Abstracts of talks

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Contents

MINI-SYMPOSIUM 1

Vector-borne diseases

Tuesday, June 28, 14:30, *Room*: UA1

Organizer: **Ben Adams**

14:30–14:55

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Evolutionary determinants of antigenic variation in malaria

Many pathogenic bacteria, fungi, and protozoa achieve chronic infection through an immune evasion strategy known as antigenic variation. In the human malaria parasite Plasmodium falciparum, this involves transcriptional switching among members of the var gene family, causing parasites with different antigenic and phenotypic characteristics to appear at different times within a population. Here we use a genome-wide approach to explore this process in vitro within a set of cloned parasite populations. Our analyses reveal a non-random, highly structured switch pathway where an initially dominant transcript switches via a set of switch-intermediates either to a new dominant transcript, or back to the original. We show that this specific pathway can arise through an evolutionary conflict in which the pathogen has to optimise between safeguarding its limited antigenic repertoire and remaining capable of establishing infections in non-naïve individuals. Our results thus demonstrate a crucial role for structured switching during the early phases of infections and provide a unifying theory of antigenic variation in P. falciparum malaria as a balanced process of parasite-intrinsic switching and immune-mediated selection.

14:55–15:20

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Optimizing pathogen fitness: the role of the antigenic archive for African Trypanosomes

Antigenic variation processes play a central role in vector-borne infectious diseases and are likely to respond to host immune mechanisms and epidemiological characteristics. A key priority in disease control and understanding pathogen evolution is the investigation of mechanisms by which pathogens regulate antigenic diversity and how these affect larger-scale population processes. While the within-host population ecology of antigen switching pathogens is not a new topic, increasing access to genetic data provides us with a rapidly widening opportunity to understand the evolutionary ecology of antigenic variation. In this work, we study the interactions between the structure and function of the antigenic archive of the African Trypanosome, the parasite responsible for sleeping sickness. We show that the genetic architecture of the archive has important consequences for pathogen fitness within and between hosts. The optimality criteria we find for the antigenic archive arise as a result of typical trade-offs between transmission and virulence. Our analysis suggests that different traits of the host population can select for different aspects of the antigenic archive, reinforcing once more the importance of host heterogeneity in the evolutionary dynamics of parasites.

15:20–15:45

Daniel Coffield Jr.
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A Model for Chagas Disease with Vector Consumption and Transplacental Transmission

Chagas disease is caused by the parasite Trypanosoma cruzi, which is spread primarily by domestic vectors in the reduviid family, and affects humans and domestic mammals throughout rural areas in Central and South America. An epidemiological model for Chagas disease in a hypothetical village setting will be presented. The model consists of a nonlinear coupled system of four differential equations, one of which has a delay, that describes the rate of change of the total number of the vectors, infected vectors, infected humans, and infected domestic mammals. In addition to birth, death, and parasite transmission due to vectors, the model

takes into account insecticide spraying, transplacental transmission, and consumption of the vector by domestic mammals. Steady state analysis of the model with constant coefficients provides a stability condition on the model parameters. In representative examples, the theory and computer simulations reveal that the endemic equilibrium is locally asymptotically stable.

15:45–16:10

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

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

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

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

References.

[1] S. Bowong, Y. Dumont, and J.J. Tewa, A patchy model for the Chikungunya Disease in Réunion Island, submitted.
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[3] Y. Dumont and F. Chiroleu, Vector Control for the Chikungunya Disease, Mathematical Bioscience and Engineering, **7**(2) (2010), 315-348.
[4] Y. Dumont and J.M. Tchuenche, Mathematical studies on the Sterile Insect Technique for the Chikungunya Disease and *Aedes albopictus*, submitted.
[5] Y. Dumont, and C. Dufourd, Spatio-temporal modeling of *Aedes albopictus* dispersal in Réunion Island. Application to the release of Sterile Insects, submitted to ECMTB 2011.
[6] E. Martin, S. Moutailler, Y. Madec, and A.B. Failloux, Differential responses of the mosquito Aedes albopictus from the Indian Ocean region to two chikungunya isolates, BMC Ecol. 10:8 (2010).

