Abstracts

of section talks

at the

8-th European Conference on Mathematical and Theoretical Biology, and Annual Meeting of the Society for Mathematical Biology, Kraków, June 28 - July 2, 2011

Contents

Bioengineering

Tuesday, June 28, 14:30, *Room*: UA3

Chaired by: **Yannis Kalaidzidis**

14:30–15:00

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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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15:05–15:25

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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.

15:25–15:45

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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.

15:45–16:05

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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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Bioimaging

Tuesday, June 28, 11:00, *Room*: CP1

Chaired by: **Włodzimierz Klonowski**

11:00–11:30

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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.

11:35–11:55

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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.

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11:55–12:15

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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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12:15–12:35

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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).

12:35–12:55

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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.

Bioinformatics and System Biology 1

Wednesday, June 29, 08:30, *Room*: **UA1**

Chaired by: **Jerzy Tiuryn**

08:30–09:00

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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.

09:05–09:25

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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.

References.

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09:25–09:45

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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.

09:45–10:05

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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.

10:05–10:25

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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.

References.

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Bioinformatics and System Biology 2

Wednesday, June 29, 11:00, *Room*: **UA1**

Chaired by: **Jerzy Tiuryn**

11:00–11:30

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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.

11:35–11:55

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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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11:55–12:15

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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.

12:15–12:35

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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.

12:35–12:55

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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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Bioinformatics and System Biology 3

Wednesday, June 29, 14:30, *Room*: **UA1**

Chaired by: **Michael Sadovsky**

14:30–15:00

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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.

15:05–15:25

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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.

15:25–15:45

Mirela Domijan
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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**].

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15:45–16:05

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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.

16:05–16:25

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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.

Bioinformatics and System Biology 4

Wednesday, June 29, 17:00, *Room*: **UA1**

Chaired by: **Michael Sadovsky**

17:00–17:30

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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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17:35–17:55

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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).

17:55–18:15

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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.

18:15–18:35

Ulyana Zubairova

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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.

18:35–18:55

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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.

Cancer 1

Tuesday, June 28, 11:00, *Room*: **AM5**

Chaired by: **Luigi Preziosi**

11:00–11:30

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CIMAB, Italy
Nadya Morozova
CNRS, France

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.

11:35–11:55

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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.

11:55–12:15

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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.

12:15–12:35

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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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12:35–12:55

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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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Cancer 2

Tuesday, June 28, 14:30, *Room*: AM5

Chaired by: **Victor M. Pérez-García**

14:30–15:00

Maciej Swat
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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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15:05–15:25

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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.

15:25–15:45

, 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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15:45–16:05

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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.

16:05–16:25

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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.

Cancer 3

Tuesday, June 28, 17:00, *Room*: **AM5**

Chaired by: **Maciej Swat**

17:00–17:30

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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.

17:35–17:55

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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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17:55–18:15

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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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18:15–18:35

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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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18:35–18:55

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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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Cancer 4

Wednesday, June 29, 08:30, *Room*: AM5

Chaired by: **Andreas Deutsch**

08:30–09:00

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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.

09:05–09:25

Maria Barbarossa
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Christina Kuttler
Technische Universität München, Chair for Mathematical Modelling

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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09:25–09:45

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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.

09:45–10:05

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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.

10:05–10:25

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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.

The designated project has been fulfilled by financial support of the Georgia Rustaveli Foundation (Grant #GNSF/ST08/3-395). Any idea in this publication is possessed by the author and may not represent the opinion of the Foundation itself.

Cancer 5

Wednesday, June 29, 11:00, *Room*: **AM5**

Chaired by: **Andreas Deutsch**

11:00–11:30

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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.

11:35–11:55

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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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11:55–12:15

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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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12:15–12:35

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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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12:35–12:55

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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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Cancer 6

Friday, July 1, 14:30, *Room*: AM8

Chaired by: **Carsten Wiuf**

14:30–15:00

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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.

15:05–15:25

Niall Deakin
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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.

15:25–15:45

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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.

15:45–16:05

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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.

16:05–16:25

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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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Cancer 7

Saturday, July 2, 14:30, *Room*: **AM5**

Chaired by: **Vitaly Volpert**

14:30–15:00

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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.

15:05–15:25

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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.

15:25–15:45

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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**].

