a speci

c protein to fold into its correct functional state. The misfolded proteins can lead to the toxic aggregation of proteins. Protein misfolding in conformational diseases often displays a threshold behavior characterized by a sudden shift between nontoxic to toxic levels of protein misfolds. In some conformational diseases, evidence suggest that misfolded proteins interact with bystander proteins (unfolded and native folded proteins), eliciting a misfolded phenotype. These bystander isomers would follow their normal physiological pathways in absence of misfolded proteins. In this paper we present a general mechanism of bystander and misfolded protein interaction which we have used to investigate how the threshold behavior in protein misfolding is triggered in conformational diseases. Using a continuous flow reactor model of the endoplasmic reticulum, we found that slight changes in the bystander protein residence time in the endoplasmic reticulum or the ratio of basal misfolded to bystander protein in ow rates can trigger the threshold behavior in protein misfolding. Our analysis reveals three mechanisms to rescue bystander proteins in conformational diseases. The results of our model can now help direct experiments to understand the threshold behavior and develop therapeutic strategies targeting the modulation of conformational diseases.

Mathematical modeling and simulations of angiogenesis II; Wednesday, June 29, 11:00

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Using mathematical modeling to assess the efficacy of oxygen for problem wounds: use of hyperbaric or topical oxygen therapies

We extend a previously developed mathematical model [1] for acute wound healing to investigate the application of hyperbaric and topical oxygen therapies to treat acute, delayed, and chronic wounds. In this talk, I will present the model, a sensitivity analysis of the model, and simulation results for treating the wound with hyperbaric and topical oxygen therapies.

References.

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Poster Session; Friday, July 1, 20:00

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Modeling of T-Cell Signaling: Anergy versus Proliferation

T-cells are activated by interactions between the T-cell receptor (TCR) and peptides bound to the major histocompatibility complex (MHC). The activation of TCRs initiates several signaling pathways that are necessary for the proper cellular response to the presented peptides. We investigated the activation of the Erk Protein by means of a data-based mathematical model, focusing on the feedback mechanisms within this pathway that could explain the observed kinetics. T-cells were stimulated by antibodies cross-linked in solution (sAbs) as well as by antibodies immobilized on microbeads (iAbs). The stimulation with sAbs shows a strong, but transient signal whereas the iAbs stimulus leads to a sustained signal that results in a strong activation of Erk. The stronger stimulus (sAbs) results in the weaker activation of Erk, which indicates that the activation of Erk is regulated by feedback. We developed a mathematical model based on ordinary differential equations, which promotes LAT as an important element of the feedback mechanisms. Depending on the input signal LAT reaches different states of phosphorylation. By splitting the signal at LAT level feedback can be regulated by those different states of LAT. First simulations with this model show that the experimental-observed dynamics can be explained much better than with a simpler model of the pathway that also includes feedback, but no signal splitting at LAT.

Noisy Cells; Saturday, July 2, 14:30

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How stochastic adaptation currents shape interspike interval statistics of neurons - theory and experiment

Trial-to-trial variability and irregular spiking is an ubiquitous phenomenon throughout the nervous system. In many cases, the origin of this neural noise is not known and difficult to access experimentally. Here, we explore the possibility to distinguish between two kinds of intrinsic noise solely from the interspike interval (ISI) statistics of a neuron. To this end, we consider an integrate-and-fire model with spike-frequency adaptation in which fluctuations (channel noise) are either associated with fast ionic currents or with slow adaptation currents. We show by means of analytical techniques that the shape of the ISI histograms and the ISI correlations are markedly different in both cases: for a deterministic adaptation current, ISIs are distributed according to an inverse Gaussian density and the ISI correlations are negative. In contrast, for stochastic adaptation currents, the ISI density is more peaked than an inverse Gaussian density and the serial correlations are positive. We applied these measures to intracellular recordings of locust auditory receptor cells in vivo. By varying the stimulus intensity, we observed intriguingly similar statistics corresponding to both cases of the model. The results suggest that stochasticity of slow adaptation currents may contribute to neural variability in sensory neurons.

References.

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Genetics and Genomics; Wednesday, June 29, 08:30

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The formation of histone modification domains

Histones proteins are key players in the gene regulation of eukaryotes. Many of their with post-translational modifications decorated isoforms are organized in spatial domains along the DNA string of a chromosome. For instance, a large part of the transcriptionally inactive genome is densely packed and forms large domains. This heterochromatin has its histones modified by methylation of the ninth amino acid (a lysine) of histone type H3 (H3K9me). We propose a simple computer model that simulates the distribution of heterochromatin over the human chromosomes by assuming a competition between H3K9 methylation and H3K4 methylation, the latter being an abundant activating modification. Both marks are related to nucleation sites on the genome and spread from these sites due to simple mechanisms. Furthermore, both marks are mutually exclusive [**2**] and therefore compete against each other. With this model, we are able to explain why heterochromatin does not occupy the entire chromosomes and could reproduce the distribution measured in the ChIP-seq experiments from [**1**]. The further extension of the model to a large number of histone modifications allows the simulation of complex switch-like behavior.

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Recent advances in infectious disease modelling I; Saturday, July 2, 11:00

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Immune Dynamics of Equine Infectious Anemia Virus

Equine Infectious Anemia Virus (EIAV) is a retrovirus that establishes a persistent infection in horses and ponies. The virus is in the same lentivirus subgroup that includes human immunodeficiency virus (HIV). The similarities between these two viruses make the study of the immune response to EIAV relevant to research on HIV. We developed a mathematical model of in-host EIAV infection dynamics that contains both humoral and cell-mediated immune responses. The model is parameterized using clinical, virological, and immunological data from horses infected with EIAV. Analysis of the model yields results on thresholds that would be necessary for a combined immune response to successfully control infection. Numerical simulations are presented to illustrate the results. These findings have the potential to lead to immunological control measures for retroviral infection.

Multi-scale mathematics of the liver: From intracellular signaling to intercellular interaction; Wednesday, June 29, 08:30

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Constructive Algorithms for Modeling Realistic Vascular Structures

The liver is the major metabolic organ in the human body as it fulfills a huge variety of vital metabolic tasks. The most important link between the liver and the rest of the organism is the blood flow through the three vascular systems (hepatic artery, portal vein, hepatic vein). In order to properly model the function of the liver, it is crucial to have an appropriate model of the blood transportation systems.

In vivo 3D CT imaging and subsequent image processing provides the structure of vascular systems with limited resolution far from the scale of individual lobule, sinusoids and liver cells on which the metabolic functions of the liver take place. To bridge this gap in resolution, models for vascular structures can be used. In the talk, we present an extension of the Constrained Constructive Optimization (Schreiner et al.) and the Global Constructive Optimization (Georg et al.) approach for hepatic blood vessels. Based on topological and geometrical analyses of many different human hepatic vascular structures, we evaluate these two algorithms. We introduce parameters and adapt them such that the generated vascular systems geometrically closely resemble natural ones. This resemblance is quantified by a statistical comparison to the geometric properties of real human hepatic vascular structures.

Mechanical Models of Movement and Growth of Cells and Tissues II;
Wednesday, June 29, 17:00

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Multiscale model of tumor-derived capillary-like network formation

Solid tumors must recruit and form new blood vessels for maintenance, growth and detachments of metastases [**1**]. Vascularization is thus a pivotal switch in cancer malignancy and an accurate analysis of its driving processes is a big issue for the development of pharmacological treatments, giving rise to multiple experimental models. In particular, *tubulogenic* assays have demonstrated that tumor-derived endothelial cells (TECs), cultured in Matrigel (a commercial gelatinous protein mixture acting as basement membrane matrix), are able to autonomously organize in a connected network, which mimics an in vivo capillary plexus [**3**]. Such a process is promoted by the activity of the soluble peptide vascular endothelial growth factor (VEGF, [**2**]) as well as by the induced intracellular calcium signals [**5**]. We here propose and discuss a multilevel hybrid model which reproduces the main features of the experimental system: it incorporates a continuous model of the microscopic VEGF-induced calcium-dependent regulatory cascades, and a discrete mesoscopic Cellular Potts Model (CPM, [**4**]) describing the phenomenological evolution of the single cells. The two components are unified and interfaced, and produce a multiscale framework characterized by a constant flux of information from finer to coarser levels: in particular, the molecular sub-cellular events realistically regulate the mesoscopic biophysical properties, behaviors and interactions of the simulated TECs. The model results are in good agreement with the analysis performed in published experimental data, allowing to identify the key mechanisms of network formation as well as to characterize its topological properties [**7**]. Moreover, by varying important model parameters, we are able to simulate some pharmacological interventions that are currently in use, confirming their efficiency, and, more interestingly, to propose some new therapeutic approaches, that are counter intuitive but potentially effective [**6**].

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Evolutionary Ecology; Friday, July 1, 14:30

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Choose your neighbourhood wisely: the importance of neighbourhood geometry in spatial agent based models of biological systems

Agent based spatial models are one of the best known mathematical tools to model biological systems. At the heart of most of these models is a lattice which these agents inhabit and where they behave depending on their interactions with other agents in their neighbourhood. Despite its importance, the choice of nearest-neighbor geometry is usually arbitrarily made without regard to the bias that it might introduce into the results from the model.

In this abstract we explore the effect of nearest neighbor geometry on the propagation of evolutionary strategies with the help of a cellular automaton in which cells play the prisoner's dilemma game. Using this CA we compare several 2-dimensional architectures (von Neumann and Moore neighbourhoods as well as a regular hexagonal lattice). We also explore how the outcomes change as we move from 2 to 3 dimensions.

Our research highlights the importance of neighbourhood architecture in agent based spatial mathematical models and suggests that some models will have to consider different neighbourhood geometries as the biological system being modeled evolves. This work has implications in many areas of biological modeling where tissue architecture changes throughout development, but is most germane to cancer, microbiology and developmental biology.

Epidemics; Wednesday, June 29, 11:00

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An investigation of the epidemic threshold phenomenon in complex networks

Classic mean-field models of epidemics are well known to exhibit threshold phenomena which are typically characterised by the basic reproductive ratio R0. A range of mathematical results can be obtained for these simple systems regarding aspects such as the final epidemic size and the likelihood of epidemics occurring.

Here we make an investigation into these quantities for more complex epidemic systems. In particular, we consider epidemics propagated on contact networks. By using stochastic simulation, we make an investigation of the threshold phenomenon and generate some novel insights with some potential significance in real, heterogeneous systems. Additionally, by relating these quantities to steady state systems, we potentially gain a theoretical handle on analysing these systems.

Regulatory Networks; Tuesday, June 28, 17:00

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Simulation of signaling and regulatory networks in B. subtilis

B. subtilis is a Gram-positive bacterium commonly found in the soil. This bacterium has been studied extensively especially for the way it manages to induce itself to sporulate [1-4]. Sporulation, the creation of a spore is a last resort alternative a bacterium chooses to undertake when the resources in the environment are not compatible with maintaining a normal metabolism, especially when there is shortage of glucose, the input of cellular respiration.

In such condition the behaviour of an isogenic population of B.subtilis is not uniform. Some bacteria sporulate, some faster than others, some do not. This kind of behaviour is called bet hedging, and it is understood as a differentiation strategy which maximize the survival of the colony. In facts if the shortage of resources is long lasting, sporulation truly gives an advantage to individuals producing spores. Spores have very strong endurance and almost a frozen metabolism. These spores can reactivate their metabolism when the conditions turn to be more favourable. On the other hand if the shortage of resource is only temporary the process of producing a spore is not advantageous because it is energetically expensive and it is not reversible; from an early stage of sporulation any quick reappearance of resources would have not been exploited by the new born spore.

Sporulation is a quite complex process which entails the activity of more than 500 genes in a period of about 10 hours.

In this work we want to consider the phase which trigger the sporulation, a phase where the cell produces the protein σ^H, a sigma factor which plays a key role in triggering sporulation in B. subtilis.

Few parameters of this regulatory network are available in the literature, these are mostly the length of genes of proteins involved in the network. Statistical description about chemical reactions rates, spatial dynamics of molecules and synthesis production are almost totally unknown.

Estimation of order of magnitude of some parameters can be made by looking at the correspondent parameters in other species like E. choli.

We combine this comparison with a rigorous approach. We have developed a software which perform a stochastic simulation of the network which produces σ^H. We then identify unknown parameters of the network by comparing the output of our simulation with experimental data.

The available experimental data is in the form of time series of proteins KinA, Spo0A, Spo0B, Spo0F and sigmaH in arbitrary unit. The measurement has been performed in bacterial colonies by using green fluorescent protein (GFP). The measurement of each protein occurred in different experiments (one for protein) where a gene of GFP was insert in a suitable location to keep track of the production of the protein. The amount of luminescence is proportional to the amount of GFP

present in the cell which can be assumed proportional to the rate of synthesis of the protein.

The simulation produces as output time series for each protein in a form homogeneous to the experimental data. We compare the two time series with the root square mean error. We use evolutionary strategies [5] to perform a black box optimization in order to find the parameters which minimize this error.

In our talk we are going to discuss the results we obtained and we compare them with the present literature.

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Population Dynamics; Wednesday, June 29, 08:30

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A simple mathematical model for the annual variation of epidemic outbreak with prevention level affected by incidence size in the last season

Annual or seasonal fluctuation of the incidence size has been observed for a variety of infectious diseases, for example, influenza, measles, rubella, mumps, chickenpox etc. Here the *incidence size in the epidemic season* means the *final size* of epidemic at the season, which gives the fraction or the size of infected population in the epidemic season. Such fluctuations have been attracting many researchers in mathematical biology, and giving discussions about its driving factors. It would be taken natural that one of the important factors is seasonally varying environment, caused by the temporal variation of contact rate, infection rate, or recruitment rate, for example due to social aggregation of hosts or seasonally restricted breeding season.

In our work, in contrast to these factors of population dynamics, we consider the effect of a change of social behavior which determines the prevention level for the considered infectious disease. In case when the incidence size in the last epidemic season is large, the people in the community would tend to increase the prevention level against the infectious disease, for instance, with promoting washing hands, gargling, wearing a mask, and available vaccination. Such increase of the prevention level is reflected to the reduction of infection rate or recovery rate according to the disease. Differently from those factors potentially causing the annual or seasonal fluctuation of the incidence size, this social factor is what is affected by the incidence size in the last season or the past seasons.

To consider the essential effect of such social factor on the potentiality of incidence size fluctuation, we construct and analyze a simple mathematical model of discrete dynamical system, which is derived from the final-size equation of Kermack–McKendrick SIR model. We demonstrate that such social factor could potentially or partially contribute to the driving force causing the annual or seasonal fluctuation of the incidence size for some infectious diseases.

Evolutionary Ecology; Wednesday, June 29, 11:00

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Evolution of Dispersal and Global Climate Change

Global climate change (GCC) can challenge species' survival by shifting and (or) shrinking suitable habitats, leading to habitat fragmentation. American pikas (*Ochotona princeps*)—small, talus-dwelling, montane lagomorphs physiologically adapted to cold climates—are thought to face precisely this sort to threat from GCC. Recent climate changes appear to have decreased suitability of pika habitat in both the Great Basin and adjacent Sierra Nevada[1,2]. On the other hand, pika populations in both these regions appear robust[3]. One hypothesis explaining these contradictory observations suggests that pikas may adapt to climate change by evolving compensatory dispersal strategies that blunt the impact of fragmentation.

Here we address this hypothesis using adaptive dynamics[4] to study the evolution of dispersal strategies in pikas. Inspired by the models of Metz and Gyllenberg[5] and Parvinen[6], we construct a novel model of pika metapopulation dynamics and derive a fitness measure of a rare mutant in an environment set by the resident. We use a semi-discrete time approach with discrete phases defined by sequential breeding seasons and continuous within-phase processes (e.g. emigration, immigration). Local catastrophes occur with a rate which can depend on the patch population size. We consider climate change as shifts in model parameters, including fecundity, survival and catastrophe rates along with dispersal cost, and analyze how such changes affect evolutionarily stable dispersal strategies.

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Bioimaging; Tuesday, June 28, 11:00

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Confidence sets for the Aumann mean of a random closed set

The objective of the talk is to develop a set of reliable methods to build confidence sets for the Aumann mean of a random closed set (RACS) as estimated through the Minkowski empirical mean. In order to do so, we introduce a procedure to build a confidence set based on an asymptotic distributional result for the Hausdorff distance between the Minkowski empirical and the Aumann means; then, we introduce another procedure based on the support function.

The methods are based on the computation of the width of the RACS on a set of directions and are therefore suitable for computerized tomography, tactile sensing and laser-radar systems. Some Monte Carlo results show how the methods work in practice.

This contribution is joint work with Christine Choirat (Universidad de Navarra, Spain).

Semigroups of Operators in Mathematical Biology I; Wednesday, June 29, 08:30

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Finite populations conditioned on non-extinction

It is well known that stochastic models of the dynamics of finite populations tend to fall into two categories (when the system is closed): those that allow for unlimited growth of the population with positive probability and those for which extinction of the population in the long run is certain.

In practice one often expects extinction times to be sufficiently long that useful conclusions such as stabilisation of population structure can be drawn from deterministic population models. The talk is about work, old and new, aiming to justify such conclusions rigorously.

Crowd Dynamics: Modeling, Analysis and Simulation (Part 2); Wednesday, June 29, 14:30

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Quantitative description of pedestrian dynamics: Experiments and Modeling

The first part of the lecture gives an introduction to empirical results in pedestrian dynamics. Basic quantities of pedestrian streams (density, flow and velocity) are introduced along the measurement methods. But density and flow are concepts of fluid mechanics where the size of the particles is much smaller than the size of the measurement area. Thus standard methods in pedestrian dynamics suffer from large scatter when local measurements are needed. A concept for measuring microscopic characteristics on the basis of trajectories is introduced. Assigning a personal space to every pedestrian via a Voronoi diagram reduces the scatter and allows analyzing the fine structure of the data.

The second part focuses on a model continuous in space. Basic ideas of a force model representing pedestrians as self driven particles interacting via a repulsive force are outlined. To get precise volume exclusion in two dimensions the model represents the velocity dependent shape of pedestrians by ellipses changing the size of their semiaxis with speed. In addition routing strategies are modeled to incorporate certain intelligence to the self driven particles. The particles perceive their environment and take their decision based on an observation of the current situation.

Poster Session; Friday, July 1, 20:00

A Finite Element simulation of the lamellipodial actin cytoskeleton

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This poster presents a Finite Element method for the simulation of the lamellipodial part of the cytoskeleton of living cells.

The numerical method resolves a mathematical model that has been developed by Ch.Schmeiser and his collaborators (V. Small, D. Oelz, N. Sfakianakis, A. Manhart, V. Milisic) in Vienna. In the model several properties of the cytoskeleton are included: polymerization and bending of actin filaments, stretching and twisting of crosslink proteins, adhesion the with the substrate and myosin contractile forces.

We present simulations of the effect of the previously mechanical characteristic of the cytoskeleton. Special emphasis is given in the simulation results propagating lamellipodia under the influence of an external force and/or variable filament polymerization rate.

Poster Session; Friday, July 1, 20:00

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Interaction of Brain Cancer Stem Cells and Tumour Microenvironment: A Computational Study

Glioblastoma Multiforme (GBM) is one of the most common and aggressive primary brain tumors, with a median patient survival time of 6-12 months in adults. It has been recently suggested that a typically small subpopulation of brain tumour cells, in possession of certain defining properties of stem cells, is responsible for initiating and maintaining the tumour. More recent experiments have studied the interactions between this subpopulation of brain cancer cells and tumour microenvironmental factors such as hypoxia, in addition to their contribution to angiogenesis and vasculogenesis. We propose a computational model that includes a heterogeneous population of cancer cells and investigate the dynamics of tumour growth as well as the effects of the tumour microenvironment. The model is compared with available experimental data.

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Epidemic models: Networks and stochasticity I; Wednesday, June 29, 14:30

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Towards understanding the correlations in epidemic dynamics on contact networks via the master equation

It is well-known that deterministic epidemic models such as mean-field or pair-approximation models can fail on contact networks because they ignore correlations that occur between populations. While there is a substantial amount of intuition about these correlations, the literature lacks a more analytic approach to these effects.

Here, by directly relating these epidemic models to the underlying master equations we can understand precisely where and why these models fail. In particular, common models such as mean-field and pair-approximation models are shown to contain implicit anomalous terms describing unbiological processes whereby individuals can be both susceptible and infectious at the same time. This contradicts the assumption of a compartmental model. It is these implicit terms which lead to the observed inaccuracies in the models.

Analysis of these terms enables us to gain a more analytic perspective on correlations in epidemic models and on the role of network clustering on epidemic propagation.

Poster Session; Friday, July 1, 20:00

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Pathogen emergence under temporal heterogeneity

One of the key factors driving the emergence of disease is changes to climate. Climate change is expected to not only alter the mean of various environmental variables but also their variability. The effect of changes to the environmental mean on pathogen emergence has received considerable attention.

In this work we propose a theoretical approach to investigate the effect of changes to environmental variability on pathogen emergence and develop a multi-type branching process incorporating temporal heterogeneity and pathogen adaptation.

Previous studies have found that increases to environmental variability cause a decrease to pathogen emergence in a non-evolutionary system. Our results agree with this finding and find this is also true when pathogens must adapt to survive and cause an epidemic. It has also been shown that the effects of incorporating evolution can often outweigh other effects, we find however even in an evolutionary system temporal heterogeneity can significantly affect pathogen emergence. The greatest effect being on pathogens whose survival is not strongly dependent on its need to adapt and pathogens already adapted to its environment but with low infectivity.

Poster Session; Friday, July 1, 20:00

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Impact of vaccine refusal on vaccine-preventable disease outbreaks

The MMR scare and resulting measles outbreak in the UK and US in 2008 prove that the effectiveness of mass vaccination program can be hampered by the public perception of vaccine risk. By coupling game models and epidemic models, we examined vaccination choice for population stratified into two behavioral groups, pro-vaccinators and vaccine hesitators. Two behavioral groups are assumed to be heterogeneous with respect to their perceptions of vaccine and infection risks. We demonstrate that the pursuit of self-interest among vaccine-hesitators often leads to vaccination levels that are suboptimal for a community, even if complete coverage is achieved among pro-vaccinators. The demand for MMR vaccine across population driven by individual self-interest was found to be more sensitive to the number of vaccine hesitators than to the extent to which vaccine hesitators misperceive the risk of vaccine. Our results show that the discrepancy between the MMR coverages that are driven by self-interest and population interest becomes larger when the cost of vaccination increases. This research illustrates the importance of public education on vaccine safety and infection risk in order to maintain vaccination levels that are sufficient to derive herd immunity.

Stochastic models in computational neuroscience I; Wednesday, June 29, 14:30

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A state space method for decoding neuronal spiking signals

Cortical neurons *in vivo* have often been approximated as Poisson spike generators that convey no information other than the rate of random firing. Recently, it has been revealed by using a metric for analyzing local variation of interspike intervals that individual neurons express specific patterns in generating spikes, which may symbolically be termed regular, random or bursty [1,2]. Two hypotheses have been proposed for potential advantage of using non-Poisson spike trains in transmitting information; neurons may signal the firing irregularity by changing it in addition to the rate of firing [3], or alternatively, the receiver may estimate the firing rate accurately by making the most of non-Poisson inter-spike dependency in the received signals [4-6]. In order to determine which hypothesis is more plausible for a given spike train, we have implemented a state space method for simultaneously estimating firing irregularity and the firing rate moment by moment [7,8]. I review the recent development of the state space analysis and demonstrate new results obtained for a variety of electrophysiological data.

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Modeling the T-cells dynamics in lymphopenic conditions

We investigated division dynamics of two types of CD8 T-cells (OT1 and F5) in lymphopenic conditions. We used two markers: 1) CFSE (Carboxyfluorescein succinimidyl ester) – to calculate the number of divisions that the cells have made at a given time, 2) 7AAD (7-Aminoactinomycin D) – to determine in what period of cell cycle cells were at a given time.

A modified Smith-Martin model was used [1, 2] for the observed data. This model assume a cell cycle consisting of two parts: A-phase with stochastic duration and following after it B-phase with deterministic duration. There were four main parameters: transfer rate from A to B-phase λ, duration of B-phase Δ, time of triggering to division T_0 and death rate δ. To estimate them we used a minimization of the sum of weighted squared residuals with comparison of: 1) predicted and observed frequencies of cells with given number of divisions that was made to a given time, 2) predictions of fraction of cells in B-phase with observed fraction of 7AAD+ cells. Comparisons between models were performed using a cross-validation criterion.

It was found that OT1 cells divides faster (higher transfer rate λ and earlier triggering to division) than F5 cells. Duration of B-phase Δ was slightly higher for OT1 cells. Using the information from 7AAD marker together with CFSE data improved parameters identifiability.

References.

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Mathematical Models in Eco-epidemiology I; Wednesday, June 29, 08:30

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Intraguild predation or not? Taking a different perspective on some eco-epidemiological models

The field of eco-epidemiology has integrated epidemiology with community ecology and similarities between host-parasitoid and host-pathogen interactions with classical intraguild predation (IGP) have been noticed. In this talk I want to show that certain eco-epidemiological scenarios not only fit into the IGP framework, but that they may suggest a different perspective on the underlying community structure. After an appropriate transformation of variables particular cases of IGP are found to be structurally similar to "simpler" community modules and this structural similarity also translates into remarkably similar community dynamics.

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Neurosciences; Wednesday, June 29, 08:30

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Firing map for integrate–and–fire models with almost periodic stimulus

In integrate–and–fire systems the sequence of consecutive spikes can be recovered via iterations of the so–called firing map. Until now analytical approaches mainly concentrated on models of the type $\dot{x} = f(t, x)$ when the function f was continuous and periodic in the time variable ([1],[2],[3]). We analyze firing maps and firing sequences for the class of integrate–and–fire models with the stimulus function almost periodic in time (either uniformly almost periodic or in a Stepanov sense) and prove that many required properties of the firing map still hold for leaky integrate-and fire $\dot{x} = -\sigma x + f(t)$ or Perfect Integrator $\dot{x} = f(t)$ models when the function f is only locally integrable. We prepare a formal framework for the study of discrete dynamics of the firing map arising from almost periodically driven integrate–and–fire systems. In particular, results concerning almost periodic displacement of the firing map and regularity properties (semi–/almost periodicity) of the sequence of interspike intervals will be shown.