16:10–16:35

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

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

MINI-SYMPOSIUM 2

Modelling dengue fever epidemiology

Saturday, July 2, 08:30, *Room*: **AM8**

Organizers: **Maíra Aguiar, Bob Kooi, Nico Stollenwerk, Ezio Venturino**

08:30–09:10

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

It is estimated that every year, there are $70 - 500$ million dengue infections, 36 million cases of dengue fever (DF) and 2.1 million cases of dengue hemorragic fever (DHF), with more than 20.000 deaths per year [**1, 2**]. In many countries in Asia and South America DF and DHF has become a substantial public health concern leading to serious social-economic costs. Mathematical models describing the transmission of dengue viruses has focussed on ADE effect and temporary cross immunity trying to explain the irregular behavior of dengue epidemics by analyzing the available data. However, no systematic investigation of the possible dynamical structures has been performed so far. Our study focuses on a seasonally forced (non-autonomous) two-strain model with temporary cross immunity and possible secondary infection, motivated by dengue fever epidemiology. We extend the previous studied non-seasonal (autonomous) model[**3, 4, 5**]. by adding seasonal forcing

and low import rate of infected individuals, which is realistic in the dynamics of dengue fever epidemics. A comparative study between three different scenarios (non-seasonal, low seasonal and high seasonal with a low import of infected individuals) is processed and the results are shown and discussed. The extended models show complex dynamics and qualitatively a very good result when comparing empirical DHF and simulation. We discuss the role of the seasonal force and import of infected individuals in such systems, the biological relevance and the implications of the new results in the analysis of the available dengue data [**6**].

References.

[1] Pediatric Dengue Vaccine Initiative. *Global Burden of Dengue.* (`http://www.pdvi.org/about_dengue/GBD.asp`).

[2] Word Health Organization. (2009). *Dengue and Dengue Hemorrhagic Fever.* (World Health Org., Geneva, Fact Sheet 117).

[3] M. Aguiar, N. Stollenwerk, *A new chaotic attractor in a basic multi-strain epidemiological model with temporary cross-immunity.* (2007) *arXiv:0704.3174v1 [nlin.CD].*

[4] M. Aguiar, B. W. Kooi and N. Stollenwerk, *Epidemiology of Dengue Fever: A Model with Temporary Cross-Immunity and Possible Secondary Infection Shows Bifurcations and Chaotic Behaviour in Wide Parameter Regions.* Math. Model. Nat. Phenom. **4** (2008) 48–70.

[5] M. Aguiar, N. Stollenwerk and B. W. Kooi, *Torus bifurcations, isolas and chaotic attractors in a simple dengue model with ADE and temporary cross immunity.* International Journal of Computer Mathematics **86** (2009) 1867–77.

[6] M. Aguiar, S. Ballesteros, B. Cazelles, B. W. Kooi, and N. Stollenwerk, *Seasonal two strain dengue model: complex dynamics and its implications for data analysis.* Manuscript in preparation.

09:10–09:30

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Why dengue and yellow fever coexist in some areas of the world and not in others?

Urban yellow fever and dengue coexist in Africa but not in Asia and South America. In this paper we examine four hypotheses (and combination of them) advanced to explain the absence of yellow fever in urban areas of Asia and South America. In addition, we examine one further hypothesis that would explain the coexistence of the infections in Africa and at the same time explaining why they do not coexist in Asia and South America. The hypotheses advanced to explain the nonexistence of yellow fever in Asia and South America are: the risk of importation

to Asia of a yellow fever viraemic person is very low; the Asian Aedes aegypti is relatively incompetent to transmit yellow fever; there would exists a competition between dengue and yellow fever viruses within the mosquitoes, as suggested by some in vitru studies, in which the dengue virus always wins; there is an important cross-immunity between yellow fever and other flaviviroses, dengue in particular, such that a person recovered from a bout of dengue would have his/her susceptibility to yellow fever diminished. This latter hypothesis is called hereafter the "Asian hypothesis". Finally, we hypothesize that the coexistence of the infections in Africa is due to the virtual absence of the mosquito Aedes albopicuts, which competes with Aedes aegypti, in Africa. We call this latter hypothesis the "African hypothesis". We construct a model of transmission that allows all the above hypotheses to be tested. We conclude that the Asian and the African hypotheses can explain the observed phenomena. The other hypotheses do not explain the observed phenomena.