References.

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15:45–16:05

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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.

16:05–16:25

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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.

References.

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Cell and Tissue Biophysics 1

Thursday, June 30, 11:30, *Room*: **AM8**

Chaired by: **Zbigniew Peradzyński**

11:30–12:00

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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.

12:05–12:25

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Eamonn Gaffney
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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.

12:25–12:45

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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.

References.

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12:45–13:05

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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.

References.

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13:05–13:25

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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.

Cell and Tissue Biophysics 2 / Neurosciences 3

Friday, July 1, 14:30, *Room*: **AM5**

Chaired by: **Zbigniew J. Grzywna**

14:30–15:00

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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.

15:05–15:25

Adelle Coster
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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.

15:25–15:45

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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.

References.

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15:45–16:05

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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.

References.

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16:05–16:25

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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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Cell and Tissue Biophysics 3

Saturday, July 2, 11:00, *Room*: **AM5**

Chaired by: **Keng-Hwee Chiam**

11:00–11:30

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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.

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11:35–11:55

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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.

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11:55–12:15

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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.

12:15–12:35

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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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12:35–12:55

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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.

Cellular Systems Biology 1

Tuesday, June 28, 14:30, *Room*: **AM7**

Chaired by: **Evgenii Volkov**

14:30–15:00

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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.

References.

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15:05–15:25

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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.

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15:25–15:45

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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.

15:45–16:05

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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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16:05–16:25

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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.

References.

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Cellular Systems Biology 2

Tuesday, June 28, 17:00, *Room*: **AM7**

Chaired by: **Jörg Galle**

17:00–17:30

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Javier Munoz-Garcia
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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.

17:35–17:55

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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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17:55–18:15

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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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18:15–18:35

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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.

18:35–18:55

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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.

Cellular Systems Biology 3

Thursday, June 30, 11:30, *Room*: **AM7**

Chaired by: **Anita T. Layton**

11:30–12:00

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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.

References.

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[3] T.S. Gardner, C.R. Cantor and J.J. Collins, *Construction of a genetic toggle switch in Escherichia coli* Nature **403** 339–342.
[4] M. Elowitz and S. Leibler, *A synthetic oscillatory network of transcriptional regulators* Nature **403** 335–338.
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12:05–12:25

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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.

12:25–12:45

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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**].

References.

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12:45–13:05

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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.

13:05–13:25

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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.

References.

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Cellular Systems Biology 4

Saturday, July 2, 11:00, *Room*: **AM7**

Chaired by: **John Tyson**

11:00–11:30

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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.

11:35–11:55

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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 subcellular 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.

References.

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11:55–12:15

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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.

12:15–12:35

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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]:

$$\begin{aligned}
\tfrac{\mathrm{da_i}}{\mathrm{dt}} &= -a_i + \tfrac{\alpha}{1+C_i^n}; & \tfrac{\mathrm{dA_i}}{\mathrm{dt}} &= -\beta(A_i - a_i)\\
\tfrac{\mathrm{db_i}}{\mathrm{dt}} &= -b_i + \tfrac{\alpha}{1+A_i^n}; & \tfrac{\mathrm{dB_i}}{\mathrm{dt}} &= -\beta(B_i - b_i)\\
\tfrac{\mathrm{dc_i}}{\mathrm{dt}} &= -c_i + \tfrac{\alpha}{1+B_i^n} + \kappa\tfrac{S_i}{1+S_i}; & \tfrac{\mathrm{dC_i}}{\mathrm{dt}} &= -\beta(C_i - c_i)
\end{aligned}$$

$$\tfrac{\mathrm{dS_i}}{\mathrm{dt}} = -k_{s0}S_i + k_{s1}B_i - \eta(S_i - Q\bar{S})$$

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. $\bar{S} = \dfrac{1}{N}\sum\limits_{i=1}^{N} S_i$, 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.

References.

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12:35–12:55

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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.

Developmental Biology 1

Wednesday, June 29, 17:00, *Room*: **AM1**

Chaired by: **Sharon Lubkin**

17:00–17:30

Michael Watson
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Dr Steven McDougall
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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.

17:35–17:55

Michael Kücken

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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.

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17:55–18:15

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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.

18:15–18:35

Heather Hardway
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Tasso Kaper
Boston University
Cynthia Bradham
Boston University

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.