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Poster Session; Friday, July 1, 20:00

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Identification of protein complexes maintaining Oct4 expression in mouse ES cells

Octamer binding transcription factor-4 (Oct4) is one of the key factors controlling the fate of embryonic stem (ES) cells. Oct4 expression at a specific level is required to maintain the ES cells' capability for self-renewal, i.e. ability to replicate indefinitely without loss of pluripotency. Whereas numerous studies focused on the target genes or direct protein interactors of Oct4, the regulation of Oct4 expression itself is less explored.

Our work aims at finding the genes and protein complexes involved in the regulation of Oct4 expression. The study is based on two independent genome-wide siRNA screens [1, 2] conducted in the mouse ES cell line, Oct4-GiP, which allows to measure the change of Oct4 expression upon siRNA knock-down of query genes.

Direct comparison of the results from both screens at the gene level did not show a statistically significant consistency between the screens. Possible causes of this disagreement include variations in the experimental setup (different siRNA libraries), variability related to high-throughput experiments and drawbacks of siRNA screening methodology (false discoveries resulting e.g. from off-target effects). We reasoned that incorporation of additional orthogonal information in the analysis might remove noise and improve the consistency between screens. We therefore mapped the genes tested in siRNA screens to known protein complexes, assuming that genes participating in the same complex should cause similar phenotypes. To identify complexes enriched with high-scoring genes, we tested several set enrichment methods (hypergeometric test, weighted Kolmogorov-Smirnov statistic, Bayesian network and regularized linear regression). The resulting scoring of protein complexes showed considerably greater consistency between screens than the original gene scores. Subsequently we combined the results from both screens in order to obtain a single set of high-confidence complexes enriched for genes causing Oct4-related phenotypes. Thereby we obtained several complexes with known functions related to cell-cycle or stem cell maintenance. Importantly, these complexes contain many genes that were not identified as significant "hit genes" in the original screens.

The performed analysis reveals that combining results of siRNA screens and adding external data helps to extract more comprehensive information from the experiments. Our analysis identifies a catalogue of protein complexes critically involved in the regulation of Oct4 expression and thus important for ES cells maintenance.

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Epidemic models: Networks and stochasticity I; Wednesday, June 29, 14:30

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Exact and approximate epidemic models on networks

The rigorous linking of exact stochastic models to mean-field pair and triple approximations is studied. Using a continuous time Markov Chain, we start from the exact formulation of a simple epidemic model on a completely connected network and rigorously derive the well-known mean-field pair approximation that is usually justified under the hypothesis that infected nodes are distributed randomly.

In addition, we propose a new approach that is based on deriving a countable system of ordinary differential equations for the moments of the distribution of the number of infected nodes. We show how the usual mean-field pair approximation can be derived from this countable system, and prove that this converges to the exact solution given by the Kolmogorov equations as order 1/N. We discuss how our new approach relates to the generally cited results by Kurtz.

Finally, the performance of the triple closure approximation is investigated numerically. It will be shown that the usual triple closure yields a solution that also converges as order 1/N to the exact solution, and we propose a novel triple closure where the rate of convergence is of order 1/N2.

Connecting microscale and macroscale models of cellular migration;
Tuesday, June 28, 17:00

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Models of collective cell spreading with variable cell aspect ratio: A motivation for degenerate diffusion models

Continuum diffusion models are often used to represent the collective motion of cell populations. Most previous studies have simply used linear diffusion to represent collective cell spreading, while others found that degenerate nonlinear diffusion provides a better match to experimental cell density profiles. In the cell modeling literature there is no guidance available with regard to which approach is more appropriate for representing the spreading of cell populations. Furthermore, there is no knowledge of particular experimental measurements that can be made to distinguish between situations where these two models are appropriate. Here we provide a link between individual-based and continuum models using a multi-scale approach in which we analyze the collective motion of a population of interacting agents in a generalized lattice-based exclusion process. For round agents that occupy a single lattice site, we find that the relevant continuum description of the system is a linear diffusion equation, whereas for elongated rod-shaped agents that occupy L adjacent lattice sites we find that the relevant continuum description is connected to the porous media equation (pme). The exponent in the nonlinear diffusivity function is related to the aspect ratio of the agents. Our work provides a physical connection between modeling collective cell spreading and the use of either the linear diffusion equation or the pme to represent cell density profiles. Results suggest that when using continuum models to represent cell population spreading, we should take care to account for variations in the cell aspect ratio because different aspect ratios lead to different continuum models.

Cell migration during development: modelling and experiment; Saturday, July 2, 08:30

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Modelling cell invasion with proliferation mechanisms motivated by time-lapse data

Cell invasion involves a population of cells which are motile and proliferative. Traditional lattice-based discrete models of cell proliferation involve agents depositing daughter agents on nearest neighbour lattice sites. Our new work is motivated by time-lapse images of cell invasion associated with the development of the enteric nervous system where a population of precursor neural crest cells invades the developing gut tissues. Using time-lapse data, we show that the traditional proliferation model is inappropriate and we propose a new proliferation model consistent with time-lapse observations. Using simulation and analysis, we show that the discrete model is related to a family of reaction-diffusion equations and can be used to make predictions over a range of scales appropriate for interpreting experimental data

Epidemic models: Networks and stochasticity I; Wednesday, June 29, 14:30

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Household epidemic models with variable infection severity

We explore SIR (Susceptible → Infective → Removed) epidemic models with household structure and the feature that infectives can be either mildly or severely infective. We analyse two different models which describe such behaviour, one where individual's severities are pre-determined (perhaps due to prior partial immunity) and one where the an individual's severity is influenced by the severity of the individual that infects it and whether this infection resulted from a within- or between-household contact. The aim is to determine whether it is possible to find which of the two models best explains the varying response when given final size household outbreak data containing mild and severe cases. We conduct numerical studies from which we conclude that this discrimination usually is possible.

This is joint work with Frank Ball (University of Nottingham) and Tom Britton (Stockholm University).

Stochastic models in computational neuroscience I; Wednesday, June 29, 14:30

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About a modification of the firing time definition in stochastic leaky integrate–and–fire neuron models

The integrate-and-fire neuron model is one of the most widely used models for studies of neural coding [1,2]. It describes the membrane potential of a neuron in terms of the synaptic inputs and the injected current that it receives. An action potential (spike) is generated whenever the membrane potential crosses some threshold level from below. In integrate-and-fire models the form of an action potential is not described explicitly. Spikes are formal events fully characterized by a 'firing time' after which the membrane potential is reset and the process starts from scratch.

The observation of experimental intracellular recordings seems to suggest that the membrane potential may cross the threshold level several times before an action potential is detected [3]. We study a modified version of the leaky integrate-and-fire neuron model where a spike is generated whenever the membrane potential remains above the threshold level for a 'sufficiently' long time. Hence the firing time is not defined by an instantaneous crossing of the level, but depends on a longer history of fluctuations of the membrane potential. Comparisons with the dynamics exhibited in the classical models are presented.

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Numerical study of Receptor-Toxin-Antibody Interaction Problem

The successful bio-medical application of antibodies is well-documented and there is increasing interest in the use of antibodies for mitigation of the effect of toxins associated with the various biological threats. Such toxins are an important potential target for designing therapies against these threats and a brood range of approaches has been taken to develop inhibitors that may be of prophylactic or therapeutic use. With the progress in bio-engineering many antibodies have been generated for this purpose with different affinity parameters and, as a result, different properties. However affinity, by itself, is a poor predictor of protective or therapeutic potential which is determined by a new consolidated kinetic parameter Receptor-Toxin-Antibody (RTA) kinetics and relative concentration of species. Generation of any new antibody necessitates development of a high fidelity model for RTA interaction.

One of the important step in improvement of this model is incorporation of the reaction-diffusion fluxes of species. Incorporation of diffusion fluxes of toxin, antibody, and associated complex into the RTA model leads to a PDEs model.

Numerical study of the protective efficiency of antibody against a given toxin in the model of cells placed into a toxin-antibody solution will be discussed.

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Noisy Cells; Saturday, July 2, 14:30

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Modeling the dynamics of enzyme-pathway coevolution

Metabolic pathways must have coevolved with the corresponding enzyme gene sequences. However, the evolutionary dynamics ensuing from the interplay between metabolic networks and genomes is still poorly understood. Here, we present a computational model that generates putative evolutionary walks on the metabolic network using a parallel evolution of metabolic reactions with their catalyzing enzymes. Starting from an initial set of compounds and enzymes, we expand the metabolic network iteratively by adding new enzymes with a probability that depends on their sequence-based similarity to already present enzymes. Thus, we obtain simulated time courses of chemical evolution in which we can monitor the appearance of new metabolites, enzyme sequences, or even entire organisms. We observe that new enzymes do not appear gradually but rather in clusters which correspond to enzyme classes. A comparison with Brownian motion dynamics indicates that our system displays biased random walks similar to diffusion on the metabolic network with long range correlations. This suggests that a quantitative molecular principle may underlie the concept of punctuated equilibrium as enzymes occur in bursts rather than by phyletic gradualism. Moreover, the simulated time courses lead to a putative time-order of enzyme and organism appearance. Among the patterns we detect in these evolutionary trends is a significant correlation between the time of appearance and their enzyme repertoire size. Hence, our approach to metabolic evolution may help understand the rise in complexity at the biochemical and genomic levels.

Modeling of immune responses and calcium signaling III; Wednesday, June 29, 17:00

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How spatial cell properties shape Ca^{2+} signals

Ca^{2+} plays a major role in many physiological processes including muscle contraction and gene regulation. The versatility is achieved by a wide spectrum of Ca^{2+} signals ranging from fast local events to cell wide repetitive spiking and plateau responses. It is still a challenge to understand how cells generate reliable cellular signals with microscopic noisy Ca^{2+} release channels like IP_3Rs. We have recently shown in experiments that the microscopic fluctuations are carried on the level of the cell by the hierarchical organization of the Ca^{2+} pathway. Here we use our detailed modelling approach to analyze how Ca^{2+} signals depend on physiological parameters. The model describes individual release channels by Markov chains the states of which act as stochastic source terms in a reaction diffusion system representing the cell. This allows for following the Ca^{2+} signal from its local triggering event to the cell wide response. In extensive simulations we analyzed how the spatial properties shape Ca^{2+} signals. The simulations can quantitatively describe experiments in which Ca^{2+} diffusion is reduced by additional buffer. In further simulations, the temperature dependence of Ca^{2+} signals could be mapped to a change in the SERCA pump strength that determines the spatial coupling between release sites. All these modelled and experimental data are in addition analyzed and compared by a moment based approach that points to a functional robustness of the Ca^{2+} pathway.

Population Dynamics; Wednesday, June 29, 11:00

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Asymptotic properties of stochastic symbiosis model

We discuss the influence of various stochastic perturbations on symbiosis system. We consider the following system of stochastic equations

$$(1)\begin{cases} dX(t) = ((a_1 + b_1Y(t) - c_1X(t))\,dt + \rho_{11}\,dW_1(t) + \rho_{12}\,dW_2(t))\,X(t) \\ dY(t) = ((a_2 + b_2X(t) - c_2Y(t))\,dt + \rho_{21}\,dW_1(t) + \rho_{22}\,dW_2(t))\,Y(t), \end{cases}$$

which describes relations between two populations living in symbiosis. We assume that $a_i, b_i, c_i > 0$ $(i = 1, 2)$ are positive constants, $W_1(t)$, $W_2(t)$ are two independent standard Wiener processes, $X(t)$, $Y(t)$ are stochastic processes which represent, respectively, the first and the second population. We consider three kinds of stochastic perturbations:

(i) weakly correlated, i.e. $\rho_{11}\rho_{22} - \rho_{12}\rho_{21} \neq 0$;
(ii) strongly correlated, i.e. $\rho_{11} > 0$, $\rho_{21} > 0$, $\rho_{12} = 0$, $\rho_{22} = 0$;
(iii) only one population is stochastically perturbed, by symmetry we assume that the second population is perturbed, i.e. $\rho_{11} = 0$, $\rho_{21} > 0$, $\rho_{12} = 0$, $\rho_{22} = 0$.

First we show the existence, uniqueness, positivity and non-extinction property of the solutions of system (1) on the assumption that $b_1b_2 < c_1c_2$. Next we prove that the probability distributions of the process $(X(t), Y(t))$ are absolutely continuous with respect to the Lebesgue measure. Let $U(x, y, t)$ be the density of the distribution of $(X(t), Y(t))$. We give a sufficient and a necessary condition for asymptotic stability of system (1), i.e. the convergence of $U(x, y, t)$ to an invariant density $U_*(x, y)$. In the case when this system is not asymptotically stable, we prove that $\lim_{t\to\infty} Y(t) = 0$ a.e. We also show that in this case $\lim_{t\to\infty} X(t) = 0$ a.e. or the probability distributions of the process $X(t)$ converge weakly to some probability measure. We give a biological interpretation of these results.

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Cellular Systems Biology; Saturday, July 2, 11:00

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Coupled sensitivity and frequency analysis of signalling pathways

Mathematical modeling of signalling pathways has gained large popularity recently. The models that have been developed describe dynamics of NFkB, JAK/STAT, p53/Mdm2 and many other pathways. One of the most important advantages of application of mathematical models in this field is their flexibility and ability to check certain aspects of the dynamics if the investigated systems before committing large resources into experimental work.

Complexity of the models that are under development varies, depending on the particular goals of the modeling. Nevertheless, regardless of model complexity, one of the key issues is proper choice of parameters. As a result, in such work sensitivity analysis is a necessary stages in analysis of simulation results.

Two main categories of sensitivity analysis methods can be distinguished: local and global. Local sensitivity analysis provides information on the effect of a small deviation a single parameter from its nominal value on the system output. Global sensitivities, in turn, describe how the system output changes when multiple parameters change in a relatively wide range.

In this work several sensitivity indices will be applied to find out which parameter subsets have the greatest impact on the dynamical behavior of several signaling pathways. However, instead of using them with reference to steady states, which is the one of the most frequent approaches, they will be coupled with frequency analysis of the models dynamics. That way, it is possible to answer one of the most important questions concerning some signaling pathways. There is an ongoing dispute about oscillations and their importance in cellular responses to external inputs. Analysis of sensitivity of main frequencies in the model outputs will push forward research in this field. If it is the oscillations that are crucial for proper cell behavior, these frequencies should be relatively insensitive to parameter changes. Moreover, sensitivity analysis will indicate the stages of the signaling pathway that are the most prone to disturbances, providing clues for experimental work.

The work was partially supported by The Fundation for Polish Science.

Neurosciences; Thursday, June 30, 11:30

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Distinguishing the Type of Input Noise in the Fitzhugh-Nagumo Neuronal Model

A nonlinear system of differential equations known as the Fitzhugh-Nagumo (FN) is used to describe the physiological state of a nerve membrane. Several different kinds of noise are added to the FN model to investigate the effect of noise on the membrane. They are Gaussian white noise, O-U process and Poisson noise. Gaussian white noise represents many small synaptic inputs and Poisson noise represents a few large synaptic inputs. The non-oscillatory region before and after the bifurcation region is used to distinguish between Wiener vs. Poisson inputs by a hypothesis test about the mean number of level crossings. The null hypothesis is the expected level crossings of the equilibrium state by a time sampled linearized FN set of differential equations with Wiener input. The test performs well in rejecting non Wiener inputs in simulation studies, both in the linearized and nonlinear F-N model. A resonance type phenomena was also observed.
Key Words: Neuron; First passage time; level crossings; Poisson process; stochastic differential equation

Recent advances in infectious disease modelling II; Saturday, July 2, 14:30

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The impact of media coverage on the transmission dynamics of human influenza

There is an urgent need to understand how the provision of information influences individual risk perception and how this in turn shapes the evolution of epidemics. Individuals are influenced by information in complex and unpredictable ways. Emerging infectious diseases, such as the recent swine flu epidemic, may be particular hotspots for a media-fueled rush to vaccination conversely, seasonal diseases may receive little media attention, despite their high mortality rate, due to their perceived lack of newness. We formulate a deterministic transmission and vaccination model to invetigate the effects of media coverage on the transmission dynamics of influenza. The population is subdivided into different classes according to their disease status. The compartmental model includes the effect of media coverage on reporting the number of infections as well as the number of individuals successfully vaccinated. A threshold parameter (the basic reproductive ratio) is analytically derived and used to discuss the local stability of the disease-free steady state. The impact of costs that can be incurred, which include vaccination, education, implementation and campaigns on media coverage, are also investigated using optimal control theory. A simplified version of the model with pulse vaccination shows that the media can trigger a vaccinating panic if the vaccine is imperfect and simplified messages result in the vaccinated mixing with the infectives without regard to disease risk. The effects of media on an outbreak are complex. Simplified understandings of disease epidemiology, propogated through media soundbites, may make the disease significantly worse.

Poster Session; Friday, July 1, 20:00

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Rule based modelling the molecular signalling pathways in synapse.

Synaptic transmission depends on a very well orchestrated sequence of protein-protein interactions on both sides of the neuronal synapse. The aggregation of protein complexes of different sizes and composition underpins synapse function, and disruptions at this level account for many neuropsychiatric and neurodegenerative diseases.

The postsynaptic compartment of the excitatory glutamatergic synapse contains hundreds of distinct polypeptides with a wide range of functions (signalling, trafficking, cell-adhesion, etc). Structural dynamics in the PSD (post synaptic density) are believed to respond for the initial steps of signalling cascades that result in long-term synaptic plasticity. Although functionally and morphologically diverse, PSD proteins are generally enriched with specific domains, which precisely define the mode of clustering essential for signal processing.

We apply a stochastic calculus of domain binding provided by the rule-based modelling (e.g. Kappa) approach to formalise the highly combinatorial signalling pathway in PSD and perform the numerical analysis of the relative distribution of protein complexes and their sizes (Danos and Schumacher, 2008, Danos et al, 2009). We specify the dynamics of PSD by rules, taking into account protein domain structure, specific domain affinity and relative protein availability. Resulting model has a hierarchical structure, composed of generic agents and generic rules and their concrete variants. This allows interrogate the critical conditions for the protein aggregation to the large complexes along with simultaneous study of effect of presence of mutated polypeptides and protein splice variants on structure and relative stability of those complexes.

Population Dynamics; Saturday, July 2, 11:00

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Multiscaling Modelling in Evolutionary Dynamics

We start from a family of continuous approximations to the probability density of a frequency dependent Moran process studied by Chalub & Souza in [1]. These approximation, depending on the scalings, can be of diffusive or non-diffusive type, the latter being equivalent to the Replicator Dynamics. We then study the small diffusion limit, and show how the Replicator Dynamics can be consistenly fitted in a diffusive approximation. Some additional results concerning the fixation probabilites in this limit are also presented. This is joint work with Fabio Chalub.

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Neurosciences; Friday, July 1, 14:30

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The identification of a neuroelectric system in the time and frequency domain when an alpha stimulation is present

In this work the identification of a neuroelectric system, called muscle spindle, is studied when it is affected by an alpha motoneuron (alpha stimulation). The muscle spindle is an element of the neuromuscular system and plays an important role in the initiation of movement and in the maintenance of the posture. The response of the muscle spindle and the stimulus imposed by the motoneuron are sequences of action potentials and therefore they are considered as realizations of stationary point processes. A frequency and a time domain approach has been employed for the identification of the system.

In the frequency domain, the muscle spindle can be described by a Volterra - type model involving one input and one output. Spectral analysis techniques of stationary point processes are applied in order to estimate two important functions, the coherence coefficient and the impulse response. The linear relation between the response of the system and the input is described by the estimate of the coherence coefficient, while the estimate of the impulse response function provides the best linear predictor for the response of the system in the presence of the input.

In the time domain approach the input and the output of the system can also be considered as binary time series and therefore the theory of generalized linear models (GLM) can be applied. The advantage of this approach is based on the fact that estimates of the system's parameters can be obtained by using the maximum likelihood function. However, there is no convergence of the maximum likelihood estimates since the phenomenon of quasi-complete separation occurs. To overcome this problem an approach based on the penalized likelihood function is used, which provides an ideal solution and it is computationally much faster compared to the Monte Carlo method that has been already used. The stochastic model which is proposed for the description of the system involves the threshold and the summation function. The estimation of the summation function is of great interest as it describes whether the system is excitatory or inhibitory. A validity test for the fitted model based on randomized quantile residuals is proposed. The validity test is transformed to a goodness of fit test and the use of Q-Q plot is also discussed.

The estimate of the impulse response function indicates that the system accelerates for 1–2 ms shortly after the effect of the alpha motoneuron, is blocked for about 30 ms and after that does not change. Similar results are obtained by the estimate of the summation function of the GLM.

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Mathematical modelling of physiological processes in patients on dialysis;
Saturday, July 2, 11:00

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Mathematical modeling of peritoneal dialysis

Peritoneal dialysis (PD) is a treatment option for patients with kidney failure that is available in most countries around the world. Its main goal is to remove waste metabolic product and excess water to the fluid infused into the peritoneal cavity that is finally drained out. The increasing usage of PD required special tools that would allow for the estimation of treatment efficiency. In particular, mathematical models allow for the quantitative description of bidirectional water and solute peritoneal transport.

Three types of mathematical models can be used for the modeling of the peritoneal transport: the classical membrane model, the three-pore model, and the distributed model. The first two models (typically applied in clinical and experimental research) use phenomenologically derived parameters that characterize peritoneal transport. However, their relative simplicity does not allow for the derivation of the information on the fundamental physiological processes that govern fluid and solute transport during peritoneal dialysis. Therefore, the distributed approach is used to provide detailed information on the peritoneal physiology and more realistic description of the complexity of the peritoneal anatomy and transport system. This approach is based on the local tissue and microcirculatory physiology and its parameters are derived from the local structure and properties of the tissue and microvasculature.

In order to describe bidirectional fluid and solute transport, the two-phase structure of the interstitium was taken into account, based on the previous experimental findings (Guyton et al, 1969). The two-phase system contains a water-rich, colloid-poor region (Fluid Phase, F), where fluid transport is driven by the hydrostatic pressure, and a colloid-rich, water-poor region (Colloid Phase, C). In general, Phase C corresponds to the matrix of macromolecules that makes up the interstitial ground substance. The system of nonlinear partial differential equation was solved numerically for the tissue layer of the muscle of 1 cm width with uniformly distributed capillary and lymphatic beds and an interstitial layer (0.015 cm) on the peritoneal surface free from cells and blood vessels using a distributed model. The model parameters were adjusted to provide a description of a typical single exchange with hypertonic glucose 3.86% solution. Diffusive and convective solute transport was analyzed on the example of plasma protein (albumin) and glucose (osmotic agent).

Numerical results of the developed model described the bidirectional water and protein transport in agreement with the data about flows and clearances from clinical studies. Computer simulation suggested that two-phase structure of the tissue allows for the separation of opposite fluid flows: fluid transport from the peritoneal cavity into the tissue (absorption) occurs mainly through the Fluid Phase, whereas the Colloid Phase is used for the water transport in the opposite direction (ultrafiltration). Moreover, the model predicted that glucose transport (mainly diffusive),

occurs across both phases. In contrast, the peritoneal transport of albumin, which leaks by convection to the peritoneal cavity, occurs mainly through the Colloid Phase.

Developmental Biology; Saturday, July 2, 11:00

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Collective migration in myxobacteria driven by adventurous motility and elongated cell shape

Myxococcus xanthus is a soil living bacterium that is capable of forming multicellular fruiting bodies. Thus, M. xanthus may serve as an attractive model system for studying organizational principles that allow individual cells to organize into and behave like a multicellular organism.

I will present our latest experimental insights on the cluster formation of adventurous myxobacteria with the main focus on statistical analysis [3]. Interestingly, initially unstructured colonies restructure into collectively migrating clusters and finally converge into a characteristic distribution of cluster sizes.

We envisage a simple mechanism for clustering based on the characteristic rod cell shape and cell motility. We made use of three modelling approaches, including a cellular Potts model, to elucidate their implications on multicellular organization [1,2]. Recently we have shown that self-propelled rods interacting just by volume exclusion exhibit a non-equilibrium transition to clustering [1]. Using both, statistical analysis and a mean field approach, we show that the models resemble the characteristics of the experimental cluster size distributions, including a clustering transition at a critical cell density.

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[3] Manuscript in preparation

Poster Session; Friday, July 1, 20:00

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Modelling the proliferation of transposons in the presence of environmental stress

Transposable elements (TEs) are DNA segments capable of changing their positions in the genome. Until recently, they have been considered to be selfish, parasitic DNA. As of late, however, they have been acknownledged to be a major driving force of genome evolution. The dynamics of TE proliferation in living organisms is not understood well. It is usually modelled with the assumption of so-called 'transposition-selection equilibrium' (TSE) a balance between the TE's selfish drive to multiply inside the host, increasing their numbers, and the deleterious influence of high TE copy number on the host, causing selective pressure against hosts with high TE counts. TSE models, however, fail to adequately explain certain behaviours observed in nature, such as explosive bursts of TE activity, dramatically varied TE counts between closely-related species, and increase of TE counts in domesticated variants of plants. I will present a non TSE-based, stochastic model of TE amplification that takes into account the stress exerted on host organisms by changing environment. Using this model, I will show how the various dynamics observed in nature (and not in TSE models) can be explained to be a result of interaction between environmental pressure, the organism's phenotype, and TE-driven adaptation.