09:30–09:50

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Simulation of a dengue vaccine

Dengue is a vector-borne disease. It is nowadays endemic in more than one hundred countries, predominantly in tropical and subtropical areas. Up to the moment, the effectiveness of the programs for vector control is low and, unfortunately, there is no specific effective treatment for dengue. For recent mathematical investigations on the subject, we refer to **[1, 2]** and references therein.

There are no commercially available dengue clinical cures or vaccine, but efforts are underway to develop one **[3]**. So far, the difficulties in elaborating a vaccine stemmed from the fact that the vaccine must protect simultaneously against the four serotypes of dengue. This is a difficult but crucial constraint, because protection against only one or two dengue viruses could actually increase the risk of Dengue Haemorrhagic Fever. The population effect of a vaccination programme may be thought of as the collective impact of individual vaccination on the transmission of infection in that population. While direct individual protection is the major focus of mass vaccination programmes, population effects also contribute indirectly to individual protection through herd immunity, providing protection for unprotected individuals.

We present a SVIR-ASI epidemiological model for the human and mosquito populations, respectively. It is considered an imperfect vaccine, where a proportion

of population is vaccinated. Some simulations, with different levels of vaccine efficacy, are studied. It is shown that the efficacy of the vaccine has a preponderant role in the reduction of the spread of the disease.

References.

[1] H. S. Rodrigues, M. T. T. Monteiro and D. F. M. Torres, Dynamics of dengue epidemics when using optimal control, Math. Comput. Modelling **52** (2010), no. 9-10, 1667–1673.
[2] H. S. Rodrigues, M. T. T. Monteiro, D. F. M. Torres and A. Zinober, Dengue disease, basic reproduction number and control, Int. J. Comput. Math. (2011), in press.
[3] WHO, Immuniological correlates of protection induced by dengue vaccines, Vaccine **25** (2007), 4130–4139.

09:50–10:10

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Determinants of dengue virus phylodynamics.

Dengue fever (DF) and the more severe dengue haemorrhagic fever (DHF) are mosquito borne viral infections which have seen a major increase in terms of global distribution and total case numbers over the last few decades. There are currently four antigenically distinct and potentially co-circulating dengue virus (DENV) serotypes and each one shows substantial genetic diversity, organised into phylogenetically distinct lineages (genotypes). While there is some evidence for positive selection, the molecular evolution of DENV is supposed to be mostly dominated by purifying selection due to the constraints imposed by its two-host life-cycle. Results from our previous work demonstrated that although small differences in viral fitness can explain the rapid expansion and fixation of novel genotypes, their fate is ultimately determined by the epidemiological landscape in which they arise. Using a stochastic, spatially explicit model we revisit previous conclusions and address the impact of host and vector population structure on DENV molecular evolution and disease epidemiology.

10:10–10:30

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Maira Aguiar
Sebastien Ballesteros
Bob W. Kooi

On the origin of the irregularity of DHF epidemics

By using an estimated parameter set for the minimalistic multi-strain dengue model we analyse the stochastic version of the model investigating the interplay between stochasticity, seasonality and import.

MINI-SYMPOSIUM 3

Recent developments in the study of Lotka-Volterra and Kolmogorov systems

Saturday, July 2, 14:30, *Room*: **AM7**

Organizer: **Stephen Baigent**

14:30–15:10

Janusz Mierczyński
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Permanence for Kolmogorov competitive systems of PDEs

This talk is about recent results on permanence for Kolmogorov reaction–diffusion systems of partial differential equations (PDE)

$$\frac{\partial u_i}{\partial t} = \Delta u_i + f_i(t, x, u_1, \dots, u_N)u_i, \qquad 1 \le i \le N,\ t \in [0, \infty),\ x \in \Omega.$$

Here $u_i(t, x)$ measures the population density of the i-th species at time t and spatial location x, and Ω is a bounded habitat. The system is endowed with appropriate boundary conditions.

Systems are assumed to be *competitive*, which means that $\partial f_i/\partial u_j \le 0$ for $1 \le i, j \le N$, $i \ne j$ (usually much more will be assumed).

Permanence (sometimes called *uniform persistence*) means that any positive solution of the system becomes bounded away from zero, where the ultimate bound is independent of the solution.

We will give a survey of results on permanence for Kolmogorov competitive systems of PDEs, in particular with general dependence on time. Especially, connections with invasibility will be addressed.