18:35–18:55

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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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Developmental Biology 2

Thursday, June 30, 11:30, *Room*: AM3

Chaired by: **Anotida Madzvamuse**

11:30–12:00

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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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12:05–12:25

Hiroshi Yoshida
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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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12:25–12:45

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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.

12:45–13:05

Sharon Lubkin
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Oswaldo Lozoya
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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.

13:05–13:25

Victoria Mironova

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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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Developmental Biology 3

Friday, July 1, 14:30, *Room*: AM7

Chaired by: **Hiroshi Yoshida**

14:30–15:00

Tilmann Glimm
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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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15:05–15:25

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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?

15:25–15:45

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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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15:45–16:05

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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.

This work was supported by grant No. 08-01-00131 from the Russian Foundation of Basic Research.

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16:05–16:25

Sergey Nikolaev

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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.

Developmental Biology 4

Saturday, July 2, 11:00, *Room*: **AM1**

Chaired by: **Tilmann Glimm**

11:00–11:30

Yoshihiro Morishita
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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.

11:35–11:55

Jörn Starruß
Center for Infromation Services and High Performance computing, TU-Dresden
Fernando Peruani
Max Planck Institute for Physics of Complex Systems, Dresden
Andreas Deutsch

Center for Infromation Services and High Performance computing, TU-Dresden

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

11:55–12:15

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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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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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12:35–12:55

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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.

Ecosystems Dynamics 1

Tuesday, June 28, 11:00, *Room*: UA1

Chaired by: **Helen Kettle**

11:00–11:30

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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.

11:35–12:00

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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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12:00–12:25

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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.

References.

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12:25–12:50

Wonju Jeon
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Sang-Hee Lee
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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.

Ecosystems Dynamics 2

Tuesday, June 28, 14:30, *Room*: AM1

Chaired by: **Johannes Müller**

14:30–15:00

Helen Kettle
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Ruairi Donnelly
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Grietje Holtrop
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Glenn Marion
Biomathematics and Statistics Scotland

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.

15:05–15:25

Jonathan Greenman
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Virginia Pasour
US Army Research Office

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.

15:25–15:45

Toshiyuki Namba

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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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15:45–16:05

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Cornell - EEB

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.'

16:05–16:25

Joe Yuichiro Wakano
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Kota Ikeda
Meiji University
Takeshi Miki
National Taiwan University
Masayasu Mimura
Meiji University

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.

Ecosystems Dynamics 3

Tuesday, June 28, 17:00, *Room*: **AM1**

Chaired by: **Jacek Miękisz**

17:00–17:30

Norio Yamamura
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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/rihn e/project/D-04.html) in Research Institute for Humanity and Nature (http//www.chikyu.ac.jp/index e.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.

17:35–17:55

M. Vela-Pérez
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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.

References.

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[2] M. Vela-Pérez, M. A. Fontelos and J. J. L. Velázquez,*Ant foraging and minimal paths in simple graphs*, Submitted for publication

17:55–18:15

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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.

18:15–18:35

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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.

References.

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18:35–18:55

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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.

Epidemics 1

Tuesday, June 28, 11:00, *Room*: AM6

Chaired by: **Hiroshi Nishiura**

11:00–11:30

Andrea Pugliese
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Gianpaolo Scalia Tomba
Dept. of Mathematics, University of Roma Tor Vergata
Antonella Lunelli
Dept. of Mathematics, University of Trento, Italy

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.

11:35–11:55

Ellen Brooks-Pollock

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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.

References.

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11:55–12:15

Eleanor Harrison
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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.

12:15–12:35

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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.

References.

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12:35–12:55

Mateusz M. Pluciński
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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.

Epidemics 2

Tuesday, June 28, 14:30, *Room*: AM6

Chaired by: **Andrea Pugliese**

14:30–15:00

Jesus R. Artalejo
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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.

15:05–15:25

M. J. Lopez-Herrero
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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.

15:25–15:45

Rosalyn Porter
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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.

15:45–16:05

Mick Roberts
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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.

16:05–16:25

Jamie Prentice
SAC
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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.