Cell and Tissue Biophysics; Thursday, June 30, 11:30

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Stretch-dependent proliferation in a one-dimensional elastic continuum model of cell layer migration

Collective cell migration plays an important role in maintaining the cohesion of epithelial cell layers and wound healing. Disruption of cell migration can cause disease such as necrotizing enterocolitis, an intestinal inflammatory disease that is a major cause of death in premature infants. A recently developed mathematical model of cell layer migration during experimental necrotizing enterocolitis based on an assumption of elastic deformation of the cell layer leads to a generalized Stefan problem. The model is here extended to incorporate stretch-dependent proliferation, and the resulting PDE system is solved analytically and numerically. The efficiency and accuracy of adaptive finite difference and MOL schemes for numerical solution of the problem are compared. We find a large class of assumptions about the dependence of proliferation on stretch that lead to traveling wave solutions.

Stem cells and cancer; Wednesday, June 29, 14:30

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Models of stem cell differentiation in hematopoiesis and leukemia

Cancers and hematologic malignancies differ with respect to interindividual symptomatology, course of disease, treatment susceptibility and prognosis. Over the last decades oncological treatment strategies have been elaborated and optimized, nevertheless important aspects remain unknown. A systematic mathematical approach may help to better understand treatment failures and clinical heterogeneity of different cancers. Based on a model of cell differentiation and signal feedback possible scenarios of cancer development and their impact on consequences for treatment concepts will be compared. A calibration of the model to the hematopoietic system will serve to transfer theoretical results to the understanding of leukemias and myelodysplastic syndromes.

Bioengineering; Tuesday, June 28, 14:30

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Improving success rates of assisted reproduction technology by mathematical modelling

Assisted reproduction technology (ART) involves support of oocytes (eggs) and embryos in the laboratory for some period of time, and success rates are known to be highly dependent on laboratory conditions. It is believed that better reproduction of normal in-vivo conditions in the laboratory will bring improved success rates. At the very least knowledge of these conditions provides valuable guidance for setting laboratory conditions. Because measurement of in-vivo conditions is difficult, if not impossible in some circumstances, mathematical modelling is a valuable tool for gaining understanding of in-vivo environments.

We report on mathematical modeling for gaining a better understanding of the nutritional environment of mammalian oocytes in antral follicles. In particular reaction-diffusion models have been used in conjunction with experiments to investigate oxygen and glucose concentrations in the bovine follicle. Unlike oxygen which diffuses readily through cell walls, glucose molecules pass through via facilitated transport mechanisms. The model for glucose transport must reflect this fact and is, consequently, more complicated than that for oxygen. Experimental validation of our models is challenging and will be discussed.

The ultimate aim of this work is to improve the developmental competence of oocytes that have been harvested at an immature stage and matured in the laboratory, a procedure known as in-vitro maturation. The ability to successfully use such oocytes in an IVF program reduces the need for stimulation of the ovary to yield multiple mature oocytes for harvest and use in a traditional IVF program. This, in turn, makes ART available to women for whom ovarian stimulation drugs, as used in traditional IVF methods, are likely to cause life threatening illnesses. Reducing the use of these drugs also has the potential to reduce the cost of IVF.

Mechanical Models of Movement and Growth of Cells and Tissues I;
Wednesday, June 29, 14:30

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A mechanical model of cell motility and cell-subtrate interaction

Mechanical interactions between a cell and the substrate are vital for cell migration and are involved in various cellular processes, such as wound healing, embryonic development, a metastasis of cancerous tumors. In addition, experiments have shown that inter-cellular and cell-substrate mechanical interactions affect signal transduction pathways within the cell. As a result, understanding the nature of force generation by single cells and mechanical interaction of a cell with the substrate is extremely important.

In the talk, I will present a mathematical model of cell motility and cell-substrate interaction where the cell and substrate are modeled as elastic two-dimensional continua. The spatially and temporally dynamics cell-substrate attachments are treated as discrete spring-dashpot systems. A finite element implementation of the model of cell and substrate deformation is coupled to the equations governing the dynamics of the adhesions. The resulting simulations are used to better understand the oscillatory nature of amoeboid cell motility.

Epidemiology, Eco-Epidemiology and Evolution; Saturday, July 2, 11:00

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Chaos and noise in population biology

In several epidemiological and ecological case studies, the often subtle interplay between typical non-linear structures like co-existing attractors or dynamical saddles attracting in some state space directions and repelling in others and the effect of noise in these case will be investigated. Examples are dengue fever, seasonal influenza and retrospective measles studies as well as from classical predator-prey models. The findings in part come from empirical data analysis, here mainly from epidemiology due to the better data situation than in ecology, and also have impact on parameter estimation in such epidemiological systems.

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Modelling dengue fever epidemiology; Saturday, July 2, 08:30

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Sebastien Ballesteros
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On the origin of the irregularity of DHF epidemics

By using an estimated parameter set for the minimalistic multi-strain dengue model we analyse the stochastic version of the model investigating the interplay between stochasticity, seasonality and import.

Poster Session; Friday, July 1, 20:00

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Modelling population dynamics of human epithelial cell lines: the differential expression of c-erbB2 oncogene and breast tumour development

The comprehension of mechanisms underlying cancer development depends on the understanding of processes underlying tissue formation. In physiological condition, the tissues are maintained in a dynamic equilibrium, called homeostasis, where the cell number is kept essentially constant and is regulated based on reproduction, death and half-life rates of cellular population. Molecular alterations that disturb the homeostasis can be potentially dangerous. Mutations that would permit selective advantages, like a faster cell division, could lead to the formation of a clone of continuous growth. Repeated cycles of mutation, competition and natural selection form the basis of cancer development. The c-erbB2 oncogene is a membrane receptor with tyrosine kinase activity that belongs to the epidermal growth factor receptor family. C-erbB2 over-expression is observed in 25-30% of breast tumours and is an adverse prognostic factor. To study the molecular mechanism of c-erbB2, Harris at al. (1999) developed a model of c-erbB2 over-expression in conditionally immortalized mammary luminal epithelial cells. Two new lines, HB4a-C3.6 and HB4a-C5.2, expressing different levels of c-erbB2, were derived from the immortalized cell line HB4a. This work presents a computational model designed to mimic the experimental data obtained from the in vitro culture of HB4a-C3.6 and HB4a-C5.2 lineages. A discrete agent-based model, controlled by a dynamic system that represents c-erbB2 expression, simulates the cell culture dynamics. In order to validate the results, they were compared to experimental data, regarding cell cycle and population dynamics. The model will be applied to evaluate differential expression of 4 transcripts positively regulated by c-erbB2 tumours, evaluated by Real Time PCR in HB4a and HB4a-C5.2 cell lines. Their functional characterization will allow a better understanding of the molecular mechanisms behind c-erbB2 over-expression and breast tumour development.

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Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents I; Tuesday, June 28, 17:00

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Distributed Intra-Cellular Model of Hepatitis C Viral Replication and Resistance Evolution

The new generation of direct acting anti-viral (DAA) drugs for HCV led to the need for mathematical models that take in consideration the intra-cellular drug effects within clinical virology data. We have recently introduced the ICCI model that integrated the intra-cellular level of replication and resistance evolution processes with the cellular infection level (Guedj and Neumann, 2010). However, the ICCI model used a mean-field approach to treat all infected cell as the same dynamics, which we know is not accurate. Here, we present a new model (DIC) that describes the intra-cellular level dynamics integrated into the cell infection level whle taking into consideration the distribution of infected cells as function of the number of replication complexes in each cell. The DIC model shows that main novel findings of the ICCI model hold even when the mean-field assumption is released. Most importantly, the model allows for 2 modes of viral decline: either the delta model, where long term viral decline slope is governed by the loss of infected cells, or the gamma mode, where the viral decline is more rapid and related to the intra-cellular loss of replication complexes. Furthermore, the DIC model shows that while on the delta mode the distribution of cells with different number of replication complexes is held stable, on the gamma mode the distribution of cells is shifting towards intra-cellular clearance. We have also established the properties of the infected cell distribution at steady state. The model was able to show a good fit for a wide range of results observed in real patients treated either with IFN based therapy or DAA combination therapy. In a second part of the work we have established the various resistance evolution patterns observed with the ICCI model hold also without the mean-field assumption. Furthermore, we show how the distribution of cells with different number and identity, wild-type versus resistant, of replication complexes follows specific patterns during evolution of resistance. These results are important for our understanding of the DAA therapy effect and allowing us to optimize treatment and prevent resistance evolution.

Modeling of collective phenomena in biological systems; Saturday, July 2, 08:30

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Measures of heart rate complexity

For nearly three decades, human heart rate variability (HRV) has been consistently shown to display intriguing and puzzling characteristics, to a large degree defying satisfactory explanation and posing challenges for both modelling and clinical treatment. Recent findings confirm that the HRV regulatory system represents a prominent example of a biological complex system and remains a benchmark of biocomplexity.

Continued theoretical and experimental effort is required to achieve a thorough understanding of this systems complexity. From the point of view of control engineering, such an understanding should be capable of explaining regulatory mechanisms. Within a physics approach, it should reveal striking properties of universality. From a clinical perspective, it should demonstrate the utility of prognostic and predictive algorithms.

In my talk, I will provide a review of the measures of complexity utilised in various aspects of HRV signal processing, focusing on those providing a unifying thread for the challenges above. Particular stress will be laid on the most up-to-date multi-time and multiscale evaluation of non-Gaussian properties of HRV.

Mechanics of the cytoskeleton and cortical actin at the cellular level;
Saturday, July 2, 08:30

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Computational explorations of cellular blebbing

Blebbing occurs when the cytoskeleton detaches from the cell membrane, resulting in the pressure-driven flow of cytosol towards the area of detachment and the local expansion of the cell membrane. Recent interest has focused on cells that use blebbing for migrating through three dimensional fibrous matrices. In particular, metastatic cancer cells have been shown to use blebs for motility. A dynamic computational model of the cell is presented that includes mechanics of and the interactions between the intracellular fluid, the cell membrane, the actin cortex, and internal cytoskeleton. The Immersed Boundary Method is modified to account for the relative motion between the cytoskeleton and the fluid. The computational model is used to explore the relative roles in bleb formation time of cytoplasmic viscosity and drag between the cytoskeleton and the cytosol. A regime of values for the drag coefficient and cytoplasmic viscosity values that match bleb formation time scales is presented. The model results are used to predict the Darcy permeability and the volume fraction of the cortex. Applications of the model to blebbing-based cell motility are discussed.

Poster Session; Friday, July 1, 20:00

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Microarray gene expression studies and real time RT-PCR validation for the DNA damage and repair pathway

Different low-level preprocessing methods for Affymetrix microarrays data were evaluated based on concordance with a real time RT-PCR method. The aim of low-level analysis is to measure gene expression levels, and to allow comparison of the results from more than one array. In this paper three of the most popular preprocessing methods: MAS5, RMA and GCRMA, were used. Expression of genes from the DNA damage and repair pathway were analyzed through the MAS5 - single array analysis algorithm, the GCRMA - probe-specific background correction and multiple array analysis, or RMA - mismatch probes ignored and multiple array analysis.
The data were derived from experiments conducted with the Affymetrix platform U133A. For biological testing the colorectal carcinoma HCT 116 cell line was chosen. The cells were irradiated with 4 Gy of ionizing radiation, and non-irradiated cells used as a control group. After microarray data analysis, real time RT-PCR was conducted. As an indicator for concordance between microarray experiments and real time RT-PCR, the percentage of genes with the same direction of changes in irradiated and non-irradiated cells was used. The computational analysis was finished with the PLS-based (partial least squares-based) gene selection method, which enables assignment of the biological meanings for the genes with the highest weights in the PLS model. The PLS method, in contrast to the PCA (principal component analysis) criterion based on maximization of the variance of a linear combination of genes, extracts components by maximizing the sample covariance between the class variable and linear combination of genes. The information for genes included in components described by PLS can be directly related to the biological meaning of this analysis.
The results show that data preprocessed with the RMA method for microarray data has the best concordance with real time RT-PCR assays. The biological validation

for the best 10 genes with the highest weights in the PLS model proved its applicability in systems biology. Some of these genes (MSH2, RAD9A, XP) are sensors for nucleic acid damage, and others (NTHL1, TDP1 DCLRE1A, ERCC2, POLI, MPG, TREX2) are engaged in mechanisms of DNA repair. Obviously, the best score was obtained for genes responsible for signaling cellular stress after ionizing radiation.

This work was supported by grants No. N N 518497639 from the Polish Ministry of Education and Science and BK 221/Rau1/20 from the Silesian University of Technology

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Cancer; Tuesday, June 28, 11:00

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Spatio-temporal modelling of the Hes1 and p53 pathways

The correct localisation of transcription factors is vitally important for the proper functioning of many intracellular signalling pathways. Experimental data has revealed that many pathways exhibit oscillations, both temporally and spatially, in response to certain external stimuli. Negative feedback loops are important components of these oscillations, providing fine regulation for the factors involved. In this talk, mathematical models of two such pathways–Hes1 and p53–are presented. Building on previous mathematical modelling approaches, we derive systems of partial differential equations to capture the evolution in space and time of the variables in the Hes1 and p53 systems. Through computational simulations we show that our reaction-diffusion models are able to produce sustained oscillations both spatially and temporally, accurately reflecting experimental evidence and advancing previous models. The simulations of our models also allow us to calculate a diffusion coefficient range for the variables in each mRNA and protein system, as well as ranges for other key parameters of the models, where sustained oscillations are observed. Furthermore, by exploiting the explicitly spatial nature of the partial differential equations, we are also able to manipulate mathematically the spatial location of the ribosomes, thus controlling where the proteins are synthesized within the cytoplasm. The results of these simulations predict an optimal distance outside the nucleus where protein synthesis should take place in order to generate sustained oscillations.
Using partial differential equation models, new information can be gained about the precise spatio-temporal dynamics of mRNA and proteins. The ability to determine spatial localisation of proteins within the cell is likely to yield fresh insight into a range of cellular diseases such as diabetes and cancer.

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Poster Session; Friday, July 1, 20:00

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Measures of generation time problems and clarifications

Generation time is a frequently used term in biology it is for example used in estimates of rate of evolution. Further it is an important parameter for evaluations of extinction risks of species and populations in conservation biology. Generation time is used by the International Union for Conservation of Nature (IUCN) to scale time based-measures of extinction risk in species where three generations is longer then 10 years. Although the term is frequently used there is no clear definition and the three main mathematical methods to estimate generation time of populations are incoherent. Which leads to confusion when generation time is to be calculated for threatened species. A number of papers have pointed out the ambiguity connected to generation time. However an overview of the definitions and usage of the term is lacking in the literature. This work aims to bring some clarity into the measures of generation time especially in the area of conservation. It is of great concern that already threatened species are not disfavored according to inadequate calculations in the system meant to save them.

Moving Organisms: From Individuals to Populations; Wednesday, June 29, 17:00

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Cell dispersal: some nonparametric and multiscale aproaches

We provide a short overview of the current approaches to modeling cell motion through various media, thereby focussing on the model scales, ranging from the microscopic, intracellular level through the mesoscale of the joint action of population constituents toward the behavior of the entire population on the macroscopic level.

In this context we propose and analyze a multiscale model for bacterial motility in the framework of partial differential equations. Further we present an alternative approach which relies on stochastic processes accounting for the underlying motion phenotype and uses a nonparametric statistical technique in order to directly assess the macroscpic cell population density from data (if available) or numerical simulations of the cell trajectories. This nonparametric approach allows to handle detailed multiscale models in a complexity which in the context of PDEs is still prohibitive for the numerics.

We will also provide an outlook on the potential of the method for further interesting biomedical problems.

Cancer; Tuesday, June 28, 14:30

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Multi-Cell Tumor Growth Modeling Using CompuCell3D

Mathematical modeling and computer simulation have become crucial to biological fields from genomics to ecology. However, multi-cell, tissue-level simulations of development and disease have lagged behind other areas because they are mathematically more complex and lacked easy-to-use software tools that allow building and running in-silico experiments without requiring in-depth knowledge of programming. Recent advances in development of multi-scale, multi-cell simulation environments allow broad range of researchers to develop relatively easily sophisticated simulations of development or disease. In this talk I will present Glazier Graner Hogeweg (GGH) model, its extensions to support subcellular Reaction-Kinetics(RK) models and CompuCell3D a simulation environment supporting GGH and RK modeling. To demonstrate CompuCell3D [1] capabilities I will present a 3D multi-cell simulation of a generic simplification of vascular tumor growth [2] which can be easily extended and adapted to describe more specific vascular tumor types and host tissues. Initially, tumor cells proliferate as they take up the oxygen which the pre-existing vasculature supplies. The tumor grows exponentially. When the oxygen level drops below a threshold, the tumor cells become hypoxic and start secreting pro-angiogenic factors. At this stage, the tumor reaches a maximum diameter characteristic of an avascular tumor spheroid. The endothelial cells in the pre-existing vasculature respond to the pro-angiogenic factors both by chemotaxing towards higher concentrations of pro-angiogenic factors and by forming new blood vessels via angiogenesis. The tumor-induced vasculature increases the growth rate of the resulting vascularized solid tumor compared to an avascular tumor, allowing the tumor to grow beyond the spheroid in these linear-growth phases. In contrast to other simulations in which avascular tumors remain spherical, our simulated avascular tumors form cylinders following the blood vessels, leading to a different distribution of hypoxic cells within the tumor. Our simulations cover time periods which are long enough to produce a range of biologically reasonable complex morphologies, allowing us to study how tumor-induced angiogenesis affects the growth rate, size and. morphology of simulated tumors. At the conclusion of the talk I will show a live demo (5-10 minutes) of CompuCell3D and demonstrate how, starting from relatively simple toy-models of cell-sorting, contact-inhibited chemotaxis and nutrient-dependent cell growth/cell division, we can build a fairly realistic simulation of vascularized tumor growth. Such simulation can be further improved to produce simulation equivalent to the one published in [2].

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Computational toxicology and pharmacology - in silico drug activity and safety assessment; Saturday, July 2, 11:00

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Systems Biology driven Pharmacokinetics and Pharmacodynamics

Pharmacokinetics is probably the most neglected field in the medically relevant biosimulations. It is a science about the drug fate in a living organism and embraces in broader sense four main domains: absorption, distribution, metabolism, and excretion, in short ADME. It is often combined and considered together with pharmacodynamics, a science branch dealing with the influence the drug has on its target and eventually on the whole body and disease progression. At the same time, the mechanism based but in most cases drugfree models and simulations are highly appreciated and developed in the Systems Biology community. There is no doubt that the full understanding of the underlying phenomena like physiological regulation and control, phenotypes, mutations and in general diseases is essential for the progress in medicine. However, much has been achieved in the last decades without sophisticated algorithms and supercomputers. Semimechanistic models or even simple phenomenological formulas and models are in use since beginning of the 20th century providing useful insights in e.g. physiology and pharmacokinetics related issues. We are convinced, that parallel application of these two seemingly unconnected approaches can eventually converge into more effective treatments methods now or in near future. We are making an attempt to introduce a new platform combining standard phenomenological models used in the PK/PD field with mechanistically based Systems Biology models and approaches. There are many examples of wellknown 1, 2 or more compartmental models providing valuable initial guesses and insights into the metabolism, and ADME processes in general, of a particular drug. However, their use is limited due to the non-mechanistic nature of such models. We consider Systems Biology driven models as complementary to their phenomenological counterparts. The ultimate goal of a wholebody full mechanistic model for the combined PKPDADME is doable on the scale of next few decades, but to support modern drug development now, we need the imperfect but useful phenomenological models in combination with mechanistic models under development.

Bioinformatics and System Biology; Wednesday, June 29, 17:00

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Modeling and Integration of Biological Networks with BiNArr

The investigation of biological networks for their better understanding and making available for practical use is currently an important task in systems biology. The authors developed an integrated environment BiNArr (Biological Network Arranger) aimed to perform a number of practically useful operations on the network data stored in biological databases. Dissimilar to the existing tools like Cytoscape the functionality of our application is rather limited and strictly oriented for transforming structured data from real databases into graphs. This allows its further processing e.g. with use of graph mining algorithms. We proposed the unified graph representation for the structures extracted from original resources and developed the modules for their visualization and edition. Another worthy features are: the automatic coding of the resulting graphs in several formats, the ability to generate graphic files for presentation purposes and an open architecture enabling to cooperate with number of existing biological databases. In order to present capabilities of BiNArr we used the biological structures representing metabolic pathways extracted from KEGG (Kyoto Encyclopedia of Genes and Genomes) as well as protein-protein interactions provided in DIP (Database of Interacting Proteins).

Structure and Dynamics of Biochemical Reaction Networks I; Tuesday, June 28, 14:30

David Swigon
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Decomposition of chemical reaction networks

I will outline the ideas behind a novel theory for analyzing the long term dynamics of chemical reaction networks with mass action kinetics based on the combination of Deficiency Theory of Horn, Johnson, and Feinberg, and the decomposition of networks into extreme subnetworks, pioneered by Clarke. This is a work in progress, but among the results that have been obtained are the formulation of new sufficient conditions for the existence of a unique asymptotically stable positive equilibrium that generalize the Deficiency Zero Theorem.

Structure and Dynamics of Biochemical Reaction Networks I; Tuesday, June 28, 14:30

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Dynamically equivalent reaction networks: a computational point of view

It has been known from the 'fundamental dogma of chemical kinetics' that different mass action type reaction networks can give rise to the same ordinary differential equations describing the time evolution of specie concentrations. Finding dynamically equivalent network structures with preferred properties can significantly enhance the application range of the known and continuously developing strong results on the relation between network structure and qualitative dynamical properties (deficiency theorems, structural conditions on the possibility of multiple steady states, Global Attractor and Persistency Conjectures etc.). It is also known primarily from systems and control theory that the numerical feasibility of many existence and design problems can often be checked via appropriately formulated optimization tasks even if the original problem is algebraically complex to treat. In this talk, an overview of linear programming (LP) and mixed integer linear programming (MILP) techniques will be given for the computation of reaction networks with prescribed properties. This includes the computation of structures with the minimal/maximal number of reactions/complexes, detailed/complex balanced, and fully/weakly reversible realizations.

Modeling of immune responses and calcium signaling III; Wednesday, June 29, 17:00

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Bifurcation phenomena in spatially extended kinase-receptor interaction model

We consider a reaction-diffusion model of mutual interaction of membrane receptors with kinases proposed in [1]. It is assumed that membrane receptors and cytosolic kinases activate each other, which establishes the positive feedback. The kinases and the receptors are dephosphorylated by uniformly distributed phosphatases. The existence of positive feedback leads to bifurcation at which the positive stable solution appears.

In this study we consider, unlike the authors in [1], the case of nonuniformly distributed membrane receptors. We apply the Steklov eigenproblem theory [2] to analyze the linearized model and find the analytic form of solutions. This approach allows us to determine the critical value of phospahatase activity at which cell activation is possible as a function of kinase diffusion coeffcient and anisotropy of receptor distribution using only algebraic methods.

We showed that cell sensitivity grows with decreasing kinase diffusion and increasing polarity of receptor distribution. Moreover, these two effects are cooperating. The solutions to the original nonlinear system close to the bifurcation point can be approximated by the solution to the linearized one. Moreover this approximation can be improved by using the method of successive approximations.

References.

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Developmental Biology; Saturday, July 2, 11:00

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Analysis of the Lateral Root Morphology with the Use of the Fast Fourier Transform

During the lateral root (LR) development both the size and the form of the organ change continuously since the moment of its initiation in the pericycle of the mother root until it reaches its mature form. Subsequent stages of the LR formation with typical changes of its form and cell pattern are known [1]. However, our observations [2] prove that in the early stages, when the LR promordia push through tissues of the mother root, they show a great diversity of their surface morphology. Most of the forms are repeatable, few occur as single cases. From mechanical point of view the LR formation may be interpreted as a bucling and the observed changes in shape as local deflections on the root apex surface resulting from a pressure of the surrounding tissues of the mother root. This irregularity in form may suggest changeable mechanical properties of the cells on the surface of the LR apex. The aim of our study is to analyze atypicaly formed LRs in comparison with the apices of typical morhology as well as to estimate mechanical properties of the LR apex basing on deflections in their structures. The LR primordia forming in the Arabidopsis thaliana roots were photographed in Nomarski contrast microscopic technique in their axial sections. The outlines of the chosen LRs showing typical and atypical shapes were digitized. The coordinates were introduced as initial data to a program analyzing the shapes of the apices. The basic assumtion of our model were the following: (i) a surface of a typicaly shaped LR is a circular paraboloid [3]; (ii) trajectories of principal directions of stress form a pattern of paraboloids [3]; (iii) deflections (irregularities) on the organ surface are local and small in comparison to the apex size. The LR formation was analyzed in terms of mechanical buckling. In the model we applied the Fast Fourier Transform method a standard tool adopted to description of buckling [4, 5]. This allowed determining the deflection curves through the trigonometric series. Our results show that the outline of each LR apex of the unchanged geometry (independently on the stage of development) may be described by one parabolic curve, which in the parabolic coordinates refers the line 1.2. Thus the curves representing the outlines of atypicaly formed LRs where in the first step adjusted to that line. For each studied curve the Fourier spectrum (amplitude and phase) was calculated . On this basis we were able to classify atypicaly shaped LR apices. Then applying the Euler formula to the elastic buckling we estimated basic mechanical moduli for the studied cases. On the basis of the results the following connclusions can be drawn: (i) the Fourier Transform may be a useful tool to a shape annalisys of the living structures; (ii) mechanical moduli of a growing plant organ tissues can be estimated on the basis of the organ shape and its deformations; (iii) the mechanical properties of growing plant tissues

may be regulated by biological factors like plant growth hormones as well as the cell wall achitecture. The last needs additional studies.

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Modeling of immune responses and calcium signaling IV; Saturday, July 2, 08:30

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Modeling of self-regulating gene

We study the variance of the number of proteins produced in a self-regulating gene in a steady state with both one and two copies of gene. Master equations and differential equations for the first and second moments of the variable describing the number of proteins are formulated in both models. Various approximation schemes are used in order to close the set of equations for the moments. Specifically, we examine the dependence of the variance on the adiabaticity parameter measuring the relative rate of DNA-protein unbinding and protein degradation. We compare the variance obtained in models with one and two gene copies.