Epidemics 3

Tuesday, June 28, 17:00, *Room*: **AM6**

Chaired by: **Suzanne Touzeau**

17:00–17:30

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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

$$\hat{\rho} \pm z_\alpha \sqrt{\frac{\hat{\rho}^3(1-\hat{\rho}) + v^2\hat{\rho}(1-\hat{\rho})^2 \ln^2(1-\hat{\rho}/(1-q))}{n\left[\hat{\rho} + (1-\hat{\rho})\ln(1-\hat{\rho}/(1-q))\right]}} \tag{1}$$

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,

17:35–17:55

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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.

17:55–18:15

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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.

18:15–18:35

R.I. Hickson

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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.

18:35–18:55

O.A. Melnichenko
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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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Epidemics 4

Wednesday, June 29, 08:30, *Room*: **AM6**

Chaired by: **Mick Roberts**

08:30–09:00

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Bryan T. Grenfell
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John W. McCauley
MRC National Institute for Medical Research
Ian H. Brown
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University of Cambridge

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.

09:05–09:25

Ross Davidson
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Leo Zijerveld
SAC
Glenn Marion
Biomathematics and Statistics Scotland
Mike Hutchings
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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.

09:25–09:45

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Karl P. Hadeler
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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].

References.

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09:45–10:05

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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.

This work is supported by Russian Foundation for Basic Research: RFBR 09-01-00098a. Data analysis was provided via financial support of UNDP: UNDP/212/2007.

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10:05–10:25

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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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Epidemics 5

Wednesday, June 29, 11:00, *Room*: **AM6**

Chaired by: **Ludek Berec**

11:00–11:30

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Charlotte Kloft
Martin-Luther Universität Halle-Wittenberg, Germany
Christof Schütte
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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].

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11:35–11:55

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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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11:55–12:15

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Dr. Kieran Sharkey
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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.

12:15–12:35

Asher Uziel
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Lewi Stone
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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.

12:35–12:55

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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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Epidemics 6 / Population Dynamics 7

Wednesday, June 29, 17:00, *Room*: **AM2**

Chaired by: **Wilson C. Ferreira Jr.**

17:00–17:30

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Caroline Bidot
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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.

17:35–17:55

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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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17:55–18:15

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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.

18:15–18:35

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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.

18:35–18:55

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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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Epidemics 7

Thursday, June 30, 11:30, *Room*: AM6

Chaired by: **Geoffry Mercer**

11:30–12:00

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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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12:05–12:25

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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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12:25–12:45

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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.

12:45–13:05

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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.

References.

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13:05–13:25

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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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Epidemics 8

Saturday, July 2, 08:30, *Room*: AM2

Chaired by: **Roberto Saenz**

08:30–08:50

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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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08:55–09:15

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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.

09:15–09:35

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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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09:35–09:55

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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.

09:55–10:15

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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.

10:15–10:35

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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.

Evolutionary Ecology 1

Wednesday, June 29, 08:30, *Room*: **AM1**

Chaired by: **Kalle Parvinen**

08:30–09:00

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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**].

References.

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09:05–09:25

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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).

References.

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09:25–09:45

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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.

References.

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09:45–10:05

Akiko Satake
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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.

10:05–10:25

Tanya Kostova Vassilevska
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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.

Evolutionary Ecology 2

Wednesday, June 29, 11:00, *Room*: AM1

Chaired by: **Roger Bowers**

11:00–11:30

Stephen Cornell
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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.

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11:35–11:55

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Tero Klemola
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Kalle Parvinen
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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.

11:55–12:15

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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.

12:15–12:35

Ilmari Karonen
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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.

12:35–12:55

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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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Evolutionary Ecology 3

Wednesday, June 29, 14:30, *Room*: AM1

Chaired by: **Eva Kisdi**

14:30–15:00

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Yutaka Kobayashi
Department of Biological Science, University of Tokyo

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.

15:05–15:25

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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.

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15:25–15:45

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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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15:45–16:05

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Stephen Cornell
University of Leeds

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.

16:05–16:25

Jaakko Toivonen
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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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Evolutionary Ecology 4

Thursday, June 30, 11:30, *Room*: **AM1**

Chaired by: **Atsushi Yamauchi**

11:30–12:00

Kalle Parvinen
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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.

References.