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Mathematical modelling of cancer invasion: distinguishing between the relative importance of cell-cell adhesion and cell-matrix adhesion

The process of invasion of tissue by cancer cells is crucial for metastasis – the formation of secondary tumours – which is the main cause of mortality in patients with cancer. In the invasion process itself, adhesion, both cell-cell and cell-matrix, plays an extremely important role. In our talk we present a novel mathematical model of cancer cell invasion of the extracellular matrix taking into account cell-cell adhesion as well as cell-matrix adhesion. Considering the interactions between cancer cells, extracellular matrix and matrix degrading enzymes, the model consists of a system of reaction-diffusion partial integro-differential equations, with non-local (integral) terms describing the adhesive interactions between cancer cells and the host tissue, i.e. cell-cell adhesion and cell-matrix adhesion. We first describe the main results that we obtained from a mathematical analysis of the model, i.e. the existence and uniqueness of global in time classical solutions which are uniformly bounded. Then, using computational simulations we investigate the effects of the relative importance of cell-cell adhesion and cell-matrix adhesion on the invasion process. In particular we examine the roles of cell-cell adhesion and cell-matrix adhesion in generating heterogeneous spatio-temporal solutions.

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A New Mathematical Model for combining Transport and Degradation in the Small Intestine

The small intestine is responsible for the major part of feedstuffs digestion in the gastrointestinal tract. Several models have been developed for representing the digestion of a bolus in the small intestine ([**1**], [**2**], [**3**]). This work tries to go further in modeling these phenomena by representing a simultaneous model for degradation and absorption of feedstuffs and their transport in the intestinal lumen. Specifically, we determine the position of the bolus and the proportion of the constituents at each time. In the first part of this study, we present four successive models which reflect the modeling process at its different stages with our attempts to make it more realistic by inclusion of more relevant biological phenomena. The small intestine is assumed to be a one-dimensional interval and the bolus moves through its lumen due to migrating myoelectric complex. The bolus is treated as a homogeneous cylinder with a fixed length ℓ and variable radius $R(t)$. The degradation of feedstuffs is the result of volumic and surfacic transformations. This model is based on a system of coupled ordinary differential equations. These equations are solved by a classical numerical integration using Runge-Kutta method. The results of simulation are consistent with the experimental works in the literature (e.g. in the case of purified starch [**5**]), although more analysis and experimentations are needed to represent the reality more closely.

The second part of this work consists in using the homogenization method to simplify the transport equation and justify the choice of the rate of absorption by intestinal wall [**4**].

The transport of bolus inside the small intestine is induced by high frequency pulses. These pulses cause rapid variation of the bolus' velocity in the small intestine. We show mathematically that the pulses can be averaged out in an appropriate way therefore the rapidly varying velocity can be replaced by a slowly varying one.

Because of the lack of information about the properties of the small intestine wall, the local absorption rate is not precisely defined. Although, an effective or averaged rate of absorption is determined by help of homogenization methods [**6**]. To this aim, a 3-D transport-diffusion PDE in the domain Ω_ϵ with a Neumann

boundary condition (reflecting the Fourier's law) is defined. The domain Ω_ϵ describes the small intestine. It is a 3-D domain with a small radius r_ϵ and a highly oscillating boundary. The oscillation of its boundary is justified by the presence of the fingerlike villi which cover the inner surface of the small intestine. The unknown of the problem being the the absorbable nutrients, the boundary condition represents the absorption rate by intestinal wall. To justify the choice of a constant absorption rate, our method consists in a passage to the limit from this equation to obtain a 1-D transport equation with a constant averaged rate of absorption .

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Poster Session; Friday, July 1, 20:00

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Derivation of yearly transition matrix of land-use dynamics and its applications

Transition matrices have often been used in landscape ecology and GIS studies of land-use to quantitatively estimate the rate of change. When transition matrices for different observation periods are compared, the observation intervals often differ because satellite images or photographs of the research site taken at constant time intervals may not be available. For such calculation, several previous studies have utilized a linear algebra formula of the power root of matrices. However, three difficulties may arise when applying this formula to a practical dataset from photographs of a research site. We examined the first difficulty, namely that plural solutions could exist for a yearly transition matrix, which implies that there could be multiple scenarios for the same transition in land-use change. Using data for the Abukuma Mountains in Japan, we then looked at the second difficulty, in which we may obtain no positive Markovian matrix and only a matrix partially consisting of negative numbers. We propose a way to calibrate a matrix with some negative transition elements and to estimate the prediction error. Finally, we discuss the third difficulty that arises when a new land-use category appears at the end of the observation period and how to solve it. We developed a computer program to calculate and calibrate the yearly matrices and to estimate the prediction error.

Poster Session; Friday, July 1, 20:00

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Meta-stable states and macro-evolutionary transitions in an eco-evolutionary food-web model

Eco-evolutionary food-web models help elucidate the processes responsible for the emergence and maintenance of complex community structures. However, most existing community-evolution models are based on random speciation, and thus do not consider the gradual evolution of trophic traits. Furthermore, intermittent bursts of evolution associated with punctuated equilibria highlight the importance of describing not only an evolved community's structure, but also the underlying evolutionary dynamics. While models based on the concept of self-organized criticality help understand non-equilibrium community dynamics, they have so far been based on strongly simplified assumptions about ecological interactions. Using an individual-based model, here we incorporate the gradual evolution of key traits for foraging and interference interaction into a model of non-equilibrium community evolution. We find that our model communities quickly diversify into autotrophs (plants) and consumers (herbvivores), with distinctive phenotypic clusters resulting from successive speciation driven by plant-herbivore coevolution. Occasionally, all herbivores go extinct in sudden macroevolutionary transitions, with the remaining community primarily featuring plants. Our findings thus reveal a pattern of community macroevolution involving two meta-stable states, corresponding to a plant–herbivore community and a plant community, respectively. On the evolutionary timescale, our model community switches stochastically and rapidly between these two alternative community states. We explain the processes responsible for the breakdown of plant–herbivore communities in our model, as well as for the subsequent reestablishment of herbivore diversity. Our model thus helps us understand the eco-evolutionary mechanisms underlying these recurrent dynamics of rapid community breakdown and regeneration, which terminate intermittent periods of near-stasis or punctuated equilibrium.

Population Genetics; Wednesday, June 29, 14:30

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From Population Dynamics to Evolution: Oscillation in Lateral Asymmetry of Fish Induces the Evolution of Homozygote Incompatibility

Lateral asymmetry, originally found in scale eating cichlid fish in Lake Tanganyika, was first considered to follow the simple Mendelian genetics. Later, more controlled mating experiments on scale eaters and other fish reveal that they lack lefty (dominant) homozygote. Lethality of lefty homozygote explains F1 ratio, but not the high hatchability of lefty pairs. We construct models of incompatibilities of lefty homozygote and investigate the condition for the invasion and fixation of the incompatibility gene. Laterality morph frequencies in many fish oscillate due to cross-predation among prey and predators: predators feed on prey of the same laterality with them more than those of different laterality. Incompatibility gene, that prevents eggs of lefty gene from fertilizing sperm of lefty gene, spreads in case of group spawning, as long as laterality morph frequencies oscillates. Under pair spawning condition, however, incompatibility gene does not spread, as incompatibility gene prevents part of eggs to fertilize in some genotype combinations. We consider partial incompatibility where eggs of the incompatibility gene and the lefty gene fertilize with sperm of lefty gene in smaller ratio than sperm of righty gene. The incompatibility gene spreads even under pair spawning condition if its incompatibility is partial. We also study the evolution of the level of incompatibility by simulating the dynamics of frequencies of two incompatibility genes of different incompatibility levels both in prey and predator. Stronger cross predation, large predation coefficient, as well as larger survival rate lead to larger level of the lefty homozygote incompatibility.

Recent developments in the study of Lotka-Volterra and Kolmogorov systems; Saturday, July 2, 14:30

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Global stability of Lotka-Volterra equations

This presentation will review some conditions of global stability of Lotka-Volterra equations and discuss on the relationship between the stability and the structure of the systems.

Y. Takeuchi; *Global Dynamical Properties of Lotka-Volterra Systems*, World Scientific 1996.

Neurosciences; Friday, July 1, 14:30

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Detection of the first-spike latency

Response latency is the duration between the delivery of a stimulus and the response. In neurosciences, it is of interest to study the first-spike latency, i.e. the intertime between the onset of a stimulus and the first-response spike. However, when spontaneous activity is observed, this task becomes more complicated. To deal with this problem, we apply the statistical method introduced recently by Lansky et al. [1]. Some preliminary analysis on real data as well as some theoretical results on Wiener processes are here presented.

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Developmental Biology; Saturday, July 2, 11:00

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Mathematical modelling of pronuclei migration in the mammalian egg

At this time it remains unanswered how the embryonic-abembryonic axis of the mouse blastocyst is first established. Cell-fate is flexible in the sense that the development can recover from perturbations. However, the early mouse embryo is not merely a uniform ball. The cells show some preferences for adopting certain positions that will in turn govern their developmental decisions. Our main question is: When are these preferences established? Cell-fates could be decided completely at random but it is also possible that these decisions are guided by even as early contributing factors as the first cleavage of the egg. The orientation of the opposing pronuclei plays most likely a decisive role in the polarity of the developing embryo. Earlier studies of the mouse embryo development show deviating results of when patterning is initiated in the egg, [1]-[4], [6], [7]. Some of these studies that conclude that the pattern formation starts later in the embryo have however been conducted in 2D. We think it is important to see this as a three dimensional problem to reduce bias in the results. The purpose of introducing our model of the migration is to easier visualize the fertilization process to answer these questions. The usefulness of a mathematical model of the migration is not only a case for visualization, but could also be used to predict outcomes by simulating different scenarios, such as the dependence of the point of sperm entry. Also, values of model parameters can be used to quantify the effect of standard treatment or measurements of fertilized eggs in the lab. From the model we can make simulations of the migration process and plot the meeting positions for the pronuclei. As data we use stacks of confocal microscopy time-lapse images of the pronuclei migration, and realistic parameters in the models are identified by statistical methods. Given different distances between the sperm entry and the position of the second polar body, the estimated models are then used to produce distributions of orientations of the meeting plane between the pronuclei. Parameter values corresponding to the size of these forces are estimated from data of both eggs treated with a microtubule inhibitor and untreated eggs. The centralization force is modelled by two mechanisms of pushing and pulling of the microtubule exerted forces. The model is essentially based on two forces of attraction, a general migration directed towards the centre of the cell, and a second attraction force towards the other pronucleus. From this we have for example an indication that the pulling mechanism is more significant than the pushing.

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Epidemic models: Networks and stochasticity II; Thursday, June 30, 11:30

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From Markovian to pairwise epidemic models and the performance of moment closure approximations

Many if not all models of disease transmission on networks can be linked to the exact state-based Markovian formulation. However the large number of equations for any system of realistic size limits their applicability to small populations. As a result, most modelling work relies on simulation and pairwise models. In this paper, for a simple SIS dynamics on an arbitrary network, we formalise the link between a well known pairwise model and the exact Markovian formulation. This involves the rigorous derivation of the exact ODE model at the level of pairs in terms of the expected number of pairs and triples. The exact system is then closed using two different closures, one well established and one that has been recently proposed. A new interpretation of both closures is presented, which explains several of their previously observed properties. The closed dynamical systems are solved numerically and the results are compared to output from individual-based stochastic simulations. This is done for a range of networks with the same average degree and clustering coefficient but generated using different algorithms. It is shown that the ability of the pairwise system to accurately model an epidemic is fundamentally dependent on the underlying large-scale network structure. We show that the existing pairwise models are a good t for certain types of network but have to be used with caution as higher-order network structures may compromise their effectiveness.

Population Dynamics; Tuesday, June 28, 14:30

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Optimal foraging predators in Leslie Gower models with alternative prey

Optimal foraging theory defines the diet choice of a predator by imposing that it chooses the prey that is instantaneously the most beneficial for him [1]. It has been shown that this phenomenon leads to a switching diet and to the persistence of both prey and predators in generalized Lokta-Volterra models [2, 3]. This framework can be useful to study the influence of an introduced alternative prey on a one-prey-one-predator system. In a Lokta-Volterra model, this introduction can enhance predator growth and have negative effects on the main prey, which is called *apparent competition* [4].

In this work, we focus on a Leslie-Gower model with two dynamic prey, where the preyed population determines the carrying capacity of the predator population. Optimal foraging aiming at the maximization of the *per capita* growth rate of the predator population then leads to the maximization of its instantaneous carrying capacity. This optimization defines two main regions in the population state space, separated by a dividing plane, and thus three diet strategies. The predator population will have the choice between eating only the main prey, or only the alternative prey, or following a mixed diet. In each of these three regions, the dynamics which are relevant to the predator reduce to a Leslie-Gower model with a stable positive equilibrium.

Depending on the parameters of the system, different global behaviors arise. However, in all cases, there is only a single positive stable equilibrium, which can potentially lie on the dividing plane; the equilibrium is such that its predator population is larger or equal than that in the absence of the alternative prey. Also, the presence of an alternative prey is never detrimental to the main prey; so the *apparent competition* does not hold.

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Poster Session; Friday, July 1, 20:00

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Modeling of the Adaptive Network of True Slime Mold

We describe here a mathematical model of the adaptive dynamics of a transport network of the true slime mold Physarum polycephalum, an amoeboid organism that exhibits path-finding behavior in a maze. This organism possesses a network of tubular elements, by means of which nutrients and signals circulate through the Physarum. When the organism is put in a maze, the network changes its shape to connect two exits by the shortest path. By reproducing this phenomenon we introduce new method to solve shortest path problem. In addition, Physarum makes various optimal network for their environmental condition. It is similar to human transportation network. We will talk about the mathematical model of Physarum which can apply to various adaptive network.

References.

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B and T cell immune responses; Wednesday, June 29, 11:00

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Modelling CD8 T-Cell Immune Response

This work has been made in collaboration with Christophe Arpin (INSERM U851, Lyon), Fabien Crauste (Univ. Lyon 1), Clarisse Dubois (INSERM U851, Lyon), Olivier Gandrillon (Univ. Lyon 1), Stéphane Genieys (Univ. Lyon 1), Isabelle Lemercier (INSERM U851, Lyon), Jacqueline Marvel (INSERM U851, Lyon)

The primary CD8 T-cell response, due to a first encounter with a pathogen, happens in two phases: an expansion phase, with a fast increase of T-cell count, followed by a contraction phase. This contraction phase is followed by the generation of memory cells. These latter are specific of the antigen and will allow a faster and stronger response when encountering the antigen for the second time. Several works recently proposed models of the CD8 immune response [1, 2, 3, 4]. Some of these works do not consider any regulation of the immune response [1, 2, 4], whereas others propose very detailed and complex models [3].

We will present two models of the primary response, in which nonlinearities account for molecular regulation of cell dynamics. The first one, inspired by [2], is based on ordinary differential equations. The second one, inspired by [1], is based on partial delay differential equations, and the delay takes into account the time cells take to differentiate from one state to the other one. We will discuss in particular the roles and relevance of feedback controls that could regulate the response. Then, we will show some simulations we can get from the models and confront them to experimental data. Finally, we will consider the problem at the molecular scale, with a model describing the network of molecular regulations in a T-cell during the immune response.

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Population Dynamics; Wednesday, June 29, 14:30

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Optimal Treatment Strategies for Malaria Infection

We develop a numerical method for estimating optimal parameters in a mathematical model of the within-host dynamics of malaria infection. The model consists of a quasilinear system of partial differential equations. We present several numerical simulations that suggest that periodic treatments that are in synchronization with the periodic bursting rate of infected erythrocytes are the most productive strategies.

Semigroups of Operators in Mathematical Biology I; Wednesday, June 29, 08:30

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Iterative approximation of the spectral radius of a positive operator

In population models with infinite dimensional structure, the basic reproduction number often is the spectral radius of an appropriate positive linear operator on an infinite-dimensional ordered Banach space. This operator is called next generation operator in case a biological interpretation is available. Since a closed expression for its spectral radius can only be obtained in special cases, there is renewed interest in the approximation and estimation of the spectral radius. Quite a few results are available in the operator theory and and computational/numerical literature. It is the purpose of this talk to review some of these and give them a new twist.

Bioimaging; Tuesday, June 28, 11:00

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Application of variational shape models in single cell tracking

The analysis of single cells provides valuable insights into ex vivo cell assays. This is achieved by taking time series of images of cell cultures and analyzing the behavior of the individual cells with respect to migration, division, mitosis and cell-cell interaction.

However, due to the large amount of data complete manual reconstruction of the cell trajectories is not feasible, which indicates a urgent need for automated methods. As computerized approaches lack the highly optimized features of human perception, it is especially the reliability of cell detection and the tracking in the presence of object occlusion and large displacements between single images which represent the major difficulties for individual cell tracking.

We present an essentially novel approach to mitigate these problems using recently developed methods in image processing incorporating prior shape knowledge into the detection of objects. In particular, the problem of object occlusions and blurry object outlines due to noise in the data can be handled by this extension. We adapted the active contour framework with prior shape information to the problem of robust cell detection. The method is able to detect cell shapes more accurately and thus allows for the utilization of refined tracking algorithms using more robust object features for the mapping of cells between images. We further present a direct application of the active contour models to the joint detection and tracking of moving, deformable cells.

Stochastic models in computational neuroscience I; Wednesday, June 29, 14:30

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Piecewise Deterministic Markov Processes and detailed neuron models.

In this talk I will introduce the family of Piecewise Deterministic Markov Processes. Systems described by these processes undergo deterministic evolution on random intervals. I will present some results about these processes including limit theorems and diffusion approximation. Models of neurons taking into account the stochasticity of ion channels make a natural example.

Biofluids, Solute Transport, and Hemodynamics; Wednesday, June 29, 11:00

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Towards integrative multiscale models of whole kidney structure and function

Existing models of renal function have generally focused on open questions of 'local' (i.e., intrarenal) physiology rather than on providing an overall description of renal function relevant to its role in the body and incorporating sufficient detail to address the roles of transporters and channels in each nephron segment We will present our current efforts towards a multi-organ systems model of blood pressure regulation. The resulting open-source platform will be oriented towards interactive exploration of targeted pathologies and their pharmacology. Our approach will be: (1) to complete an integrated endocrine/paracrine RAAS (renin-angiotensin-aldosterone system) model, (2) to build a whole-kidney model representing essential nephrovascular relationships in the three kidney zones and operational descriptions of specific transport processes in each nephron segment and to build up a multi-nephron model capable of addressing progressive renal failure, (3) to combine the renal and RAAS models in our modular core-model (based on the classic Guyton model), (4) to calibrate and validate the models on the basis of pre-clinical and clinical data related to physiological and pathological conditions, and finally (5) to produce a large population (>100 000) of 'virtual individuals' with randomized model parameters (analogous to genetic polymorphisms) for comparison with data from cohorts of real patients from our partner clinicians (and published clinical trials). These new tools, based on virtual physiopathological models of the kidney and RAAS, will be useful to investigate dysfunctions at the clinical level as well as at the level of scientific research and education.

Modeling of immune responses and calcium signaling V; Saturday, July 2, 11:00

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Calcium alternans in a piecewise linear model of cardiac myocytes

Cardiac alternans is a beat-to-beat alternation in action potential duration and intracellular calcium cycling seen in cardiac myocytes under rapid pacing that is believed to be a precursor to fibrillation. The cellular mechanisms of these rhythms and the coupling between cellular calcium and voltage dynamics have been extensively studied leading to the development of a class of physiologically detailed models, which are often expressed as coupled nonlinear differential equations. Here we establish that the key dynamical behaviours of the model developed by Shiferaw and Karma are arranged around a set of switches. Exploiting this observation we show that a piecewise linear caricature of the Shiferaw-Karma model can be constructed that preserves the physiological interpretation of the original model whilst being amenable to a systematic mathematical analysis. We compute the properties of periodic orbits without approximation and show that alternans emerge via a period-doubling instability. We also demonstrate that when coupled to a spatially extended description for calcium transport the model supports spatially varying patterns of alternans. We analyse the onset of this instability with a generalisation of the master stability approach to accommodate the non-smooth nature of our system.

Modeling of immune responses and calcium signaling V; Saturday, July 2, 11:00

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Hierachic stochastic modelling of intracellular Ca(2+) signals - a new concept based on emergent behaviour of biomolecules

Biological systems often exhibit complex spatio-temporal dynamics and are stochastic at the same time. That is a challenge for mathematical modelling, since standard techniques then either apply rude assumptions like mean-field theories, or they lead to astronomic numbers of system states. As a new concept, we formulate a theory in terms of interevent interval distributions describing mesoscopic cluster states.

Here we consider intracellular Ca(2+) dynamics, where channel clusters are known to evoke local Ca(2+) release events that eventually induce cellular concentration spikes by diffusive coupling. However, the new modeling framework can potentially also be applied to other systems consisting of coupled clusters of biomolecules, like T cell receptor clusters or chemotaxis. Describing system dynamics in terms of probability distributions instead of rate-laws implies that the model becomes non-Markovian, but it has the advantage that the shape of the distributions reflects the microscopic dynamics without considering them in detail. Moreover, probability distributions of cluster state-changes can often be measured in vivo or calculated from known constraints, in contrast to kinetic parameters of state-changes of individual proteins.

Despite of the rather complicated integral equations appearing in the complete description of the dynamics, we arrive at simple expressions for stationary statistics at regular cluster arrangements, and stochastic simulations run quite efficiently. For Ca(2+) dynamics, we verify data input and output by fluorescence microscopy in HEK cells and thus provide strong support for the proposed stochastic model. Furthermore, we find valuable robustness properties of the stochastic mechanism, which might be one of the reasons for ubiquity of the Ca(2+) signalling toolkit in cell signalling.

Publications: Thurley and Falcke, PNAS 108:427-32 (2011); Thul, Thurley and Falcke, Chaos 19:037108 (2009).

Cell and Tissue Biophysics; Thursday, June 30, 11:30

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A multiscale model of mineralized fibril bundles - a homogenization approach

Modeling complex biological tissues like musculoskeletal mineralized tissues (e.g bone or tendon) is a challenging task. These tissues are characterized by one common building block, the so called mineralized collagen fibril (MCF). Depending on the tissue type the fibrils are organized in different pattern across many length scales. One important aim is to predict the elastic behavior of the tissue at a coarser length scale (effective stiffness) based on the structure and the material properties at a finer scale. This can be achieved using homogenization.

Most homogenization methods estimate the effective stiffness based on different structural assumptions at the finer scale and achieve hence different estimates. The choice of these methods is therefore a crucial part of the model definition. We analyze the influence of different homogenization methods, i.e. self-consistent method, Mori-Tanaka and asymptotic homogenization, on the effective stiffness estimates using a simple collagen-mineral material. Based on these results we build up a multiscale model for mineralized fibril bundles as present in mineralized tendon. In these fibril bundles the MCFs are aligned in parallel and additional stiffness is achieved by extrafibrillar mineralization. We apply this model to experimental data from circumferential tissue of the mineralized turkey leg tendon (MTLT) assessed by Scanning Acoustic Microscopy.

Our stiffness estimates are in very good agreement with the experimental data. The experimental studies of the MTLT also revealed that this tissue exhibits (besides circumferential tissue) another fine structure: loosely packed fibril bundles with high porosity (interstitial tissue). Its specific porous structure needs to be incorporated in the model through a further homogenization step.

Cellular Systems Biology; Thursday, June 30, 11:30

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Genetic Regulation of Cholesterol Biosynthesis

The regulation of cholesterol production is fundamental to maintaining good human health. Sterol regulatory element binding protein (SREBP) is a key regulatory transcription factor for lipid synthesis. In this work we present a nonlinear ordinary differential equation model of SREBP transcription in the context of the HMGR cholesterol biosynthesis pathway. SREBP transcription is regulated by forming an inactive complex with its end product, cholesterol, to control homeostatic concentration levels of cholesterol within the cell. Mathematical analysis of the dynamical system of equations shows it admits three distinct types of behaviour: (i) oscillations in the mRNA, HMGR protein and cholesterol expression levels; (ii) oscillations in the mRNA, HMGR protein and cholesterol expression levels which decay in time; and (iii) non-oscillatory solutions. The number of binding sites between cholesterol and SREBP and SREBP and the genes are shown to be crucial factors in determining the system behaviour. We discuss the consequences of our work and show how our results provide a receipe for synthetic biology in the context of homeostasis.

Evolutionary Ecology; Wednesday, June 29, 14:30

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An adaptive trade-off between seed size and germination time

I consider a model of an annual plant where seedlings compete for patches that are just big enough to support one plant each. The seeds are characterized by two qualities, their size and the time of their germination. Both qualities affect the competitive ability of the seedlings: big seeds produce more competitive seedlings and early seedlings are more competitive than seedlings that emerge later. I do not assume any physiological trade-off between seed size and germination time. However, I show that there is a Nash equilibrium strategy such that there emerges nevertheless a correlation between the two. If we assume a large resident population and an initially rare mutant population, the Nash equilibrium is also an Evolutionarily Stable Strategy (ESS).

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Poster Session; Friday, July 1, 20:00

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Interaction of opportunistic pathogenic fungi and human phagocytes: A multi-agent-based modeling approach

The fungal pathogen *Aspergillus fumigatus* causes severe systemic diseases in immunocompromised patients [1,2]. Although this fungus is found worldwide and its small conidia are present in air and food [2] it is almost harmless to healthy people, since inhaled conidia are phagocytosed by macrophages and neutrophil granulocytes [1]. However, neither the cellular dynamics, the per-cell efficiency, the outcome of this interaction, nor the environmental impact on this process are known [3]. Live imaging shows that the interaction of phagocytes and fungal conidia is a dynamic process of touching, dragging and phagocytosis [3].

Using multi-agent-based modeling, the interactions of human neutrophil granulocytes and *Aspergillus fumigatus* are simulated to gain knowledge about different behavioral strategies by optimizing parameter settings such as velocity of cells, dragging and phagocytosis efficiency as well as movement directions. Behavior of simulated cells is compared to those of living cells in liquid cultures gained by live imaging data.