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12:05–12:25

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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

12:25–12:45

Tuomas Nurmi
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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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12:45–13:05

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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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[2] M. Gyllenberg, E. Kisdi, M. Utz, *Variability within families and the evolution of body condition dependent dispersal* Journal of Biological Dynamics (in press).

[3] M. Gyllenberg, E. Kisdi, M. Utz, *Body condition dependent dispersal in a heterogeneous environment* (submitted).

13:05–13:25

Chelsea Liddell
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Dorothy Wallace
Dartmouth College

Nicci Owusu-Brackett
Dartmouth College
Kristen Klepac
Dartmouth College

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.

Evolutionary Ecology 5

Friday, July 1, 14:30, *Room*: **AM1**

Chaired by: **Tanya Kostova Vassilevska**

14:30–15:00

Bernt Wennberg
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and
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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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15:05–15:25

Dorothy Wallace
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Erin Dauson
Dartmouth College
Catherine Pinion
Dartmouth College

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.

15:25–15:45

Wojciech Borkowski
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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/`

References.

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15:45–16:05

Judith Miller
Georgetown University
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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.

16:05–16:25

Jacob Scott
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David Basanta
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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.

Genetics and Genomics 1

Wednesday, June 29, 08:30, *Room*: **AM7**

Chaired by: **Stanisław Cebrat**

08:30–08:50

Veit Schwämmle
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Ole Nørregaard Jensen
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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.

References.

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08:55–09:15

Richard Kollár
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Katarína Boová
Department of Applied Mathematics and Statistics, Comenius University, Bratislava, Slovakia

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.

09:15–09:35

Paweł Błażej
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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.

09:35–09:55

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Richard Kollár
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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.

09:55–10:15

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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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10:15–10:35

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Rafał Pokrzywa
Institute of Informatics, Silesian University of Technology
Andrzej Polaski
Institute of Informatics, Silesian University of Technology

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.

Immunology 1

Wednesday, June 29, 14:30, *Room*: AM6

Chaired by: **Urszula Foryś**

14:30–15:00

Julia Kzhyshkowska
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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

Julia Kzhyshkowska, Anna Marciniak-Czochra, Alexei Gratchev University of Heidelberg, Germany.

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.

15:05–15:25

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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.

References.

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15:25–15:45

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.

15:45–16:05

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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.

References.

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16:05–16:25

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Tetsuko Tada
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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.

Immunology 2

Wednesday, June 29, 17:00, *Room*: AM6

Chaired by: **Julia Kzhyshkowska**

17:00–17:30

Jessica Conway
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Dr. Daniel Coombs
University of British Columbia

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.

17:35–17:55

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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.

17:55–18:15

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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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18:15–18:35

Koichi Saeki
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Yoh Iwasa
Kyushu University

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.

18:35–18:55

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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.

References.

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Immunology 3 / Medical Physiology 2

Saturday, July 2, 08:30, *Room*: **CP2**

Chaired by: **John Ward**

08:30–09:00

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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.

References.

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09:05–09:25

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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.

09:25–09:45

Galina Gramotnev
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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.

References.

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09:45–10:05

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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 .

References.

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Medical Physiology 1

Tuesday, June 28, 11:00, *Room*: UA3

Chaired by: **Jerry Batzel**

11:00–11:30

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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.

11:35–12:00

Martina Gallenberger*
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Christina Kuttler
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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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12:00–12:25

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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.

12:25–12:50

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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.

Neurosciences 1

Wednesday, June 29, 08:30, *Room*: **UA2**

Chaired by: **Petr Lansky**

08:30–09:00

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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.

09:05–09:25

Daniel Forger
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Casey O. Diekman
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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.

09:25–09:45

Jan Pyrzowski
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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.

References.

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09:45–10:05

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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.

References.

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10:05–10:25

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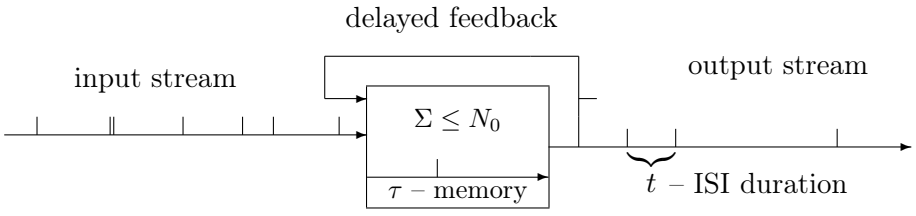
Delayed feedback results in non-markovian statistics of neuronal firing

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.

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Neurosciences 2

Thursday, June 30, 11:30, *Room*: AM5

Chaired by: **Petr Lansky**

11:30–12:00

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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

$$\delta h_i(t) = \eta_h \left\{ \langle S_i(t+1,r) \rangle_r - \langle \tanh[H_i(t,r))] \rangle_r \right\} \quad (1)$$

$$\delta J_{ij} = \eta_J \left\{ \langle S_i(t+1,r) S_j(t,r) \rangle_{rt} - \langle \tanh[H_i(t,r)] S_j(t,r) \rangle_{rt} \right\} \quad (2)$$

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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12:05–12:25

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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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12:25–12:45

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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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12:45–13:05

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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.

13:05–13:25

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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

Population Dynamics 1

Tuesday, June 28, 11:00, *Room*: AM2

Chaired by: **Mirosław Lachowicz**

11:00–11:30

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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.

11:35–11:55

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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.

11:55–12:15

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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.

12:15–12:35

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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.

Population Dynamics 2

Tuesday, June 28, 14:30, *Room*: **AM2**

Chaired by: **Carlos A. Braumann**

14:30–15:00

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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.

References.

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15:05–15:25

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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.

15:25–15:45

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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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15:45–16:05

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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.

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16:05–16:25

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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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Population Dynamics 3

Tuesday, June 28, 17:00, *Room*: AM2

Chaired by: **Marek Kimmel**

17:00–17:30

Peter Jagers
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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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17:35–17:55

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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.

17:55–18:15

Iwona Mroz
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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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18:15–18:35

Andrew Savory
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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.

18:35–18:55

Wayne M. Getz
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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 4

Wednesday, June 29, 08:30, *Room*: AM2

Chaired by: **Peter Jagers**

08:30–09:00

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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.

09:05–09:25

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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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09:25–09:45

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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.

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09:45–10:05

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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.

10:05–10:25

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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.

Population Dynamics 5

Wednesday, June 29, 11:00, *Room*: AM2

Chaired by: **Andreas Bohn**

11:00–11:30

Nicholas F. Britton
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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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11:35–11:55

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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.

11:55–12:15

Urszula Skwara
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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

$$(1)\begin{cases} dX(t) = ((a_1 + b_1 Y(t) - c_1 X(t))\,dt + \rho_{11}\,dW_1(t) + \rho_{12}\,dW_2(t))\,X(t) \\ dY(t) = ((a_2 + b_2 X(t) - c_2 Y(t))\,dt + \rho_{21}\,dW_1(t) + \rho_{22}\,dW_2(t))\,Y(t), \end{cases}$$

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 $b_1 b_2 < c_1 c_2$. 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.

References.

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12:15–12:35

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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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12:35–12:55

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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.

Population Dynamics 6

Wednesday, June 29, 14:30, *Room*: **AM2**

Chaired by: **N. F. Britton**

14:30–15:00

Luis Fernando Chaves
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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.

15:05–15:25

Christian Winkel
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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.

15:25–15:45

Nick Jagiella
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Benedikt Müller[1], **Irene Vignon-Clementel**[2], **Margareta Müller**[1], **Dirk Drasdo**[2]
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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.

15:45–16:05

Jeong-Mi Yoon
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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.

16:05–16:25

Jeremy Thibodeaux
Loyola University New Orleans
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Timothy P. Schlittenhardt
University of Central Oklahoma

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.

Population Dynamics 8

Thursday, June 30, 11:30, *Room*: AM2

Chaired by: **Eva Kisdi**

11:30–12:00

Peter Pang
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H. L. Li
Southeast University, China
M. X. Wang
Harbin Institute of Technology, China

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).

12:05–12:25

Fabio Chalub
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Max Souza
Universidade Federal Fluminense

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.

12:25–12:45

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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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12:45–13:05

Hiroshi Toyoizumi
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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.

References.

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13:05–13:25

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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.

Population Dynamics 9

Friday, July 1, 14:30, *Room*: AM6

Chaired by: **Peter Pang**

14:30–15:00

Christina Cobbold
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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.