Implemented in the multi-agent modeling environment NetLogo [4], neutrophil granulocytes and conidia of *Aspergillus fumigatus* are modeled as distinct agents, whose individual behavior is determined by spatial settings, e. g., density of cells, communication between cells, individual states and is influenced by random effects. Moreover, chemotaxis and random movement of immune cells are compared to get insight into advantages in regard to phagocytosis efficiency.

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Cell and Tissue Biophysics; Friday, July 1, 14:30

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A Nutrient-Quided Chemotaxis-Haptotaxis Approach for Modeling the Invasion of Tumor Cells

We propose a hybrid continuum-discrete model to simulate nutrient-guided malignant brain tumor cell invasion. The lattice-based spatio-temporal model consists of three reaction–diffusion equations that describe interactions between cancer cells, the extracellular matrix (ECM) and nutrients. In addition to random diffusion and haptotactic movement, the migration of cancer cells is directed towards the gradient of the diffusible nutrients as oxygen and glucose [3], which is referred to as chemotaxis. As for the description of the initial migratory response of endothelial cells to the tumor angiogenic factors and the extracellular matrix macromolecule fibronectin [2], we model a system of nonlinear partial differential equations. While [1] focuses on tumor cell adhesion, we model both, the effects on the migration of tumor cells by the ECM and, additionally, by the attraction of higher nutrient concentrations. Moreover, we assume that every cell is able to push a neighboring cell of the same size towards an empty site.

Simulation studies show that the model is consistent with experimental in-vitro invasion results as regards the spatial distribution of the tumor interacting with the ECM. Furthermore, we demonstrate the flexibility of the model realizing simulations with varying arrangements of nutrient delivering blood vessels.

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Stem cells and cancer; Wednesday, June 29, 14:30

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The role of symmetric and asymmetric division of cancer stem cells in developing drug resistance for various types of tumor growth

Often, resistance to drugs is an obstacle to a successful treatment of cancer. Many attempts to study drug resistance have been made in the mathematical modeling literature. Clearly, in order to understand drug resistance, it is imperative to have a good model of the underlying dynamics of cancer cells. One of the main ingredients that has been recently introduced into the rapidly growing pool of mathematical cancer models is stem cells. Surprisingly, this all-so-important subset of cells has not been fully integrated into existing mathematical models of drug resistance. In this work we incorporate the various possible ways in which a stem cell may divide into the study of drug resistance. We derive a new estimate of the probability of developing drug resistance by the time a tumor is detected, and calculate the expected number of resistant cancer stem cells at the time of tumor detection. We are also able to obtain analytical results for cases where the average exponential growth of cancer has been replaced by other, arguably more realistic types of tumor growth. Finally, to demonstrate the significance of this approach, we combine our new mathematical estimates with clinical data to show that leukemic stem cells must tend to renew symmetrically as opposed to their healthy counterparts that predominantly appear to divide asymmetrically. (Part of this work is joint with D. Levy, University of Maryland)

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Mechanical Models of Movement and Growth of Cells and Tissues II;
Wednesday, June 29, 17:00

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The particle-based model of foraminiferal morphogenesis

Foraminifera are a large group of single cellular organisms. About 275,000 species are recognized, both living and fossil. They produce shells made of calcium carbonate, agglutinated sediment grains and/or organic compounds. Shells are typically built from several chambers organized in very elaborated way. The question what govern their morphology to produce such great wealth of forms was unanswered for decades. Early suggestions come from D'Arcy Thomson (1919) who recongnised that simple physical forces associated with fluid dynamics are responsible for cell morphogenesis. First theoretical morphospace was defined over 40 year ago by Berger. His model included only simple geometrical operation (rotation, translation) and produced simple spiral form. Subsequent models used a similar approach and were able reproduce only narrow group of forms.

We showed that diversed shell patterns forms can be produced by using a simple optimization process. It is assumed that foraminifera locally optimizes the way of intracellular transport between the chambers. When every new chamber is formed, a new aperture is located at the shortest distance from the previous aperture. This simple formula produced several diversed forms. However, the model works well only for spheroidal chambers, it does not work for other shapes of chambers.

The next stage in research on the formation of foraminiferal shells is to build a low-level emergent model that can be able explained why "local optimization rule" was so accurate. We are searching for a model of processes that occur just before a new chamber is formed. Foraminifera create a "bubble" of cytoplasm attached to the shell which is mineralized preserving its shape. The "bubble" is not only deformed by external factors but mainly by internal organization of the cytoskeleton. We want to reflect this processes in the computer model and present its impact on final shapes of chambers. The cytoplasmic "bubble" is sourrounded by thin membrane made of lipid bilayer.

Lipid bilayer is an example of complex fluid phenomena so we employed the DPD (Dissipative Particle Dynamics) method. In this simulation technique a set of interacting particles is considered and their time evolution is governed by Newton's equation of motion. In our model lipid bilayer is modelled by two types of DPD particles: "A" which reflects hydrophilic heads and "B" for hydrophobic tails. Additional two types of particles denote extracellular fluid (water) and intracellular fluid (cytoplasm). Particles "A" and "B" are arranged into chained amphiphilic molecules by establishing constant "spring" connections. In order to avoid bending in chains of particles we apply force that streighten each triplet of connected "A"

and "B" particles. Depending on types of particles that interact in pair we choose different potentials of interaction. In our simulation we study the behaviour of planar membranes affected by external forces.

Acknowldgements This research is supported by the Polish Ministry of Science and Higher Education, project no. 0573/B/P01/2008/34.

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Poster Session; Friday, July 1, 20:00

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Time-resolved integration of Flux Balance Analysis, Elementary Flux Modes, and transcriptomics data for characterization of the temporal metabolic response to temperature stress in *S. cerevisiae*

The increased availability of large-scale metabolic network models and the improved quality of high-throughput data provide the basis for system-wide network analysis. Flux Balance Analysis (FBA) [**2**] and its extensions have been successfully applied to determine steady-state systemic characteristics from the constituent elements. In addition, FBA has recently been extended to facilitate the study of transient behavior of metabolic networks. While FBA-based methods, due to their mathematical programming formulation, can readily be applied to large-scale metabolic networks, the application of approaches relying on Elementary Flux Modes (EFMs) [**1**] is hindered by large computational demands. Here we address the problem of time-resolved integration of FBA and EFMs based on transcriptomics data capturing the adaptation of metabolic networks to stress conditions.

Our approach integrates time-resolved transcriptomics data with large-scale metabolic networks to identify active subnetworks by using a novel FBA-based optimization method. To perform the integration, the results from a statistical analysis of differential gene expression, translated into carefully tailored weights, are employed to extract temporal subnetworks that not only show significant changes in expression values in response to stress conditions, but also represent a minimal subset of the whole metabolic network. We present three possible ways in which the extraction of such minimal active temporal subnetworks can be achieved. The found subnetworks are then used to determine the set of EFMs for each time point, reflecting the temporal stress response. We show empirically that the objective of minimality allows the identification of all EFMs for each time point in a feasible time frame. Finally, the sets of EFMs are used in a comparative analysis based on set-similarity measures to identify putative transitions.

We apply the proposed approach to time-resolved transcriptomics data sets from temperature shock experiments in *S. cerevisiae*. The results demonstrate that FBA-based optimization approaches can be used in conjunction with EFMs-based analysis and high-throughput data to reveal the temporal behavior of large-scale networks in an integrative and systematic manner.

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Crowd Dynamics: Modeling, Analysis and Simulation (Part 1); Wednesday, June 29, 11:00

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A multiscale look at crowd dynamics by time-evolving measures

The dynamics of particle-like living systems, such as human crowds, are mainly ruled by mutual interactions among the individuals. This is because the latter have the ability to express different behavioral strategies depending on the presence of other individuals in the environment. For instance, pedestrians heading for a certain destination deviate from their preferred paths when encountering other pedestrians. Remarkably, interactions are usually non-cooperative, i.e., walkers do not pursue a goal collectively.

Due to the intrinsic granularity (discreteness) of the system (the number N of pedestrians is possibly large, yet the approximation $N \to \infty$ may not be acceptable), interactions are better described at an individual-based level. On the other hand, an ensemble representation of the crowd is often preferable over an agent-based one, in order to catch the average group behavior spontaneously emerging from interactions (self-organization) and also in view of further analysis, numerics, and optimization issues. Measure-theoretic stochastic approaches, such as those that will be discussed in this talk, offer useful conceptual tools to this purpose. Indeed, they make possible an Eulerian particle-free representation of the crowd, in which single pedestrians are blurred into the probability distribution of their spatial positions. At the same time, they allow the description of the interactions to stem from (stochastic) individual-based reasonings. Finally, they enable one to treat discrete and continuous models under a common framework, as well as to deduce models at intermediate scales with interesting implications on the predicted dynamics.

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Epidemics; Wednesday, June 29, 17:00

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Estimating scrapie epidemiological parameters: comparison between a population dynamic model and an individual-based model

Classical scrapie is a transmissible spongiform encephalopathy that affects small ruminants (prion disease) and is submitted to eradication measures. Transmission mechanisms are still incompletely understood and difficult to quantify. Scrapie is characterised in sheep by a genetic susceptibility factor. Its long infectious and undetectable incubation period makes direct data analyses difficult, hence the interest of a modelling approach to estimate the epidemiological parameters.

Two models were developed to represent the spread of the disease within a sheep flock: a realistic structured population model (PDE) and an individual-based model. Both take into account the same epidemiological processes, based on similar assumptions, including seasonality in transmission, genetic and age-dependent susceptibilities, long and variable incubation periods. To focus on the estimation of the epidemiological parameters, demographic processes consisting of seasonal lambings, routine culling and reform, directly derive from the flock data. The data used in this study originate from the Langlade experimental sheep flock (SAGA, INRA, Toulouse, France), in which a natural scrapie outbreak occured.

The criterion implemented to estimate the epidemiological parameters is based on the scrapie incidence observed in the Langlade data and simulated by the two models. As there are quite many parameters to estimate (23, that can be reduced to 11 with simplifying assumptions), an optimisation method based on a random-search minimisation algorithm was chosen.

The parameter values obtained for both models are comparable and realistic, *i.e.* consistent with what is known from the disease and expert opinion. The robustness of these results was tested by a sensitivity analysis, which showed that some parameters are highly sensitive and need to be identified with care.

Population Dynamics; Thursday, June 30, 11:30

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The dynamics of social queues

A wide variety of animals are known to form simple hierarchical groups called social queues, where individuals inherit resources or social status in a predictable order. Queues are often age-based, so that a new individual joins the end of the queue on reaching adulthood, and must wait for older individuals to die in order to reach the front of the queue. While waiting, an individual may work for her group, in the process often risking her own survival and hence her chance of inheritance. Eventually, she may survive to reach the head of the queue and becomes the dominant of the group. Queueing has been particularly well-studied in hover wasps (Hymenoptera: Stenogastrinae). In hover wasp social groups, only one female lays eggs, and there is a strict, age-based queue to inherit the reproductive position. While the dominant individual (queen) concentrates on breeding, subordinate helpers risk death by foraging outside the nest, but have a slim chance of eventually inheriting dominance. Some explanations for this altruistic behavior and for the stability of social queues have been proposed and analyzed [**1, 2**]. Since both the productivity of the nest and the chance to inherit the dominant position depend critically on group size, queueing dynamics are crucial for understanding social queues, but detailed analysis is lacking. Here, using hover wasps as an example, we demonstrate that some basic queueing theory[**3**] and non-homogeneous birth and death processes are useful for analyzing queueing dynamics and the population demographics of social queues. Our work leads to better understanding of how environmental conditions and strategic decision-making by individuals interact to produce the observed group dynamics; and in turn, how group dynamics affects individual decision-making.

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Cancer; Saturday, July 2, 14:30

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Dynamics of blood diseases and the hierarchy of hematopoiesis

Hematopoiesis is a process that is based on a hierarchical organization of cell types, with stem cells at the very basis that differentiate into more specialized cells. A simple mathematical model to describe this process has been proposed [**1**]. This hierarchical structure has important effects on the dynamics of diseases, including blood cancers [**2**]. For example, it is becoming increasingly clear that our bodies harbor numerous mutant clones that do not give rise to no disease at all, although the mutations are typically associated with diseases. The fate of any mutant clone will depend on the target cell and on the fitness advantage, if any, that the mutation confers on the cell [**3**]. In general, we can expect that only a mutation in a hematopoietic stem cell will give long-term disease; the same mutation taking place in a cell located more downstream may produce just a ripple in the hematopoietic ocean [**4**].

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Modeling of immune responses and calcium signaling III; Wednesday, June 29, 17:00

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Traveling Waves in the Buffered FitzHugh-Nagumo Model

In many physiologically important excitable systems, such as intracellular calcium dynamics, the diffusing variable is highly buffered. In addition, all physiological buffered excitable systems contain multiple buffers, with different affinities. We will discuss the properties of wave solutions in excitable systems with multiple buffers, and how multiple buffers interact.

Mathematical Modelling of Macromolecules and Molecular Aggregates;
Saturday, July 2, 14:30

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Genome Organisation and Assembly of RNA Viruses: Where Geometry Meets Function

Cryo-electron microscopy and X-ray crystallography have revealed ordered features in the genome organisation of a number of ssRNA viruses. These include a dodecahedral RNA cage in Pariacoto virus and a double-shell organisation in bacteriophage MS2. We show here that these ordered features are due to symmetry constraints on the overall organisation of these particles.

We moreover show that these mathematical results can be used to better understand the mechanisms underlying the formation (assembly) of viruses. In particular, we demonstrate that the geometric constraints on genome organisation result in a strong reduction of the combinatorially possible pathways of assembly and hence contribute to the remarkable assembly efficiency of these viruses. Since assembly efficiency is important for viruses in order to outcompete their hosts immune system, these results provide important insights into the strategies and mechanisms underlying the viral infection process.

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Poster Session; Friday, July 1, 20:00

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Random Matrix approach to fMRI data

We apply random matrix techniques to analyse correlations in Human Brain fMRI data. We reconstruct correlations between different regions of brain. These regions are selected either by purely geometrical voxel position or by physiological a classification given by Brodmann's areas. We analyse spectral properties for covariance matrices and compare the results to some classical results from random matrix theory including Marcenko-Pastur eigenvalue density for Wishart matrices. These result provide us with reference points - a sort of a null hypothesis. We also perform graph theoretical analysis of correlation matrices applying ideas of threshold graphs. Such graphs are constructed using the idea of metric space that is constructed from the correlation matrix for the set of vertices representing different voxels or Bordmann's areas. A threshold graph is a graph between vertices whose distance in this metric space is smaller than a given threshold.

Poster Session; Friday, July 1, 20:00

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Modelling the regulation of thermal adaptation by Hsf1 and Hsp90 in *Candida albicans*, a major fungal pathogen of humans

The heat shock response is one of the most highly conserved and well studied networks in eukaryotic cells. Upon sensing a sudden temperature upshift, the heat shock transcription factor is rapidly activated, leading to the induction of numerous genes that mediate thermal adaptation, including heat shock genes that encode molecular chaperones. We have shown that the major fungal pathogen of humans, *Candida albicans*, has retained a bona fide heat shock response even though it is obligatorily associated with warm blooded mammals [**1**]. Furthermore, this thermal adaptation is essential for the virulence of *C. albicans*. We have predicted that interactions between Hsf1 and the essential chaperone Heat shock protein 90 (Hsp90) play critical roles in the regulation of thermal adaptation in *C. albicans* [2]. We have now tested this prediction using a combination of mathematical modelling and experimental dissection. Our model predicts that chronic exposure to heat leads to protein unfolding, which in turn sequesters Hsp90, thereby releasing Hsf1 from inactive Hsp90-Hsf1 complexes. This allows Hsf1 to become activated leading to the transcriptional activation of heat shock genes including *HSP90*. Our model, which predicts the dynamic molecular responses of *C. albicans* with reasonable accuracy, has yielded a number of novel predictions. For example, Hsf1 activation appears to be acutely sensitive to the concentration of unfolded proteins. Also, Hsp90 levels appear to be regulated at post-transcriptional as well as transcriptional levels. Furthermore, our model provides an explanation for the observation that *C. albicans* cells retain a 'molecular memory', rendering them more resistant to subsequent heat shocks. Therefore our mathematical modelling has provided novel insights into the regulation of this evolutionarily conserved environmental response.

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Regulatory Networks; Saturday, July 2, 11:00

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Modeling hormonally dependent genetic networks

Usual approaches to regulatory genetic network modeling follow a feed-forward methodology, where the network represents a black-box within the cell. The operation of the black box is modeled as an input-output relation and research tries to identify the proper relation that holds for several observed cases; this relation may be expressed in various formalisms (typically boolean networks [1], but also Bayesian networks, etc.).

Our proposal follows a developmental perspective and borrows theoretically from modern accounts of the gene as an information-carrier and as a complex entity and concept [2-5]. These theoretical developments belong to the broad evo-devo trend and attempt to use the gene as a functional biological entity or as a developmental molecular process instead of a well-delimited structural entity encoding for a specific trait.

Within this theoretical context, it is worthwhile to study enhanced relations between genetic network and cellular behavior that include control in the loop in the form of memory : in regulatory networks with memory, subsequent activations of the network with the same input vector will yield different output vectors, i.e. the transfer function of the whole network will be itself dynamic. From an external point of view, this may be seen as the network prefering some inputs already seen, or dismissing them, or in general specializing to certain activity pathways. We expect a cell to behave in such a way so as to resist to abrupt changes and to external manipulation, for example by viruses. In a medium term, a genetic network with memory will behave in a more autonomous and prudent manner and it will be less dependent on quick changes in its environment.

From a technical point of view, one way to introduce a sort of memory is to define individual gene functions that are not uniquely defined but that vary for different environmental conditions. One such controlling condition may be the level of an hormone [6]. This model represents the dependence of various genes on external factors that change slowly in comparison with the time scale of the behavior of the gene. We have studied gene functions that differ according to the level of an external hormone that follows its own dynamics. In this case, long complex (irregular) attractors emerge within the genetic network. We have also studied genetic networks that interact with the hormone in one of the following ways: the hormone does not have intrinsic dynamics but its production is triggered or hindered either by each of the gene functions per hormonal level, or by each of the genes that may be in on or off state. In both of these cases, the networks reach a co-attractor with the hormone (that is, the network state and the hormonal level reach coupled attractors). In the first case, these attractors are very often irregular and longer that usual attractors of RBNs, while in the second case they resemble more the short point and periodic attractors of RBNs. A few higher connectivity studies (K = number of inputs per gene > 2) and perturbation studies have been

performed, that are indicative of enhanced robustness of these models: for example the genetic-hormonal systems appear robust to the exact ranges of the hormonal levels considered per gene but not to their number.

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Applications of nonnegative Radon measure spaces with metric structure to population dynamic models; Wednesday, June 29, 17:00

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Two-sex, age-structured population model

The subject of the presentation is a two-sex, age-structured population model introduced first by A.Fredrickson and F.Hoppensteadt. The model consists of a system of three PDE's describing the evolution of males and females populations and the process of couples formation. The age structure plays here a crucial role, because individuals of different ages usually have different preferences for entering into a marriage. Also environmental limitations and influences are taken into consideration - a birth rate, death rate, divorce rate and marriage function depend on the state of the whole system.

Existence and uniqueness of the weak solutions in the space of nonnegative finite Radon measures equipped with a flat metric is proved. The proof bases on the operator splitting algorithm. Splitting transport terms (which describe aging and death) and boundary terms (which describe an influx of the new individuals) allows for obtaining necessary estimates. Hence, the continuous dependence with respect to time, initial data and model coefficients is proved.

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Evolutionary Ecology; Thursday, June 30, 11:30

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Body Condition Dependent Dispersal in a Heterogeneous Environment

Body condition dependent dispersal is a widely evident but barely understood phenomenon. Empirical data display diverse relationships between individual body condition and dispersal between as well as within species.

I develop models that study the evolution of dispersal strategies that depend on individual body condition. In a patchy environment where patches differ in environmental conditions, individuals born in rich (e.g. nutritious) patches are on average stronger than their conspecifics that are born in poorer patches. Body condition (strength) determines competitive ability such that stronger individuals win competition with higher probability than weak individuals. Individuals compete for patches such that kin competition selects for dispersal. Survival probability during dispersal may depend on body condition.

I determine the evolutionarily stable strategy (ESS) for different ecological scenarios. In a fixed environment, patches are abandoned that are too unsafe or that would not produce enough successful dispersers in the future so that all offspring disperse from these patches. In a fluctuating environment where patch qualities change randomly from year to year, all patches are equally worth keeping so that all families keep the same competitive weight in their natal patch and disperse the rest.

From families that invest in both retaining their natal patch and gaining other patches through successful dispersers, offspring with the highest survival probability during dispersal disperse whereas individuals that are less suitable for dispersal defend their natal patch. However, this clear within-family pattern is often not reflected in the population-wide body condition distribution of dispersers or non-dispersers. This may be an explanation why empirical data do not show any general relationship between body condition and dispersal.

When all individuals are equally good dispersers, then there exist equivalence classes of dispersal strategies that are defined by the competitive weight that remains in a patch. An equivalence class consists of infinitely many dispersal strategies that are selectively neutral. This provides an explanation why very diverse patterns found in body condition dependent dispersal data can all be equally evolutionarily stable.

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Epidemics; Wednesday, June 29, 11:00

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Predicting the period in seasonally driven epidemics

Seasonality strongly affects the transmission and spatio-temporal dynamics of many infectious diseases, and is often an important cause for their recurrence. However, there are many open questions regarding the intricate relationship between seasonality and the complex dynamics of infectious diseases it gives rise to. For example, in the analysis of long-term time-series of childhood diseases, it is not clear why there are transitions from regimes with regular annual dynamics, to regimes in which epidemics occur every two or more years, and vice-versa. The classical seasonally-forced SIR epidemic model gives insights into this phenomena but due to its intrinsic nonlinearity and complex dynamics, the model is rarely amenable to detailed mathematical analysis. Making sensible approximations we analytically study the threshold (bifurcation) point of the forced SIR model where there is a switch from annual to biennial epidemics. We derive, for the first time, a simple equation that predicts the relationship between key epidemiological parameters near the bifurcation point. The relationship makes clear that the epidemic period will decrease if either the birth-rate () or basic reproductive ratio (R0) is increased sufficiently, or if the strength of seasonality () is reduced sufficiently. These effects are confirmed in simulation studies and are also in accord with empirical observations. For example, in the pre-vaccination era, the increase in birth-rate in the United States and in the United Kingdom was the factor responsible for driving measles dynamics from biennial to annual oscillations. Moreover, it is argued that the strong seasonality in India (high) may be responsible for the erratic polio outbreaks. Correspondingly, our equation identifies the first bifurcation in the expected period-doubling route to chaos that continues as seasonality increases.

Cellular Systems Biology; Thursday, June 30, 11:30

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Protein Cost and Metabolic Network Structure Underlie Different Modes of Metabolic Efficiency

When growth rate increases, many unicellular organisms shift from an energetically efficient to an energetically inefficient metabolic pathway to break down glucose. An example is baker's yeast *Saccharomyces cerivisiae*, which ferments glucose to ethanol if the glucose concentration is high, even in aerobic environments that allow for more efficient catabolism of glucose [1]. Recently, a new explanation for this paradoxical behaviour has been proposed: because cells can only pack a limited volume of metabolic enzymes, inefficient metabolism can maximise the growth rate of the cell, because efficient metabolic pathways require more enzymes than inefficient pathways [2,3]. Indeed, Vazquez *et al.* [2] explained the concurrent use of the efficient and inefficient pathway by *Escherichia coli* in this way. However, it is unknown why, at high growth rates, some microbes only use efficient metabolism, while others only use inefficient metabolism and again others use both concurrently.

Here we apply Vazquez' method on genome-scale metabolic models of three organisms that use different modes of inefficient metabolism, *E. coli*, *S. cerevisiae* and *Lactococcus lactis*: *E. coli* does not downregulate its efficient pathway at high growth rates, while *S. cerevisiae* and *L. lactis* do. The Vazquez method incorporates a protein cost for each reaction in the genome-scale metabolic network. This cost is proportional to enzyme volume divided by enzyme turnover number (k_{cat}). Because these protein costs are not known for each reaction individually, we created 1000 networks, each with protein costs for each reaction drawn randomly from an experimentally-obtained distribution. For only a subset of these networks inefficient metabolism is the optimal strategy. This allowed us to study the protein costs of this inefficient subset in more detail.

We found that for cells with low glycolytic protein cost, inefficient metabolism is the optimal strategy, in all these organisms. Furthermore, for *S. cerevisiae* and *L. lactis* optimal growth yield is bimodally distributed over these 1000 networks: metabolism is either efficient or inefficient. In contrast, for *E. coli* we observed that optimal growth yield varies continuously over these 1000 networks. This could explain why *S. cerevisiae* and *L. lactis* truly switch off efficient metabolism, while *E. coli* uses inefficient and efficient metabolism concurrently. We show that differences in metabolic network structure underlie this qualitative difference between

E. coli on the one hand and *S. cerevisiae* and *L. lactis* on the other hand. Concluding, protein costs determine whether inefficient metabolism is optimal, while the metabolic network structure determines the mode of inefficient metabolism.

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Regulatory Networks; Saturday, July 2, 11:00

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Quantitative modeling of gene expression in Arabidopsis flowers

Flowers have a complex structure in which tissues and organs obtain their identities and arrangements in a very special way. According to the so-called ABC(DE) model [1], the different floral organs in Arabidopsis are specified by the expression of five types of MADS box genes. During development, the floral meristem gets divided into four concentric areas (whorls) in which different combinations of MADS gene expressions are observed: A+E in the sepal whorl, A+B+E in the petal whorl, B+C+E in the stamen whorl, and C+E in the carpel whorl.

In [2] we proposed an ODE model for the interactions of the gene regulatory network that underlies the development of the MADS domain proteins. We showed that this model type is well suited for testing hypotheses on formation and functioning of higher order complexes, transcription activation and DNA binding.

For the predictive power of such a model, accurate estimation of parameter values plays an essential role. To this end, we developed a spatiotemporal data set of in vivo protein concentrations, using a state of the art protein tagging procedure. We used a novel image analysis technique to estimate relative protein concentrations from the resulting confocal images [3].

We also developed a novel parameter estimation procedure that explicitly incorporates the temporal expression development, as well as the measured standard deviations. The estimation results will give a direct feedback on the proposed hypotheses, and they will be presented at the conference.

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Mathematical modeling of biomechanical regulation in bone tissue (Session I); Wednesday, June 29, 08:30

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A theory for load-adaptive bone remodeling at the cellular level

It is well known that bone tissue can adapt its shape and density to the mechanical demands it is subjected to. However, how, exactly, this process is regulated is not well known. Over the last decade we have developed a theory for load adaptive bone remodeling that is based on the hypothesis that osteocyte cells in the bone tissue can sense local loading conditions and based on this information regulate the activity of bone forming cells (osteoblast) and bone resorbing cell (osteoclasts) [1]. We tested this hypothesis using computational models that included finite element models to represent trabecular bone architectures and to calculate loading conditions at the location of osteocytes, In the earlier of these studies [2], only the net result of bone formation and resorption was represented by changes in the model geometry. In these studies we demonstrated that this theory can explain many aspects of bone remodeling that could not be explained before. First, it was shown that this theory can explain the formation of typical trabecular architectures (osteogenesis). Second, it was shown that the theory can explain the adaptation and alignment of trabecular bone as the result of a local adaptation process. Third, it was shown that the theory could explain the development of osteoporosis as the result of changes in cell activity or loading magnitude. In later studies [3] we increased the resolution to also represent individual cells. In these studies we demonstrated that the theory can explain the coupling between osteoclast and osteoblast cells in basic multicellular units as the result of changes in local loading condition sensed by osteocytes. It could also explain the formation of osteons in cortical bone and why these are oriented in the loading direction. Finally, although the biochemical pathway by which the osteocytes regulate the other cells was never specified, we were ble to demonstrate that both a stimulatory pathway, in which inicreased loading leads to increased stimulation of osteoblast, and an inhibitory pathway, in which increased loading leads to decreased inhibition of osteoblast (typically for sclerostin) could work. Presently it is investigated if this theory can be transformed into a clinical tool to predict bone remodeling in patients as expected due to changes in cell metabolism or loading conditions.

References.

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Information, human behaviour and disease; Saturday, July 2, 11:00

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Modeling Adaptive Behavior in Influenza Vaccination Decisions

Classic game-theoretic approaches, whereby individuals are assumed to evaluate their options deductively based upon available information and perceptions, have previously been used to model vaccination-related decision making. However, for the case of influenza, individuals may rely on their memories and past experiences of having vaccinated. They thus use adaptation by evaluating their vaccination options inductively. We explore this concept by constructing an individual-level model of adaptive-decision making. Here, individuals are characterized by two biological attributes (memory and adaptability) that they use when making vaccination decisions. We couple this model with a population-level model of influenza that includes vaccination dynamics. The coupled models allow individual-level decisions to influence influenza epidemiology and, conversely, influenza epidemiology to influence individual-level decisions. By including the effects of adaptive-decision making within an epidemic model we show that severe influenza epidemics could occur due to the behavioral dynamics in vaccination uptake without the presence of a pandemic strain. These severe epidemics can be prevented if vaccination programs offer incentives. We find that when a family-based incentive is offered, the frequency of severe epidemics is increased. Instead, this frequency could be reduced if programs provide several years of free vaccines to individuals who pay for one year of vaccination. We conclude that individuals memories and flexibility in adaptive decision-making can be extremely important factors in influenza and voluntary vaccination determining the success of influenza vaccination programs. Finally, we discuss the implication of our results in success of a universal flu vaccine and for the case of a pandemic, and discuss some extensions of the model.

References.

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Ecosystems Dynamics; Tuesday, June 28, 17:00

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Geodesic paths in simple graphs for some social insects

Social insects are an important example of complex collective behavior. In particular, ant colonies develop different tasks as foraging, building and allocation [**1**]. While they search for food they deposit a pheromone that it is considered as a crucial element in the mechanism for finding minimal paths. The experimental observations suggest that the model should include the presence of pheromone and the persistence (tendency to follow straight paths in the absence of other effects).

In our study, we will consider ants as random walkers where the probability to move in one or another direction is influenced by the concentration of pheromone near them (*reinforced random walks*). We are mainly interested not in an individual random walker but rather on a large number of random walkers, their collective behavior, and the possibility for them to aggregate forming geodesic paths between two points in some simple networks.

We investigate the behavior of ants in a two node network and in a three node network (with and without directionality constraint). Our analytical and computational results show that in order for the ants to follow shortest paths between nest and food, it is necessary to superimpose to the ants' random walk the chemotactic reinforcement. It is also needed a certain degree of persistence so that ants tend to move preferably without changing their direction much. Another important fact is the number of ants, since we will show that the speed for finding minimal paths increases very fast with it.

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Epidemiology, Eco-Epidemiology and Evolution; Saturday, July 2, 11:00

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On an age- and stage-dependent epidemic model.

A very general epidemic model will be introduced in which the disease spreads by contact among a population which is age-dependent. A stage structure is introduced in the disease, to describe its progression. The model formulation thus hinges on a system of highly nonlinear hyperbolic partial differential equations. The well-posedness is discussed. Numerical simulations reveal the occurrence of recurrent epidemic outbreaks, under suitable circumstances.

Mathematical Models in Eco-epidemiology I; Wednesday, June 29, 08:30

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A two-strain ecoepidemic model

In this talk we present a model in which two strains are considered. In a predator-prey demographic model, two contagious diseases are assumed to spread among the predators. Under the relatively strong assumption that one individual cannot be affected by both, we analyze the system to determine its long term behavior. While in some other already published models both populations have been considered subject to a disease, or the same disease is able to cross the species barrier, to our knowledge this is the first ecoepidemic model accounting for two diseases affecting the same population.

Undergraduate Biomathematics Education Beyond BIO 2010 (Part II);
Saturday, July 2, 08:30

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Computational Systems Biology: Discrete Models of Gene Regulatory Networks

In this talk we will describe a hands-on project in computational systems biology for students and that can be used in a variety of settings, from high school to college, with a particular focus on the use of discrete mathematics. The biological focus is the Escherichia coli lactose operon, one of the first known intracellular regulatory networks. The modeling approach uses the framework of Boolean networks and tools from discrete mathematics for model simulation and analysis.

The talk is based on materials from a workshop for high school teachers described in Martins et al. [1] and conducted as a collaboration between the Virginia Bioinformatics Institute (VBI) at Virginia Tech and the Institute for Advanced Learning & Research (IALR) in Danville, VA. The workshop structure simulated the team science approach common in today practice in computational molecular biology and thus represents a social case study in collaborative research.

During the workshop the participants were provided with all the necessary background in molecular biology and discrete mathematics required to complete the project, and developed activities intended to show students the value of mathematical modeling in understanding biochemical network mechanisms and dynamics.

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Bioinformatics and System Biology; Wednesday, June 29, 11:00

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Biological Information, Biological Interaction and Anticipation

Understanding biological organisations and interactions is becoming ever more important. In this talk, a concept of information designed to handle information conveyed by organizations is introduced. This concept of information may be used at all biological scales: from molecular and intracellular to multi-cellular organisms and human beings, and further on into collectivities, societies and culture. This concept is based on whole-part graphs, a mathematical model for biological organization introduced earlier [1]. This model supports the formal investigation about properties of biological organisations, allowing for mathematical proofs and the definition of organisation transformations [2].

Another concept, necessary for developing the definition, will also be introduced. It is the concept of synexions, or organisations immersed in space-time. The definition of information also formalizes perception, observers and interpretation; although observers appear just as acknowledgers of changes. In this setting, information and interpretation stand as seminal elements of (biological) interaction and of transformation of organisations. Some aspects of these concepts will be clarified while arguing why the immersion of whole-part graphs in (the physical) space-time is needed. This immersion connects the definition of information to issues related to anticipation.

Methods for identifying organisations in biological data may be derived based on whole-part graphs. However, methods for inspecting and identifying organisations in bio-chemical networks grounded solely on network information and not considering interactions with the environment do not work satisfactorily [4] for the following reason. It can be proved that de-organizing things into their interconnected parts is a deterministic process, while re-organizing associated parts into wholes is a non-deterministic process. This implies that raw relational data [6], like bio-chemical networks, is insufficient to determine their natural organisation and how biological organisations come to be, indicating the importance of neatly considering interactions in the organisation process.

It has been suggested that information exchange is the distinctive mode of interaction in biological phenomena [5]. The arguments presented in support to this claim are grounded on Shannon's information, what keeps information more as an investigatory aid than as something intrinsically entailing the phenomenon. Shannon himself called attention to the fact that his definition of information-contend precludes meaning and interpretation, addressing only the communication (signal transmission) aspect of information exchange [7].

The present definition of information ties interpretation to changes in organisation [3]. Therefore, information-grounded biological interactions mold organisations. The fact that the definition is grounded on synexions rather than whole-part graphs intertwines anticipation to information recognition. Indeed, the perception of an interpretation event relies on the violation of the anticipation by an observer

about propensities in the behaviour of the interpreter of a signal. In this sense, biological information and anticipation are at the very core of biological interactions and the consequent formation and transformation of biological organisations.

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Towards predictive modeling of patient-specific Glenn-to-Fontan conversions: boundary conditions and design issues.

Single-ventricle defects are a class of congenital heart diseases that leave the child with only one operational pump, requiring the systemic and the pulmonary circulations to be placed in series through several operations performed during young childhood. The last procedure (the Fontan palliation) artificially connects both venae cavae to the pulmonary arteries, which improves oxygeneration of the baby at the cost of blood flowing passively into the lungs. Numerical simulations may be used to investigate the nature of the flow and its connection to post-operative failures and sources of morbidity. However they heavily rely on boundary condition prescription. We present our recent work on predictive patient-specific modeling of the Glenn-to-Fontan conversion. Three-dimensional patient-specific preoperative models are developed based on clinical data. Results include a sensitivity analysis of several hemodynamics factors to the input data. In addition, previous studies have demonstrated that the geometry plays an important role in Fontan hemodynamics. A novel Y-shaped design was recently proposed to improve upon traditional designs, and results showed promising hemodynamics. In this study, we show how geometry and boundary conditions affect the performance of these virtual surgical designs. In particular, we investigate if and how the inferior vena cava flow (which contains an important biological hepatic factor) can be optimally distributed amoung both lungs. Finally, we present a multiscale (three-dimensional to reduced model of the entire circulation) predictive framework for this Glenn-to-Fontan conversion, which provides a means to relate global response to local changes in geometry and hemodynamics in the circulatory system. Results illustrate that the local graft geometry plays essentially no role in the workload on the heart. While the offset and Y-graft designs result in reduced energy loss, this does not appear to have any significant impact on the cardiac dynamics. This result suggests that future work should focus not just on energy loss, but on other clinical relevant parameters, such as hepatic flow distribution.

Immunology; Saturday, July 2, 08:30

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Self-Nonself discrimination and the role of Costimulation and Anergy

The problem of self-nonself discrimination is a long standing problem in immunology. So far, it has been unclear whether T cells can perform perfect and efficient self-nonself discrimination, in populations with arbitrary diversity. I will discuss a mechanism that allows performing perfect self-nonself discrimination if both positive and negative repertoire education processes are used, and furthermore if costimulation and anergy mechanisms are afterwards considered during cellular activation. These results provide compiling evidence that the main driving force shaping the adaptive immune could be the ability to perform prompt and accurate self-nonself discrimination. They also provide insights on the possible role of positive selection, costimulation and anergy in the adaptive immune system.

Mechanical Models of Movement and Growth of Cells and Tissues I;
Wednesday, June 29, 14:30

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Cellular Traction as an Optimal Control Problem

Force Traction Microscopy is the determination of the stress exerted by a cell on a planar deformable substrate on the basis of pointwise measured displacement. This classical inverse problem in biophysics is typically addressed inverting the displacement field using the Green functions of linear elasticity, under suitable regularizing conditions.

An alternative method formulates an adjoint problem for the direct two-dimensional plain stress operator by minimization of a convenient functional. The resulting coupled systems of elliptic partial dfferential equations (the forward and the adjoint problem) can then be solved by a finite element method. One advantage of such an approach is that can be extended to three dimensional case, including inhomogeneity and anisotropy and even finite displacements of the material.

This work deals with the rigorous statement of the inverse problem Some results of well posedness for the linear case are first given, using standard techniques. The theory is then extended to the less trivial case of pointwise observations with boundary control in 2D and 3D. The model is numerically approximated in 2D and a critical discussion of the results is addressed. Early results of the major biophysical problem of pointiwise observations with boundary control will be shown.

item Ambrosi D. et al. em Traction pattern of tumor cells, J Math Biol (2007) item Ambrosi D. em Cellular traction as an inverse problem, SIAM J Appl Math 66: 2049-2060 (2006) item Lions J.L. em Optimal control of systems, Springer Verlag (1971) item Casas E. em Boundary Control of a Semilinear Elliptic Equation with Pointwise state Constraint, SIAM J. Opt. Contr. (1996)

Cellular Systems Biology; Thursday, June 30, 11:30

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Dynamics of coupled repressilators: the role of mRNA kinetics and transcription cooperativity

Regulatory molecular networks are collections of interacting molecules in a cell. One particular kind, oscillatory networks, has been discovered in many pathways. Well-known examples are the circadian clock [1] and the cell cycle [2], where the oscillatory nature of the process plays a central role.

These natural regulatory networks are very complex and include many types of molecules, from genes to small messengers. It is necessary to study the regulatory mechanisms by means of highly simplified models. These models are particularly valuable because *artificial* regulatory networks can be engineered experimentally [3, 4, 5]. Our computational study [6] suggests that the oscillatory mechanisms implemented in regulatory oscillators are qualitatively different. Comparing various artificial networks helps revealing general principles of cellular regulation.

We study an artificial oscillatory network called the repressilator [4], which borrows the idea of a ring oscillator coming from engineering. The oscillatory mechanism of the repressilator is based on connecting an odd number of inverters (negative control elements) in a ring. Its genetic implementation uses three proteins that cyclically repress the synthesis of one another by inhibition of corresponding mRNA production.

A challenging area of the research is communication among cells in a population or organism. It has been proposed theoretically to design artificial interaction among cellular oscillators using quorum sensing [7, 8]. A small molecule, autoinducer (AI), carries out the coupling function. Synchronization is only one and simplest outcome of such interaction. It is suggested that the outcome depends on the structure of the network. A phase-attractive (synchronizing) and phase-repulsive coupling structures were distinguished for regulatory oscillators. In this paper, we question this separation.

We study an example of two interacting repressilators. We show that increasing the cooperativity of transcription repression (Hill coefficient) and changing the reaction time-scales dramatically alter synchronization properties. The network

demonstrates in- and anti-phase oscillatory regimes and can be birhythmic, choosing between those two types of synchronization, in a wide range of parameters. In some region of parametric space there are whole cascades of complex anti-phase oscillatory solutions, which coexist with in-phase regime. Thus, the type of synchronization is not characteristic for the network structure. However, we conclude that the specific scenario of emergence and stabilization of synchronous solutions is much more characteristic.

In particular, anti-phase oscillations emerge at elevated cooperativity values. We choose the maximal synthesis rate for the mRNA as the main control parameter for our analysis. We calculate bifurcation diagrams with respect to this parameter and study how regimes found in these diagrams depend on other parameters. At the initial cooperativity value of 2.0, the in-phase synchronization remains stable and anti-phase remains unstable at any synthesis rate. When the cooperativity is elevated only to 2.6, the anti-phase solution becomes stable at a sufficiently high synthesis rate. In contrast, the in-phase solution loses its stability at these elevated cooperativity and high synthesis rate.

Additionally, fast mRNA kinetics provides birhythmicity in a wide range of the synthesis rate. Initially, the time-scales of the protein and mRNA kinetics were identical. We make mRNA kinetics much faster than protein, which is a more natural case. The sequence in which the oscillatory solutions emerge from Hopf bifurcations changes — the anti-phase emerges first. As a result, the anti-phase solution emerges stable, and the in-phase emerges unstable. In the birhythmic parameter regime, both solutions must be stable. Three bifurcations always precede the birhythmic parameter regime when the synthesis rate increases. The in-phase solution becomes stable as a result of a repelling invariant torus emanating from the limit cycle. The other two bifurcations are unexpected: The anti-phase limit cycle first loses its stability, and then regains it. Both transitions are pitchfork bifurcations of limit cycles. The second bifurcation cancels the effect of the first one on the stability of the anti-phase solution. Thus, both in-phase and anti-phase solutions are stable in a very wide range of the synthesis rate.

Our work presents a novel scenario of emerging birhythmicity and switching between the in- and anti-phase solutions in regulatory oscillators. Since the types of synchronization coexist in one network, they are not characteristic for the network structure. However, the bifurcation scenario may be much more characteristic. This may help to address a central question in the analysis of regulatory networks — how to connect structural characteristics to dynamical and functional properties of a network.

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Multiscale modeling of biological systems: from physical tools to applications in cancer modeling I; Saturday, July 2, 08:30

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Hybrid models of normal and leukemic hematopoiesis

We develop hybrid models of cell population dynamics where cells are considered as individual objects, intracellular regulatory networks are described by ordinary differential equations while biochemical species in the extracellular matrix by partial differential equations. We use this approach to various biological and medical application. In particular, to model normal and leukemic hematopoiesis and leukemia treatment.

Plants, growth and transport processes II; Tuesday, June 28, 14:30

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Nonlinear dynamics of plant growth

We model plant growth with free boundary problems where the moving boundary corresponds to the mersitem, a narrow layer of proliferating cells. Cell cycle progression and transport of nutrient and metabolites are taken into account. Nonlinear dynamics of plant growth, endogeneous rhythms and branching patterns are discussed.

Epidemics; Wednesday, June 29, 11:00

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A Mathematical Modelling Framework to Assess the Impact of Antiviral Strategies on HIV Transmission

Stopping the AIDS epidemic constitutes a major challenge to mankind. Up to now, HIV infected individuals cannot be cured. However, one possible way of stopping the epidemic is to disrupt its transmission. In 2009, approximately 370,000 infants became infected with HIV during pregnancy, delivery and breastfeeding [1]. A single dose of nevirapine (NVP) can reduce HIV transmission by half, when administered to the mothers before birth and to their newborns shortly after birth. This simple and cost-efficient method is widely applied in resource-constrained settings.

Based on a ugandan program for the prevention of mother-to-child transmission, we assessed the pharmacokinetics of NVP in HIV infected pregnant women and their newborns. The derived pharmacokinetic parameters were used in a stochastic model of HIV dynamics and -transmission. Subsequently, we used the model to predict HIV transmission rates during the first two years after birth with different alterations of the basic NVP scheme. The model predictions were in excellent agreement with data from seven independent HIV prevention trials. We found that the maternal NVP constitutes a major risk for resistance development and subsequent treatment success in the HIV infected mother [2]. However, maternal NVP decreases HIV transmission to the newborn substantially. Our model revealed a perplexing mechanism: Maternal NVP does not reduce the number of viral particles that come into contact with the child during birth. Instead, maternal NVP reduces HIV transmission by providing NVP trans-placental to the child, so that protective NVP levels are available at the moment of viral contact during delivery. Our model also revealed, that extended newborn NVP administration can protect the infant from acquiring HIV during the breastfeeding period without further risk of resistance selection.

Extended newborn NVP, as well as single-dose maternal NVP protect the newborn from HIV acquisition by a mechanism, which could best be termed 'pre-exposure prophylaxis' (PrEP). In view of the predictive power of our model, we are encouraged that a very similar modeling framework may be useful to study the impact of PrEP on sexual transmission of HIV, which could become a central tool to curb the HIV epidemic in the near future [3].

References.

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Population Genetics; Friday, July 1, 14:30

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Single–crossover recombination and ancestral recombination trees

Modeling the dynamics of populations under recombination leads to a large coupled non-linear dynamical system that is notoriously difficult to treat. In my talk, I will present a model that describes recombination in an 'infinite' population with single crossovers only.

The common way to solve these systems relies on a certain nonlinear transformation from (gamete or haplotype) frequencies to suitable correlation functions. This provides an elegant solution in principle, but the price to be paid is that the coefficients of the transformation must be constructed via recursions that involve the parameters of the recombination model [1], i.e. an explicit solution of the dynamics cannot be stated.

I will describe a new approach to infer an explicit solution to the dynamics. To this end, I use the underlying stochastic process to trace recombination backwards in time, i.e. by backtracking the ancestry of the various independent segments each type is composed of. This results in binary tree structures, which can be used as a tool to formulate an explicit solution of the dynamics.

References.

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The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits II; Wednesday, June 29, 17:00

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Interacting cell system models for cell sorting and collective motion

Biological structure and function in cell populations often result from the complex interaction of a large number of components. In particular when cells that are in direct physical contact or located close to each other are known to interact, possibly in a type-specific manner, one is interested in concluding characteristics of the global, collective behavior of the cell configurations from the individual properties of the cells and the details of the intercellular interaction. To understand the determinants of these processes and to conclude the tissue level traits, it is necessary to design and analyze appropriate mathematical models.

It is argued that the model class of interacting particle systems is well-suited for this task. For two exemplary problems, cell sorting and collective motion of oriented cells with ferromagnetic alignment, cell based lattice models are developed which describe the major details of the respective intercellular interaction. If suitably simplified, these models are analytically tractable. Several results concerning the long-time behavior and the emergence of structure are presented and interpreted in biological terms. Challenging mathematical problems that require further theoretical developments are identified.

Ecosystems Dynamics; Tuesday, June 28, 14:30

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Reduction from reaction-diffusion model to two-patch compartment model

Two-patch compartment models have been explored to understand the spatial processes that promote species coexistence. However, a phenomenological definition of the inter-patch dispersal rate has limited the quantitative predictability of these models to community dynamics in spatially continuous habitats. Here, we mechanistically rederived a two-patch Lotka-Volterra competition model for a spatially continuous reaction-diffusion system where a narrow corridor connects two large habitats. We provide a mathematical formula of the dispersal rate appearing in the two-patch compartment model as a function of habitat size, corridor shape (ratio of its width to its length), and organism diffusion coefficients. For most reasonable settings, the two-patch compartment model successfully approximated not only the steady states, but also the transient dynamics of the reaction-diffusion model. Further numerical simulations indicated the general applicability of our formula to other types of community dynamics, e.g. driven by resource-competition, in spatially homogeneous and heterogeneous environments. Our results suggest that the spatial configuration of habitats plays a central role in community dynamics in space. Furthermore, our new framework will help to improve experimental designs for quantitative test of metacommunity theories and reduce the gaps among modeling, empirical studies, and their application to landscape management.

Fractals and Complexity I; Wednesday, June 29, 14:30

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On dynamics of growth of prostate cancer; Towards the objective fractal system of tumor grading

Cellular growth is the fundamental biological phenomenon. A mathematical model shows that the emergence of simplistic macroscopic dynamics of growth, such as Gompertzian dynamics results from a coupling of a number of events at the microscale level. The coupling is associated with the emergence of at least three features, i.e. fractal structure of space-time, in which growth occurs, conditional probability of events, which eliminates sensitivity to the initial conditions, and a temporal function of entropy. The latter one is dependent on macroscopic dynamics of growth, and determines a capability of the supramolecular system for coding or transfer of biologically relevant information. Indeed, experiments with growth of prostate cancer spheroids suggest that both intra- and intercellular interactions play a significant role in fractal dynamics of growth.

The pattern of growth during tumor angiogenesis changes. Growth in space results in formation of the spatial fractal tissue structures as reflected by the spatial fractal dimension. The spatial fractal dimension for the normal-appearing prostate epithelium was 1.451 (018) (n=18 cases), for the Gleason 3 pattern 1.469 (022) (n = 15 cases), for the Gleason 4 pattern 1.601 (019) (n=18 cases), and for the Gleason 5 pattern 1.769 (011) (n=10 cases). In addition, different areas of the same tumor possessed a similar value of the spatial fractal dimension. With regards to the morphometric cell analysis, the minimal cell radius, aspect ratio, cell roundness and compactness were all statistically different across all Gleason score cases (ANOVA $p<0.05$). Sphericity, solidity shape and circularity were statistically different between cases with Gleason score 3, and those with a score of 4 and 5 (ANOVA $p<0.05$). However, these parameters were not different between cases with a Gleason score of 4 and 5. Based on the cellular morphology parameters, discriminant analysis with leave one out showed that 60% of Gleason score 3 and 4 cases, 63% of Gleason score 4 and 5 cases and 62% of Gleason score 3 and 5 cases could be correctly classified. This dropped to 45% when all the three groups were analyzed.

Tumor growth in time during angiogenesis is not of Gompertzian nature anymore. The long-term temporal evolution of PSA in 50 prostate cancer patients during growth ($b>0$) or decay ($b< 0$) phase describes the exponential function of the algebraic form $p(t) = p0\exp(bt)$ with the coefficient of non-linear regression $R > 0.95$ and the Poisson probability distribution, in which p(t) stands for PSA concentration, p0 is the initial PSA concentration in time t0, b stands for the coefficient, t denotes scalar time. Such evolution suggests a decay of intercellular interactions. Those results define clinically relevant prostate cancer as the first order dynamic system. The novel approach based upon the parameters p0, p' and b can be used to compare objectively dynamics of growth of different prostate cancers or to identify

cancer recurrence. The spatial fractal dimension allows the objective and numerical grading of prostate cancer.