15:05–15:25

Erwan Hingant
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Pascaline Fontes
Centre CECEMA, Montpellier, France.
Teresa Alvarez-Martinez
Institut Fédératif de Biologie de Montpellier, Montpellier, France.
Jacques-Damien Arnaud
Institut Fédératif de Biologie de Montpellier, Montpellier, France.
Jean-Pierre Liautard
Centre de Recherche sur les Pathogènes et Biologie pour la Santé, Montpellier, France

Laurent Pujo-Menjouet
Institut Camille Jordan, Lyon, France.

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.

References.

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15:25–15:45

Jennifer Reynolds
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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.

15:45–16:05

Xuxin Yang
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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 10

Saturday, July 2, 11:00, *Room*: AM2

Chaired by: **Christina Cobbold**

11:00–11:30

Max O. Souza
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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.

References.

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11:35–11:55

Atiyo Ghosh
Leiden University
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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.

11:55–12:15

Ryan Chisholm
Smithsonian Tropical Research Institute
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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.

12:15–12:35

Wes Maciejewski
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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.

References.

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12:35–12:55

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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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Population Dynamics 11

Saturday, July 2, 14:30, *Room*: **AM2**

Chaired by: **Dorothy Wallace**

14:30–15:00

Isaias Chairez Hernández[1], **J. Natividad Gurrola Reyes**[1] **and Cipriano García Gutiérrez**[2]
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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.

15:05–15:25

Joanna Jaroszewska
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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.

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15:25–15:45

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Juan Cordovez
Universidad de los Andes
Esteban Payan
Panthera Foundation

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.

15:45–16:05

Yo-Hey Otake
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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].

References.

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Population Genetics 1

Wednesday, June 29, 14:30, *Room*: **AM3**

Chaired by: **Adam Bobrowski**

14:30–15:00

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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.

Acknowledgements: Research supported by the Ministerio de Ciencia e Innovación, the Junta de Extremadura and the FEDER, grants MTM2009-13248 and GR10118.

15:05–15:25

Thiemo Hustedt
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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.

References.

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15:25–15:45

Satoshi Takahashi

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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.

15:45–16:05

Meike Wittmann
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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.

16:05–16:25

Małgorzata Pułka
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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.

Population Genetics 2

Wednesday, June 29, 17:00, *Room*: AM3

Chaired by: **Reinhard Bürger**

17:00–17:30

Sivan Leviyang
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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.

17:35–17:55

Wojciech Bartoszek[(1)] **and Małgorzata Pułka**[(2)]
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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 $\mathbf{Q} \in \mathfrak{Q}$.

17:55–18:15

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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.

References.

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18:15–18:35

Sandra Kluth
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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.

18:35–18:55

Su-Chan Park
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Kavita Jain
Jawaharlal Nehru Centre for Advanced Scientific Research, India
Joachim Krug
University of Cologne, Germany

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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Population Genetics 3

Friday, July 1, 14:30, *Room*: AM3

Chaired by: **Manuel Mota**

14:30–15:00

Reinhard Bürger
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Ada Akerman
University of Vienna

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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15:05–15:25

Ada Akerman
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Reinhard Bürger
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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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15:25–15:45

Marina Rafajlovic
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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.

References.

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15:45–16:05

Ute von Wangenheim
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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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16:05–16:25

Robert Puddicombe

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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.

Regulatory Networks 1

Tuesday, June 28, 17:00, *Room*: **AM4**

Chaired by: **Jarosław Śmieja**

17:00–17:30

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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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17:35–17:55

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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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17:55–18:15

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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.

18:15–18:35

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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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18:35–18:55

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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.

References.

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Regulatory Networks 2

Friday, July 1, 14:30, *Room*: **AM2**

Chaired by: **John Tyson**

14:30–15:00

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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.

15:05–15:25

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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.

References.

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15:25–15:45

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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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15:45–16:05

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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.

References.

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16:05–16:25

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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.

Regulatory Networks 3

Saturday, July 2, 11:00, *Room*: **AM6**

Chaired by: **Daniele Muraro**

11:00–11:30

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Richard Immink
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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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11:35–11:55

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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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11:55–12:15

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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.

12:15–12:35

Ben Fitzpatrick
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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.

12:35–12:55

Anna Ochab-Marcinek
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Marcin Tabaka
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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

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