Evolutionary Ecology; Friday, July 1, 14:30

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Sexually differentiated death rates in the presence of an efficient mating strategy

Darwin noted that some sexually differentiated genetic traits, such as the bright plumage of male birds that seems to make them more visible to predators, appear to contradict the main assumption of natural selection. Darwin proposed the notion of sexual selection to explain this phenomenon, and other explanations have been offered. In this study, we use a system of four nonlinear ordinary differential equations to model male and female populations of two species that have identical, efficient mating strategies but do not interbreed. One species has a higher death rate for males than for females. These otherwise identical species are placed in competition, resulting in a system with multiple fixed points and strong dependence on initial conditions. We show that, with some choices of parameters, increasing the death rate of the male in one of the two species enlarges the basin of attraction in which that species survives and the competitor is driven to extinction, and thus is an adaptive response. We also offer a heuristic argument as to why this should be so.

Poster Session; Friday, July 1, 20:00

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Cell Polarization by Wave-Pinning: Conditions, Stochastic Behaviour, and Relevance to Plant Development

Cell polarization is an important response of eukaryotic cells to external cues, which allow cells to sense and react to signals in their environment.

Members of the family of Rho GTPases have emerged as important components of the polarization machinery of cells: these switch-like proteins have a distinct active (membrane-bound, low diffusivity) and inactive form (mostly cytoplasmic, high diffusivity), and localization of the active form (accumulation in a small portion of the cell) has been shown to act as a necessary cue for cell polarization (e.g. rearrangement of the cytoskeleton). To this end, Rho localization (short timescale) signals the cell where its front and back are and this information is usually imprinted in more committed processes such as cytoskeleton remodelling (long timescale).

Mori et al. [1] established a reaction-diffusion system as a model of the dynamics of Rho GTPases and derived conditions under which their model predicts Rho localization. These conditions include mass conservation, uniformity of the inactive form, and an invasion criterion on a local pulse in the active form. Mori et al. named this mechanism wave-pinning due to the nature of how the Rho localization pattern forms over time.

We provide a short overview of Rho localization due to wave-pinning, conditions for wave-pinning, and discuss biological properties and phenomena that wave-pinning is capable of reproducing. Furthermore, we introduce local pulse analysis (LPA) as a useful tool for determining conditions that meet an invasion criterion necessary for wave-pinning.

In a recent effort, [4], we studied a stochastic version of the wave-pinning mechanism (spatial Gillespie algorithm, [2], [3]) which models Rho localization in a low copy-number regime of Rho: this model includes biologically relevant stochastic noise, and behaves markedly different from the deterministic model established by Mori et al. We discuss differences between the determinstic model, [1], and our

stochastic model, and reason about conditions under which wave-pinning is lost in the latter.

Relevant to plant science, our current work focuses on plant homologues of the Rho GTPase family, Rho of Plants (ROP), and a model of ROP localization due to wave-pinning established by Grieneisen et al. In this effort we attempt to find links between ROP localization as a result of auxin gradients (external signal), and localization of auxin efflux carriers (PINOID, PIN) as a readout of cell polarization.

We hope that linking short-timescale ROP localization with long-timescale PIN localization will reveal biologically relevant feedback loops between external auxin gradients, internal cell polarization, and eventual modification of the external auxin gradient. We argue that feedback loops of this kind may be relevant for the development of the plant embryo and establishment of biological phenomena such as the auxin maximum in the quiescent centre of the root.

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Poster Session; Friday, July 1, 20:00

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Stability Analysis of a Kind of Three-Species Food System with Time Delay

A kind of three-dimensional model of food system including Giant Panda , bamboo and arbor with delay is considered. Absolute stability and Hopf bifurcation of the model are studied by using systematic analysis method. Sufficient conditions of absolute stability are obtained, it is shown that the delay is locally harmless. Furthermore, it is proved that the time delay may destabilize the positive equilibrium, and Hopf bifurcation occurs under certain conditions.

Medical Physiology; Tuesday, June 28, 11:00

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Mathematical modelling of wound healing and the development of chronic wounds

Epidermal wound healing is often described in broad terms as a 3 stage process, 1) inflammation (initial responses to the trauma), 2) granulation and re-epitheliasation (leading to wound closure) and 3) remodelling (strengthening of the new skin at the wound site). Progression through the granulation phase is crucial in the wound healing process and it is this stage that is typically arrested in chronic wounds. Factors that can lead to such an arrest include locally poor circulation (particularly for ulcers and pressure sores in the elderly and diabetic patients) and bacterial infection. The costs involved in patient care is a significant burden to health services throughout the world.

Presented in this talk is a spatio-temporal model of the healing processes during the granulation phase, that incorporates tissue growth (granular and epithelial) and migration, immune response, fibroblast activity and angiogenesis, all of which dependent on nutrients and growth factor levels. Simulations highlighting the key factors that influence normal and abnormal healing will be presented. For larger wounds, normal healing is characterised by the formation of travelling wave solutions towards wound closure. Results assessing the effectiveness of a range of bolus and topical therapies will also be discussed.

Developmental Biology; Wednesday, June 29, 17:00

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Development of the Murine Retinal Vasculature: Mathematical Modelling and Numerical Simulation

Tumour-induced angiogenesis has been extensively explored by the mathematical community. However, despite the availability of animal models with experimentally accesible and highly ordered vascular topologies, there have been few attempts to model angiogenesis during normal development. In this talk we present a mathematical model of the developing retinal vasculature, based on a coupled experimental program of investigation in neonatal mice. Formation of the superficial retinal vascular plexus (RVP) occurs in a spatio-temporally defined pattern. Prior to birth, astrocytes migrate away from the optic nerve over the surface of the inner retina in response to a chemotactic gradient. Astrocytes express further chemotactic, and haptotactic, signals which induce endothelial cell sprouting and growth of the RVP. Adopting a hybrid PDE-discrete approach, the model allows tracking of individual astrocytes and endothelial cells in response to these migratory cues. The simulations provide an excellent correlation with the extent and pattern of astrocyte migration and vascular network formation observed in vivo. The model is extended to include simulation of blood flow through the nascent vessel networks, and oxygen delivery to the surrounding tissues. Dynamic remodelling of the vasculature is then performed, again producing excellent agreement with experimental observations.

Poster Session; Friday, July 1, 20:00

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The random walk and Langevin approaches to diffusive model of the BKCa ion channel kinetics.

Up to date, several different theoretical approaches were introduced to describe open and closed states of ion channels. They describe correctly dwell-time distributions, however many of them are incapable of predicting and explaining long-term correlations between the dwelling times of subsequent states of a channel, found in experimental patch clamp time series. In this work, we have proposed a new diffusive model for the kinetics of voltage and Ca2+-activated potassium channels (BKCa). We have considered and compared two theoretical approaches towards the construction of modeled states: the random walk and Langevin ones. Our results show that the kinetic properties of experimental time series and the corresponding simulated data obtained from the model, turn out to be quite concurrent. Moreover, the rescaled range analysis (R/S analysis, Hurst analysis), which in our investigations measures the correlation in the time series of adjacent openings and closings dwell times of the BK channel, gives close results for experimental and modeled data.

Mathematical modeling and simulations of angiogenesis I; Wednesday, June 29, 08:30

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Complex Cellular Automata based on particle dynamics as a framework for modeling solid tumor growth and angiogenesis

To simulate the growth dynamics of tumor in both its avascular and angiogenic phases we propose a novel computational paradigm based on, so called, complex automata approach (CxA). It combines the cellular automata modeling (CA) with off-grid particle dynamics coupled by continuum reaction-diffusion equations. The particles represent both tissue cells and fragments of vascular network. They interact with their closest neighbors via semi-harmonic central forces simulating mechanical resistance of the cell walls. The particle dynamics is governed by both the Newtonian laws of motion and the cellular automata rules. The rules represent cell life-cycle stimulated by various biological processes such as carcinogenesis and diffusion-reaction processes involving nutrients and tumor angiogenic factors. We discuss the main advantage of CxA model such as its ability of simulating mechanical interactions of tumor with the rest of the tissue. We show that our model can reproduce realistic 3-D dynamics of the entire system consisting of the tumor, normal tissue cells, blood vessels and blood flow. We conclude that the CxA paradigm can serve as an efficient and elegant general framework of more advanced multiple-scale models of tumor coupling microscopic in-cell processes with its macroscopic evolution. Finally, we discuss the main requirements and design components of an interactive visualization engine based on CxA paradigm. Such the system can be used as a valuable tool for educational purposes and, in the nearest future, for in silico experiments, which can play the role of angiogenesis assays in planning cancer treatment.

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Modeling tumor development in liver

As recently demonstrated for liver regeneration after drug-induced damage, organization and growth processes can be systematically analysed by a process chain of experiments, image analysis and modeling [1]. In that paper our group was able to quantitatively characterize the architecture of liver lobules, the repetitive functional building blocks of liver, and turn this into a quantitative mathematical model capable to predict a previously unrecognized order mechanism. The model prediction could subsequently be experimentally validated. Here, we extend this model to the multi-lobular scale and study, guided by experimental findings, cancerogenesis in liver. We explore the possible scenarios leading to the different tumor phenotypes experimentally observed in mouse. Our model considers the hepatocytes, the main cell type in liver, as individual units with a single cell based model and the blood vessel system as a network of extensible objects. The model is parameterized by measurable values on the cell and tissue scale and its results are directly compared to the experimental findings.

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Population Dynamics; Wednesday, June 29, 17:00

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A model of self-induced thigmotactism in ants

Ants display thigmotactic behaviour which is a tendency to align with a border and move along it for some time. In many cases, ants' activity results in the formation of environmental heterogeneities that in turn modify the motion of ants and trigger a thigmotactic behaviour as they reach a critical size. We have analyzed this phenomenon during object clustering experiments in the ant *Messor Sanctus*. The experimental investigation of the motion of ants in presence of objects (Casellas et al. [1] and subsequent experimental work) leads to a new thigmotactic random walk model, in which ants tend to walk around the emerging piles rather than crossing them. In this contribution we analyze the properties of this model and show that its predictions are in quantitive agreement with the experimental observations. We then show the essential role played by the coupling between the clustering dynamics and the motion of the ants in the object clustering experiments. We finally discuss the implications of the model for the study of the nest building process in ants, and for understanding the shape transition in the clustered items observed when ants are facing low-speed air currents.

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Evolutionary Ecology; Friday, July 1, 14:30

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Sympatric speciation and its dependence on competition and strength of reinforcement

Sympatric speciation is the evolutionary split of one species into two or more species in the same environment. We consider a mathematical model for this phenomenon, in which reinforcement plays an important role. By reinforcement we mean a phenotypic trait that influences the choice of mating partner, but has no impact on the adaptation to the environment. The model is individual based, implemented as a discrete time Markov process in a space $\mathcal{Z}^N$, where $\mathcal{Z}$ is the phenotype space of an individual and N is the number of individuals. Reproduction is modelled as the result of the interaction of pairs of individuals, but does not involve different genders, and the size of the offspring depends on the parents's adaptation to the environment. The basic model is presented in [1], where simulations simulation results are presented that show that reinforcement is essential for speciation to take place. In this paper the model is further developed, and in particular we investigate the impact of specialization to the environment on the rate of speciation events, and on the long term survival of the decendants of a species.

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Identification of fractional subdiffusive dynamics of mRNA molecules

Identification of fractional subdiffusive dynamics of mRNA molecules

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In this talk we propose a statistical methodology how to distinguish between three mechanisms leading to single molecule subdiffusion, [1-2]. Namely, fractional Brownian motion, fractional Levy stable motion and Fractional Fokker-Planck equation. We illustrate step by step that the methods of sample mean-squared displacement and p-variation can be successfully applied for infinite and confined systems. We already identified fractional subdiffusive dynamics on biological data describing the motion of individual fluorescently labeled mRNA molecules inside live E. coli cells [3-5], but it may concern also many other biological experimental data.

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Poster Session; Friday, July 1, 20:00

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Improving statistical models for discovering cell type specific genes

Analysis of gene expression is one of the fundamental methods of characterizing cell populations. One of the major cells in the immune system are "helper" T cells expressing CD4 surface marker. The majority of these cells constitutes a population of conventional CD4+ T cells which supports functions of other cells of the adaptive and innate immune system. A smaller population, called regulatory CD4+ T cells (Treg), has opposite function and suppresses immune response and is responsible for the homeostasis of the immune system. The most characteristic gene expressed by Treg cells is a transcription factor Foxp3. Both conventional and Treg cells are generated in the thymus from bone marrow-derived progenitors. Treg cells produced in the thymus are called natural Treg cells. Under certain conditions, conventional CD4 T cells can express Foxp3 and acquire suppressor function. These Treg cells are called adaptive Treg.

One of the methods of investigating different subsets of CD4 T cells is to compare their gene expression profiles. This approach allows insight into cellular functions of individual cell subsets and allows for analysis of functions of differentially expressed genes. Analysis of the global expression profiles is commonly done using microarrays.

To reveal genetic control of various subsets of CD4 T cells we compared gene expression profiles of resting and activated conventional CD4 T cells, resting and activated natural Treg cells and adaptive Treg cells. RNA was isolated from the respective T cell populations and hybridized to Affymetrix GeneChip M430 2.0 Plus microarrays. Three individual samples of each kind were processed.

In order to make our data set more representative, followin a similar approach described in [**1**], we included microarrays from the respective CD4 T cell subsets from other laboratories. These data were obtained from the GEO database: www.ncbi.nlm.nih.gov/geo.

To deal with the problem we produced a framework combined from several available statistical approaches: Linear models for Microarray data, Bayesian approach, Non-Negative Matrix Factorisation [**2**].

Comparisons of data from multiple laboratories introduces additional levels of variability which need to be accounted for during data normalization.

Normalization attempts that adjusted mean values and standard deviation of gene expression resulted in the sets of differentially expressed genes that differed

between laboratories instead of between different T cell populations. Our computations indicated that lab origin has more influence on gene expressions then investigated cell types among laboratories.

To account for multi-dimensionality of the normalization problem we developed a heuristic approach.

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Fractals and Complexity I; Wednesday, June 29, 14:30

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Origins of Allometric Growth: A Contemporary Perspective

The theoretical allometry relation (AR) between the size of an organism Y and that of an organ within the organism X is of the form $X = aY^b$ and has been known for nearly two centuries. The allometry coefficient a and allometry exponent b have been fit by various data sets over that time. In the last century the phenomenological field of allometry has found its way into almost every scientific discipline and the ARs have been reinterpreted with Y still being the size of a host network and X a function of the network. For example, in biology the measure of size is often taken to be the total body mass and the function is the metabolic rate, or heart rate, breathing rate, or longevity of animals. Most theories purporting to explain the origin of ARs focus on establishing the proper value of b entailed by reductionist models, whereas a few others use statistical arguments to emphasize the importance of a.

On the other hand, statistical data analysis indicates that empirical ARs are obtained with the replacements $X \to \langle X \rangle$ and $Y \to \langle Y \rangle$ and the brackets denote an average over an ensemble of realizations of the network and its function. Networks in which these empirical ARs are established include the metabolism of animals, the growth of plants, species abundance in econetworks, the geomorphology of rivers, and many more. The resulting empirical AR can only be derived from the theoretical one by averaging under conditions that are incompatible with real data. Consequently another strategy for finding the origin of ARs is required and for this we turn to the probability calculus and fractional derivatives.

We assume that the statistics of living networks can be described by fractional diffusion equations (FDEs) and hypothesize that FDEs can explain the origin of ARs. We obtain the Fourier-Laplace transform of the general solution to the FDE that contains both historical information and nonlocal influences on the dynamic variables, that is, fractional derivatives in both time and phase space, complexity commonly found in living networks. The scaling properties of the resulting solution to the FDE enable us to interrelate the network's size and function by means of the mechanism of strong anticipation. The analysis shows that strong anticipation and scaling taken together support the hypothesis and is sufficient to explain the origin of empirical ARs.

Ecology and evolution of infectious diseases; Friday, July 1, 14:30

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The evolution of host-parasite range

Understanding the coevolution of hosts and parasites is one of the key challenges for evolutionary biology. Adaptive dynamics techniques have examined coevolutionary outcomes in classical infectious disease model frameworks in which infection depends on absolute rates of transmission and defence [**1**]. These models typically predict either that one strain dominates or that there is evolutionary branching, where disruptive selection around a fitness minimum causes the emergence of two distinct strains. This may therefore provide insight into the onset of diversity but does not fully explain the generation and maintenance of the wide range of variation in host and parasite strains observed in natural systems. Here we present a fully coevolutionary host-parasite model using the assumptions of adaptive dynamics, but rather than assuming that transmissibility and defence are absolute we approximate an 'all or nothing' infection process where the success of infection depends upon the relative 'range' of host resistance and parasite infectivity. A parasite that can infect a wide range of host strains will pay a cost in terms of disease transmission compared to parasites that infect a narrower range of hosts. A similar trade-off exists in terms of the range of parasite strains a host can resist and the host reproductive rate. Infection success therefore depends on the specific characteristics of both the parasite and the host. We show that considerable diversity can be generated and maintained due to epidemiological feedbacks, with strains differing in the range of host and parasite types they can respectively infect or resist [**2**]. The patterns of resistance and infectivity are also in close agreement with laboratory results that assess the evolutionary behaviour in a bacteria-phage system.

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Reports from US - African BioMathematics Initiative: Conservation Biology; Saturday, July 2, 14:30

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The effects of disturbance, fire, and elephants on savanna woodlands

The extent to which ecological systems are experiencing disturbance and change in function and structure is critical for the long-term conservation of biological diversity. The savanna, the dominant ecosystem of sub-Saharan Africa, is characterized by the coexistence of a variety of woody plants and grasses. Vegetation modification from woodland to grassland has most often been attributed to the coupled effects of elephant herbivory and fire. Therefore, to better inform management strategies for woodland savanna ecosystems, the objective of our study was to model the impact of fire and herbivory on tree survival. We used density-dependent, stochastic Lefkovitch matrix models to simulate the population dynamics of woody plants in Kruger National Park, Mpumalanga, South Africa. Our model was run on biannual time steps, including wet and dry seasons, for 50 years. Elephant herbivory was assumed to occur every dry season, while the occurrence of fire was stochastic. We tested different frequencies and intensities of fire and herbivory in our model, and also altered the variance of the fire parameters. Preliminary results indicated an average fire return interval of 3-4 years produced an approximately stable population growth. Our sensitivity analysis showed that under baseline conditions adult tree survival was the most important factor affecting population growth rates. We also found that different fire regimes, varying intensities of disturbance, and even altering the variance of these parameters can profoundly affect the pattern of savanna structure over time. Therefore, our results indicate that savanna woodland structure is sensitive to both the frequency and intensity of disturbance which has important management implications.

Poster Session; Friday, July 1, 20:00

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Modelling Immunomodulation of Tumor Growth

The physical presence and activities of cancer cells elicit an immune response in the host. In turn, this immune response has been shown to be both stimulatory and inhibitory to tumor growth. This interplay therefore has complex implications for tumor development. To explore these, we have developed a system of differential equations to investigate the role of the immune response in tumor growth. The two-compartment model consists of both cancer and immune cells: the cancer cells proliferate on their own and their growth can either be inhibited or stimulated by immune cells in a manner dependent on the states of each, while the immune cells are recruited to the tumor site by either the cancer cells or by the interaction of the cancer cells with the immune cells. Cancer cells, innate immune cells (such as platelets, dendritic cells, macrophages, and natural killer cells) and adaptive immune cells (such as T and B lymphocytes) communicate with each other through cytokine and chemokine production which controls and shapes tumor growth. The cummulative result of the interactions of these diverse cells determines whether tumor-promoting inflammation or antitumor immunity occurs, and it is this wholistic response that we attempt to capture in our model. Most mathematical models of the immune response to cancer focus on single immune cells and their specific function in cancer cell killing. One of the main advantages of this model is that it combines the effects of all immune cell types and the physical process of inflammation into one quantitative model setting. Thus, it is better positioned to predict immunomodulation of tumor growth, and to assist in the design of novel treatment approaches that exploit immune response to improve tumor suppression.

References.

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Developmental Biology; Saturday, July 2, 11:00

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Biosilica nanoscale pattern formation in diatoms

Over the last 200 million years, a number of aquatic unicellular eukaryotic organisms have evolved mechanisms to sequester and assemble biominerals into exogenous structures. The results seen today are high-fidelity, mineralized shells featuring patterned complex nanoscale ornamentations that defy synthesis in vitro. Among these organisms, diatoms are topical owing to their fundamental role in the carbon cycle, in food chains ascending to fish, and the potential uses of their biosilica shells in developing nanotechnologies. Their species-specific mineralized shells have diverse morphologies, with structures that span scales from 5 nm to 0.5 mm. At the finest scale are structures called pore occlusions, which in a matter of minutes assemble and solidify under ambient physiological conditions into roughly deterministic patterns that are conserved within species, but which vary between species. Very little is known about the physical processes governing this biosilica patterned assembly. In an attempt to identify the physical processes governing pore occlusion formation, we are investigating new pattern forming probabilistic (spin-like) lattice models in coordination with diatom culturing experiments, which have produced some promising results.

Population Dynamics; Wednesday, June 29, 14:30

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Mathematical model(s) for the dynamics of (TNF-) Receptor Clustering

Responses of the immune system are coordinated by immune hormones, called cytokines. Tumor necrosis factor (TNF) is a cytokine regulating the innate immune system, including cells like dendritic cells, macrophages and neutrophils. Disregulated TNF has been recognized as the main factor in progression of many autoimmune diseases, like Rheumatoid Arthritis and Morbus Crohn. TNF is a homotrimeric protein capable to bind three receptors. But also unligated receptors occur on the cell surface as homomultimers due to a homophilic interaction domain. Based on these two interaction motivs (ligand/receptor and receptor/receptor) we present two different modelling and simulation strategies.

Firstly, we use a mass action kinetics approach to propose an ordinary differential equations model for the dynamics of subsequent formation of signal clusters on the cell membrane. Thereby, we focus our attention on the essential components of the system of elementary ligand/receptor complexes that can initiate intracellular signaling processes eventually leading to caspase mediated cell death. Therefore we develop our model in a way that not only receptor cross-linking by ligand but also homophilic interaction of receptors leading to homodimer formation in the absence of ligand is encompassed.

It turns out that using parameter values for binding affinities consistent with experimentally determined values the analysis of our model suggests that in the case of high ligand and low receptor concentration no substrate inhibition in the receptor cross-linking can be observed. In contrast, our model shows that an increasing ligand concentration leads to a saturation in receptor cross-linking and therewith illustrating the persistence of the downstream signaling events even in the case of ligand excess. These results are underlined by numerical simulations, which are confirmed by experimental data.

Secondly, we apply a population balance model with simultaneous growth and breakage processes in order to describe the forming of the signaling clusters along

with the evolution of the cluster sizes and couple this with a further equation characterising the concentration of free receptors. For the numerical solution of this system in its integro-differential form we use several discretization techniques including finite differences and semi-discrete moment preserving finite volume schemes which can be extended to incorporate further spatial effects on cell surfaces. Thereby we examine the results obtained not only with regard to biological relevance but also with respect to stability and robustness of the discretization.

Poster Session; Friday, July 1, 20:00

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Surfactant dynamics in lung alveoli

During breathing, the mammalian lung exchanges oxygen and carbon dioxide in bubble-like structures called lung alveoli. Their interior is covered by a thin film of water on which lipids act as surfactant. The surfactant ensures that the inner surface of the alveoli remains wetted in spite of a continuing expansion and compression. Atomic force microscopy has revealed, that the lipid surfactant undergoes phase seperation into a high- and a low-density phase. In order to describe the spatial separation of the two lipid phases, we have constructed a phase field continuum model. Thereby, the free energy of the system seperates the two phases by a barrier depending on overall lipid density and volume fraction of the low-density phase. The equations for transition profiles and resulting interface speed can be reduced to a set of nonlinear degenerated ODEs, which we solve numerically. For further insights elucidating the microsopic scale, we additionally perform computer simulations of rod-like lipids on a rigid water surface. The lipid-water interaction arises from a varying submersion of hydrophilic head- and hydrophobic tail-parts of the model lipids. Together with explicit, polar interaction forces between pairs of lipid rods, we obtain phases seperation and spatial cluster aggregates.

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Population Genetics; Wednesday, June 29, 14:30

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Genetic effects of introduced species on their native competitors in habitats with different spatial structures

When a new species is introduced to a habitat where it did not occur before, it interacts with the members of the local community and influences them in many ways. Most empirical and theoretical work so far has focused on how introduced species cause changes in population sizes of interacting native species. However, little is known on the genetic effect of introduced species on their native competitors, predators, or prey species. Using analytical arguments and computer simulations, we aim to understand how the amount and spatial structure of genetic variation in a native species changes after the introduction of an ecologically similar competitor. Genetic variation measured in terms of the expected heterozygosity at a neutral locus declines after the introduction event, reaches a minimum, and eventually rises again provided that the native species does not go extinct. The severity of this reduction as well as the time scale on which it occurs depend on the number of introduced individuals, the size, and the spatial structure of the native population. The expected impacts differ between single homogeneous populations, subdivided populations, and metapopulations subject to local extinction and recolonization. These results for neutral loci suggest that also variation at loci for ecologically important traits may be affected by competition with introduced species, thus influencing the species ability to adapt to new environmental conditions.

Cancer; Wednesday, June 29, 11:00

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Stochastic Modeling and Analysis of DNA Sequence Data from Heterogeneous Tumors

Many cancers are believed to have clonal origin, starting from a single cell with a defining mutation and further acquiring one or more additional mutations before the first cancerous cell is established. For example, in *Follicular Lymphoma*, a blood cancer, the total number of required mutations M is believed to be two of which the first is a translocation called t(14;18).

A population of cancer cells evolves further over time and accumulates genetic changes, many of which are random and others potentially beneficial for the cancer. Consequently, cells in different parts of a tumor might show differences in their genomes, or DNA. This phenomenon is referred to as genetic tumor heterogeneity and is comparable to the genetic heterogeneity observed in individuals in a population.

Here, I address the problem of modeling how the tumor evolves over time and accumulates changes in the DNA, starting from the initial cell with the defining mutation. The model is stochastic and relies on birth-death processes; it allows the first required M mutations to be under selective pressure, while the subsequent mutations are neutral. I show that there is a simple description of how the (stochastic) number of tumor cells in the system changes over time and that the model imposes constraints on parameters that determine the reproducibility and the survival of cells; thus the model leads to biological insight.

Further, the model leads to a simple way of simulating tumor evolution. Based on this, I show how a sample of DNA sequences taken from distinct parts of a heterogeneous tumor might be used to draw inference on model parameters and date the origin of the tumor, as well as the defining and subsequent mutations. The latter might have clinical importance as it provides an estimate of the time from tumor initiation to diagnosis.

Finally, I show a simple application to DNA sequence data from *Follicular Lymphoma* patients and outlining some further mathematical and statistical work to be done.

Poster Session; Friday, July 1, 20:00

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Computational Model of Genetic Demographic Networks

Demographic network is defined as a set of populations evolving from a single ancestral population with a beginning at the time 0. The structure of the network is described by two types of events: split of a single population into two populations and merger of two populations. Additionally, we incorporate migration between populations coexisting in the model.

There are several models available in the literature that can be used to analyze data from such demographic networks. Most of them are based on backward-time coalescent simulations and require considerable computational power. In this paper we introduce a forward-time and time-continuous model that allows to calculate the exact values of the entries of the infinite matrixes $R_{ij}(t)$ being the joint distributions of pairs of alleles sampled at the time t from populations i (first allele from a pair) and j (second allele). We assume that individuals in each population in the network are described by the same allelic space model and we introduce mutation to the model using intensity matrices Q_i of the Markov chain of the mutation process in population i. Mutation model is assumed unchanged between two adjacent demographic events. Population size growth can be specified for each population. Evolution of the joint distributions between network events is described by Lyapunov differential equations.

In our work we present mathematical details of the model and a computer program implementing this model along with several applications. We also discuss some improvements to our model, such as optimization of the computational complexity for some common mutation models and calculating the joint distributions of a sample of size greater that 2.

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Poster Session; Friday, July 1, 20:00

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Qualitative analysis of lamella and cell body shape during cell migration

The aim of our work is to investigate migration of single cells on two-dimensional substrata. To this end, we label adhesion sites and the interior keratinocyte cell body by staining vinculin and tubulin with fluorescence dyes. This enables us to reliably distinguish between cell body and the surrounding lamella.

For time-lapse image processing we quantitatively determine the lamella edge as well as the cell body outline by an adaptive *stochastic chain* algorithm [**1**], also known as *active contour* model [**2, 3**]. The stochastic chain adapts to the cell outline by interpreting the information given by phase contrast micrographs or corresponding fluorescence images. Chain adaption follows from different "image forces", which involve (i) chain stiffness, (ii) retrograde centripetal pulling and (iii) gradients in picture brightness. The evolution of the chain stops when the stochastic fluctuations have become stationary.

Our statistical analysis investigates cell body and lamella shape, which are independently quantified by the positions of the interior body chain and the exterior edge chain, respectively. Spatio-temperal auto- and cross-correlations reveal the time-lag relation between mean protrusion vector and cell migration velocity. Moreover, we find that the cell body has an elliptic shape during forward migration, whereas upon turning it becomes almost circular. The overall lamella dynamics is mainly influenced by the underlying cell body shape. Significant deviations from this protrusion pattern appear, particularly when the cell changes its migration direction.

References.

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Semigroups of Operators in Mathematical Biology I; Wednesday, June 29, 08:30

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Do the aggregating cells attain a tight packing state?

We consider models of chemotaxis which take into account volume-filling effects such that an *a priori* threshold for the cell density corresponding to a tight packing state is taken into account (for more information we refer to a survey [2]). Our study concerns quasilinear parabolic systems with singular or degenerate diffusion of cells which include recent models by Wang and Hillen(2007) and Lushnikov (2008). It is proved in [3] that for some range of parameters describing the relation between the diffusive and the taxis part of a cell flux there are global-in-time classical solutions which in some cases are separated from the threshold uniformly in time. Existence and uniqueness of global in time weak solutions as well as the set of stationary states are studied as well. In the recent preprint [1] it is proved for parabolic-elliptic version of the model that if the taxis force is strong enough with respect to self-diffusion and the initial data are chosen properly then there exists a classical solution which reaches the threshold in finite time provided the diffusion of cells is non-degenerate.

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Cell migration during development: modelling and experiment; Saturday, July 2, 08:30

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A computational model of neural crest chain migration provides mechanistic insight into cellular follow-the-leader behavior

Follow-the-leader chain migration is a striking cell migratory behavior observed during vertebrate development, adult neurogenesis, and some cancer metastases. An example of chain migration is found in the embryonic neural crest (NC), a multipotent, invasive cell population. Although some aspects of chain migration have been well described, the mechanisms involved in the persistence of NC cell chain migration are unclear. We developed a quantitative agent based modeling framework to investigate three distinct model mechanisms of chain migration. The models relied on biological data from the NC and involved extracellular matrix and cell contact mediated promotion of chain migration. Sensitivity analysis revealed specific criteria for high chain migration persistence and suggested possible mechanism that may sustain follow-the-leader behavior. Our approach offers a means to test mechanistic hypotheses of collective NC cell chain migration in an in silico framework that is applicable to studying collective chain migration in other biological systems.

Ecosystems Dynamics; Tuesday, June 28, 17:00

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Different Social-ecological Networks in Grassland and Forest SystemsImplication for their sustainable management

Many ecosystems have been seriously degraded by human activities in the world. In order to consider management of those systems, we should grasp the systems as social-ecological networks as a whole. Remarking specially the network structure of social-ecological systems, we are executing a project titled Collapse and Restoration of Ecosystem Networks with Human Activity (http//www.chikyu.ac.jp/rihne/project/D-04.html) in Research Institute for Humanity and Nature (http//www.chikyu.ac.jp/indexe.html).

We found that the networks have remarkable difference between grassland and forest systems, by analyzing data from grassland in Mongolia and forests in Sarawak, Malaysia. In Mongolia, the vegetation itself (grasses) has no direct value for humans the value is stored in livestock that feeds on the grasses. Therefore, global economy affects the behavior of inhabitants, leading to overuse of the vegetation and degradation of the grassland. In this case, the effective solution to the problem should involve changing the behavior of inhabitants. On the other hand, in Sarawak, the economic value is stored in the vegetation (trees). Therefore, enterprises and governments tend to severely develop the forests, causing both reductions in the amount of forest available to inhabitants and biodiversity loss. The effective solution here should involve regulation of enterprises and governments.

We here explore the model representing the difference of networks, and examine effective strategies for sustainable management of each type of systems, using the model. In Mongolian social-ecological system, the equilibrium is always stable even if price of livestock products increases because of negative feedback between grassland quality and livestock biomass. However, considering climate fluctuation of grassland quality, the risk of system collapse is lower for the higher equilibrium value. In Sarawak social-ecological system, when logging rate reflecting global economy exceeds a critical level, usable forests for habitants rapidly decreases to 0 because of positive feedback between decreases of such forests and inhabitant utilization activity for forests. The system has the essential nature of instability. We discuss that general social-ecological systems with environmental problems can be placed at some positions between two types of Mongolia and Sarawak networks.

Evolutionary Ecology; Wednesday, June 29, 14:30

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Joint evolution of sex ratio and reproductive group size under local mate competition with inbreeding depression

Local mate competition (LMC) may involve some amount of inbreeding between siblings. Because sib-mating is generally accompanied by inbreeding depression, natural selection may favor a reduced rate of sib-mating, possibly affecting the evolution of sex ratio and reproductive group size. The present study theoretically investigated the evolution of these traits under LMC in the presence of inbreeding depression. When the reproductive group size evolves, the determination mechanism of sex ratio is important because the time scale of the sex ratio response to reproductive group size can affect the evolutionary process. We consider a spectrum of sex ratio determination mechanisms from purely unconditional to purely conditional, including intermediate modes with various relative strengths of unconditional and conditional effects. This analysis revealed that both the evolutionarily stable reproductive group size and ratio of males increase with higher inbreeding depression and with a larger relative strength of an unconditional effect in sex ratio determination. Unexpectedly, when the sex ratio is controlled purely conditionally, the reproductive group size cannot exceed three even under the severest level of inbreeding depression (i.e., lethal effect). The present study reveals the conditions for LMC to evolve through the analysis of the joint evolution of reproductive group size and sex ratio.

Ecosystems Dynamics; Tuesday, June 28, 17:00

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Global asymptotic stability of solutions of nonautonomous master equations

We discuss the *master equation* $\frac{dx}{dt} = A(t)x$, here $A(t)$ is an nxn matrix whose off-diagonal entries are the *transition rates* $a_{ij}(t)$ and whose columns sum to zero. These conditions ensure that the sum of the entries of a solution of the master equation is conserved and that nonnegative solutions remain nonnegative. Such matrices are called W-matrices by van Kampen. In this talk, we give some new results for the master equation concerning Earnshaw and Keener's conjecture.

Population Dynamics; Friday, July 1, 14:30

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Permanence of a logistic type impulsive equation with infinite delay

Many evolution processes are characterized by the fact that at certain moments of time they experience a change of state abruptly. Theses processes are subject to short-time perturbations whose duration is negligible in comparison with the duration of the process. Consequently, it is natural to assume that these perturbations act instantaneously, that is, in the form of impulses. It is known, for example, that many biological phenomena involving thresholds, bursting rhythm models in medicine and biology, optimal control models in economics, pharmacokinetics and frequency modulated systems, do exhibit impulsive effects.

In this presentation we give an introduction to theory of impulsive differential equations. Impulsive differential equations, that is, differential equations involving impulse effects, appear as a natural description of observed evolution phenomena of several real world problems. We investigate a non-autonomous Logistic type impulsive equation with infinite delay. For the general non-autonomous case, some sufficient conditions which guarantee the permanence of solutions are obtained. Our results extend a known result of Seifert [**1**]. This presentation is based on the paper [**2**].

References.

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Population Dynamics; Wednesday, June 29, 14:30

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Population Dynamics of Glassy-winged Sharpshooter in Texas Vineyards

Pierce's Disease (PD) is a bacterial disease of grapevines with the capacity to kill an entire vineyard in one year. Outbreaks of the disease threaten California vineyards and are a chronic problem in Texas, particularly along the Gulf Coast. The disease is caused by a bacterium, *Xylella fastidiosa* and is transmitted by xylem-feeding insects commonly called sharpshooters. To understand the role of sharpshooter ecology on PD epidemiology, the USDA-APHIS has funded sharpshooter trap data from 50 Texas vineyards from 2003-to present under the direction of Dr. Forrest Mitchell, Texas A&M University. Among the insects monitored, *Homolodisca vitripennis* (Glassy-winged sharpshooter-GWSS) is the most abundant insect captured across all vineyards in Texas. Modeling of the enormous GWSS data set is an excellent opportunity to have both biology and mathematics students and apply modeling techniques to temporal changes in insect populations in order to predict future PD risk and determine the optimal management protocols.
This collaborative research has been funded by the NSF Grant: The Interdisciplinary Training for Undergraduates in Biology and Mathematical Sciences (UBM). During year 2009-2010, our group has developed a population model based on the time-delayed logistic equation for the dominant single species in the central Texas hill regions (Ecoregion 7: Edwards Plateau) for the years 2003-2009. The chosen model was transformed as one-parameter delayed equation by the non-dimensional technique. The existence of the periodic cyclic solution was explained by the local stability analysis of the linear model near the carrying capacity analytically. Undergraduate students worked on obtaining the optimal values of parameters which could guarantee the periodic solution numerically using software, MATLAB and compared it to the experimental histogram. From the fall of 2010 we have been working on the revision model with harvesting and immigration terms which could include the environmental factors such as insecticide use, information campaigns, weeds cleaning, and temperature changes. We will test the autonomous and also the non-autonomous harvesting terms. In the future, the model will be extended to a spatio-temporal model based on the Fisher's equation with delayed logistic population growth.

Developmental Biology; Thursday, June 30, 11:30

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A condition for regeneration of a cell chain based on *Dachsous:Fat* heterodimer system

Regeneration phenomena have been studied through various models. Taking cockroach leg regeneration for instance, it has been studied through the positional information model [6], the polar coordinate model [3], and the boundary model [5].

Beyond theoretical models, recent studies have led to models at the single cellular level [1]. Within a cell, Dachsous (Ds) and Fat molecules, and between cells, Ds:Fat heterodimers, are considered to facilitate regeneration. The Ds:Fat signaling system looks like an entity to realize the steepness hypothesis where the leg size and regeneration are regulated through a *gradient* across cells [4].

In this work we modeled a cell chain based on the Ds:Fat system. It has been said that the heterodimer is produced from free active Ds and Fat molecules within cells. Ds and Fat molecules are redistributed when a cell divides into two, so that Ds:Fat heterodimers become redistributed accordingly. Little is, however, known about the way they are redistributed because the metabolism of the Ds:Fat signaling and heterodimers remains obscure [2]. We hence modeled this redistribution and calculated a condition for regeneration. The derived equations show that some degenerated redistribution ratio of heterodimers provides a cell chain with the ability to regenerate.

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Regulatory Networks; Saturday, July 2, 11:00

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Model gene regulatory networks under mutation-selection balance

Gene regulatory networks typically have low in-degrees, whereby any given gene is regulated by few of the genes in the network. They also tend to have broad distributions for the out-degree. What mechanisms might be responsible for these degree distributions? Starting with an accepted framework of the binding of transcription factors to DNA, we consider a simple model of gene regulatory dynamics. There, we show that selection for a target expression pattern leads to the emergence of minimum connectivities compatible with the selective constraint. As a consequence, these gene networks have low in-degree, and "functionality" is parsimonious, *i.e.*, is concentrated on a sparse number of interactions as measured for instance by their essentiality. Furthermore, we find that mutations of the transcription factors drive the networks to have broad out-degrees. Finally, these classes of models are evolvable, *i.e.*, significantly different genotypes can emerge gradually under mutation-selection balance.

Modeling of collective phenomena in biological systems; Saturday, July 2, 08:30

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Emergence of sparsity and motifs in gene regulatory networks

We consider a simple model of gene regulatory dynamics derived from the statistical framework describing the binding of transcription factors to DNA. We show that the networks representing essential interactions in gene regulation have a minimal connectivity compatible with a given function. We discuss statistical properties using Monte Carlo sampling. We show that functional networks have a specific motifs statistics. In the case where the regulatory networks are to exhibit multi-stability, we find a high frequency of gene pairs that are mutually inhibitory and self-activating. In contrast, networks having periodic gene expression patterns (mimicking for instance the cell cycle) have a high frequency of bifan-like motifs involving four genes with at least one activating and one inhibitory interaction.

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits II; Wednesday, June 29, 17:00

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Knowing their neighbours - correlation structures in the development of related stem cells

Time lapse video microscopy enables the tracking of stem cell development in bioengineered culture conditions on a single cell level. The resulting cellular genealogies retain information on cellular characteristics, divisional history, and differentiation. Analysing the topology, the dynamical features, and the correlation structure within these pedigree-like genealogies provides information about underlying processes such as migration, cell growth, and differentiation.

For a systematic analysis of cellular genealogies we compare experimental data for different hematopoietic stem cell cultures with a single- cell based, mathematical model of hematopoietic stem cell organisation. In particular we illustrate how ancestral relation between cells influences their current behaviour and decision making. Furthermore we derive emerging contact networks based on spatial positioning of the cells within the time lapse video data. In particular we analyse whether ancestral information is conserved within the community structure of these networks and whether these mutual interactions between cells correlate with secondary read-outs such as cell cycle distribution or the occurrence of cell death events.

The presented framework for a comprehensive description and analysis of cellular development on the level of individual cells and their progeny is an important advancement to support experimental single cell tracking approaches. By combining experimental and modeling data our results demonstrate that the analysis of cellular genealogies and corresponding interaction networks can provide valuable insights into processes of cellular development and differentiation that can not be obtained on a population level.

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Population Dynamics; Wednesday, June 29, 11:00

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Trait diversity promotes to stabilize community dynamics

The dynamics of marine communities are generally modeled through the McKendrick-von Foerster equations describing the biomass flow along the size spectrum. This modeling disregards the distribution of individual growth rate among different species due to the ignorance of species identities. The potential consequence is that predictions from this model might deviate from the reality by either being overestimated or underestimated. Using the novel size- and trait-based species model where the distribution of individual growth rate is explicitly included, the community size spectrum can be represented as an output of the total species size spectra. A significant stabilizing mechanism is recognized for the first time. It is demonstrated that the distributed individual growth rate tends to smoothen out the fluctuations in the resulting community spectrum and thus individual experiences less variable prey and predator fields. Effectively, trophic waves are smoothed out due to different growth rates among the individuals at a given point in the wave. The finding infers that the traditional community modeling is to some extent over-simplified.

Mathematical Models in Eco-epidemiology I; Wednesday, June 29, 08:30

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Cellular automata modeling applied in eco-epidemiology - Simulation of the spatial spread of epidemics with individual contact

The spread of epidemics should be complex phenomena. As the exchange of economics and culture among different countries and areas become much closer in recent years, it has been an ecological issue that influences public health for invading of epidemics to new areas. Generally, there are two types of mathematical models to describe the spread of epidemics, determinate models and network dynamics models. Most of the existing mathematical models of simulating epidemics are built on the basis of ordinary and partial differential equations traditionally. These determinate models have an obviously weakness that the local characteristics of transmission were neglected. In particularly ,they could not simulate the problems properly as following: the process of individual contactthe effects of the individual behaviorthe spatial problems of epidemical transmissionthe effects of mixed pattern of individual.

As a typical representative of network dynamics models, cellular automata model has provided a useful and powerful tool for the research of complex systems. According to the definite of cellular automata model, it can be represented as an array of four elements, A=(Ld,S,N,f),where A is the cellular automata system; Ld is the cellular space; S is set of states; N is the set of neighbors of cell, N=(S1,S2,S3,,Sn),n is the number of neighbors of cell; f is the map of state transfer from Sn to S. Based on cellular automata, a simple theoretical model was presented in this work to simulate the spatial spread of epidemics with individual contact. Population is divided into three classes: infected, immunized and susceptible. Each state of the cell stands for one class of the populations. The epidemic model with the characteristic of vertical transmission and contact was considered particularly. The model, moreover, is extended to include the effect of population vaccination. This kind of effect can reduce the epidemic propagation. The proposed model can serve as a basis for the development of algorithms to simulate the spatial spread of epidemics using real data.

Keywords: Cellular Automata; Epidemics; Spatial Spread; Computer Simulation

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Improving functional coherence of gene signatures by using Gene Ontology terms

Molecular classifiers based on gene expression profiles obtained in DNA microarray expreriments are very extensively studied due to their potential to be apllied in a variety of areas, such as diagnosis, prediction of therapy results etc. The secific property of classification of gene expression profiles is the importance of the feature selection step. This stems from the fact that in DNA microarray experiments very large numbers of values of genes expressions are obtained for relatively small number of samples.

Therefore in recent years significant effort has been paid to development of feature selection algorithms leading to choosing appropriate subsets of genes, called gene signatures, which are then used as arguments for discriminant function in the molecular classifier.

Among methods for gene selection, proposed in the literature, an interesting group are algorithms using the idea of combining the information on expressions of genes with the information on functional coherence of the set of selected genes. Several papers in the literature showed that such an approach can lead to improvement in classification quality.

In our study we propose an algorithm based on the Steiner tree metrics, which was recently proposed as a tool for measuring functional coherence of subsets of genes. The proposed method uses a recursive procedure for signature slimming by removing least coherent genes. The obtained signature has largest measures of functional coherence. We present the use of the proposed algoritm for classification of several publicly available DNA microarra datasets.

This work was financially supported by the Polish Ministry of Science under Grant No. N516 441938 Efficient methods of genome browsing based on the Burrows Wheeler Transform.

Bioinformatics and System Biology; Wednesday, June 29, 17:00

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The Cell Growth and Division Can Destroy Stem Cell Niche in a Reaction-Diffusion Model

A minimal 1D-model of stem cell niche structure regulation along vertical axis of the SAM was developed on the basis of a qualitative hypothesis of interplay between the CLV and WUS genes. Previously it was shown that there is a set of parameters supplying a stationary solution in qualitative correspondence with experimental observations. But the question arises what will be the model dynamics under cell growth and division.

Using DL-system formalism we developed a mathematical model of stem cell niche structure regulation on 1D-array of growing and dividing cells. A number of computer simulations were performed to study the model dynamics.

In the issue the dependence of probability of the stem cell niche destruction on cell cycle duration relative to diffusion time scale was obtained. Increase of the specific cell growth rate results in monotonic increase of system destruction probability and in decrease of its mean lifetime.

Cell divisions account for relevant perturbation in the SAM structure and may result in destruction of it. The stem cell niche survivability depends on relations between model parameters.

Cell and Tissue Biophysics; Thursday, June 30, 11:30

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Hyperosmolarity of the tear film in dry eye syndrom.

The biophysical factors that dictate hyperosmolarity and the observed patterns of tear film break-up in dry eye are poorly understood and are difficult to interrogate experimentally, highlighting the need for mathematical and computational modelling in this field. We have examined a model incorporating the influence of polar lipids overlying an aqueous layer, while tracking the evolution of osmolarity. Our strategic objective was to identify factors which may influence the risk of developing or exacerbating dry eye as well as exploring how such factors differ between evaporative dry eye and aqueous tear deficient dry eye. In particular, we focus on the dynamics of the solute concentration for the duration of a single blink and interblink. Our mathematical model tracks the thickness of the aqueous layer, the concentration of the polar lipid, together with the concentration of the solute. Firstly, we have observed that tear film osmolarity is very sensitive to the evaporation rate, with salt concentrations readily exceeding irritation thresholds when using dry eye parameters. The results also highlight the importance of diffusion in reducing osmolar stress in the vicinity of black lines during the interblink. Nonetheless, in these regions diffusion is not sufficient to prevent potentially damaging osmolarities, especially as the evaporation rate is increased (constituting evaporative dry eye) or the tear volume is decreased (i.e. aqueous deficient dry eye). Simulations also indicate that saccades (rapid eye movements) could have a positive effect on osmolarities in the vicinity of the black lines.

Modeling of immune responses and calcium signaling II; Wednesday, June 29, 14:30

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Stochastic switching in a spatially extended, bistable kinase autoactivation model

In this study we consider a spatially extended kinase autoactivation model with underlying bistability. We assume that kinases may diffuse on the cell membrane (or its restricted domain) and can be in one of three states: unphosphorylated, single or doubly phosphorylated. Catalitic activity of the kinase is regulated by its phosphorylation level; unphosphorylated kinases have the lowest activity, doubly phosphorylated – the highest. The emerging reactions are following:
$K_p \xrightarrow{d} K$, $K_{pp} \xrightarrow{d} K_p$ – dephosphorylation,
$K + K \xrightarrow{c_1} K + K_p$, $K + K_p \xrightarrow{c_1} K + K_{pp}$ – phosphorylation by K,
$K_p + K \xrightarrow{c_2} K_p + K_p$, $K_p + K_p \xrightarrow{c_2} K_p + K_{pp}$ – phosphorylation by K_p,
$K_{pp} + K \xrightarrow{c_3} K_{pp} + K_p$, $K_{pp} + K_p \xrightarrow{c_3} K_{pp} + K_{pp}$ – phosphorylation by K_{pp},
where d and $c_3 > c_2 > c_1$ are dephosphorylation and phosphorylations coefficients. Let us notice that for $c_1 = 0$ the state in which all kinases are unphosphorylated is absorbing.

We consider two limits:

(1) infinite diffusion for which the system can be considered as perfectly mixed and its dynamics is described by the two-dimensional Markov process, and simulated using the Gillespie algorithm,
(2) continuous limit in which evolution of concentrations is given by the system of partial differential equations.

We numerically investigated the activation process in the original model in SpatKin, a program designed to simulate reaction-diffusion processes on a triangular lattice. We observed that for biologically justified values of parameters the behavior of the system cannot be described in any of the two limits even qualitatively. In particular, we found that probability density distributions depend on the diffusion coefficient: bimodal distributions observed in the infinite diffusion limit become unimodal with decreasing diffusivity. We also found that in the bistable case the expected extinction time (i.e. the time in which the absorbing state is reached when $c_1 = 0$) grows with diffusivity and only in the infinite diffusion limit it becomes exponentially proportional to the number of molecules.

We conclude that the original Gillespie algorithm is not appropriate for simulations of spatially extended systems.

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Plants, growth and transport processes I; Tuesday, June 28, 11:00

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A dual porosity model for the uptake of nutrients by root hairs

Root hairs are thought to play an important role in mediating nutrient uptake by plants. In this talk we develop a mathematical model for the nutrient transport and uptake on the scale of a single root. We treat soil as a double porous material, since nutrients are assumed to diffuse both in the soil fluid phase and within the soil particles, while they can also bind to the soil particle surfaces by reversible reactions. Using homogenization techniques we derive a macroscopic model for nutrient diffusion and reaction in the soil which includes the effect of all root hair surfaces. Various numerical simulations of a simplified version of the macroscopic model highlight the importance of root hairs for the uptake of nutrients by the plant in a variety of different soil moisture scenarios.

Multiscale modelling of reaction kinetics in biology; Tuesday, June 28, 14:30

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Alternative formulations of the Chemical Langevin Equation

The Chemical Langevin Equation is a Stochastic Differential Equation that describes the time evolution of molecular counts of reacting chemical species D. Gillespie, Journal of Chemical Physics, 113(1), pp 297-306 (2000)). It stands as a bridge between the deterministic ODE model and the discrete probabilistic chemical Master equation.

Suppose n chemical species react through m reaction channels, and the n x m stoichiometry matrix is denoted by S. Gillespie formulated the CLE with m independent standard Brownian motions. In this talk we describe an alternative formulation of the CLE which in general leads to a SDE with a smaller number of Brownian motions. For example if r is the number of pairs of reversible reactions, then in Gillespie's formulation there would be 2r Brownian motions for the reversible reactions, while in our formulation there would only be r. We illustrate that such a reaction leads to significant computational savings.

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