15:10–15:30

Zhanyuan Hou
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Stephen Baigent

Demartment of Mathematics, UCL

Heteroclinic limit cycles in Lotka-Volterra systems

In this talk, we are concerned with the global, rather than local, attraction (repulsion) of a heteroclinic limit cycle in competitive Lotka-Volterra systems. Conditions will be explored for omiga (alpha) limit sets to be a single heteroclinic cycle for almost all interior initial points in the nonnegative cone.

15:30–15:50

Yasuhiro Takeuchi
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Global stability of Lotka-Volterra equations

This presentation will review some conditions of global stability of Lotka-Volterra equations and discuss on the relationship between the stability and the structure of the systems.

Y. Takeuchi; *Global Dynamical Properties of Lotka-Volterra Systems*, World Scientific 1996.

15:50–16:10

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

In this talk we consider a nonautonomous systems of PDEs

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

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

16:10–16:30

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

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

MINI-SYMPOSIUM 4

Connecting microscale and macroscale models of cellular migration

Tuesday, June 28, 17:00, *Room*: **CP1**

Organizers: **Ruth Baker, Matthew Simpson**

17:00–17:25

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Dr Matthew Simpson
School of Mathematical Sciences, Queensland University of Technology

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

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

17:25–17:50

Matthew Simpson
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Models of collective cell spreading with variable cell aspect ratio: A motivation for degenerate diffusion models

Continuum diffusion models are often used to represent the collective motion of cell populations. Most previous studies have simply used linear diffusion to represent collective cell spreading, while others found that degenerate nonlinear diffusion provides a better match to experimental cell density profiles. In the cell modeling literature there is no guidance available with regard to which approach is more appropriate for representing the spreading of cell populations. Furthermore, there is no knowledge of particular experimental measurements that can be made to distinguish between situations where these two models are appropriate. Here we provide a link between individual-based and continuum models using a multi-scale approach in which we analyze the collective motion of a population of interacting agents in a generalized lattice-based exclusion process. For round agents that occupy a single lattice site, we find that the relevant continuum description of the system is a linear diffusion equation, whereas for elongated rod-shaped agents that occupy L adjacent lattice sites we find that the relevant continuum description is connected to the porous media equation (pme). The exponent in the nonlinear diffusivity function is related to the aspect ratio of the agents. Our work provides a physical connection between modeling collective cell spreading and the use of either the linear diffusion equation or the pme to represent cell density profiles. Results suggest that when using continuum models to represent cell population spreading, we should take care to account for variations in the cell aspect ratio because different aspect ratios lead to different continuum models.

17:50–18:15

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Discrete and continuum modelling of growth and signalling in biological tissue

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

References.

[1] Fozard JA, Byrne HM, Jensen OE, King JR, *Continuum approximations of individual-based models for epithelial monolayers.* Math Med Biol. (2010) **27**(1) 39–74.

18:15–18:40

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Leonard Sander
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Fronts of cells invading a wound: from discrete stochastic approach to continuum description

We present a stochastic model that describes fronts of cells invading a wound. In the model, cells can migrate, proliferate, and experience cell-cell adhesion. We find several qualitatively different regimes of front motion and analyze the transitions between them. Above a critical value of adhesion and for small proliferation, large isolated clusters are formed ahead of the front. This is mapped onto the well-known ferromagnetic phase transition in the Ising model. The results are compared with experiments, and possible directions of future work are proposed. We also focus on a continuum description of this phenomenon by means of a generalized Cahn-Hilliard equation (GCH) with a proliferation term. As in the discrete model, there are two interesting regimes. For subcritical adhesion, there are propagating "pulled" fronts, similarly to those of Fisher-Kolmogorov equation. The problem of front velocity selection is examined, and our theoretical predictions are in a good agreement with

a numerical solution of the GCH equation. For supercritical adhesion, there is a nontrivial transient behavior, where density profile exhibits a secondary peak. The results of continuum and discrete models are in a good agreement with each other for the different regimes we analyzed.

18:40–19:05

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From particles to PDEs: continuum approximations to models of cellular migration

Cell migration is a fundamental process in biology. Examples range from the development of multi-cellular organisms, through to the emergence of complex spatial patterns in bacterial populations. Mathematical models of cell migration can help increase our understanding of the underlying biology. However, the models that capture the molecular scale interactions are typically rather complex and can be difficult to analyze. Here, we explore this problem by developing a model based on Langevin dynamics, whereby short-range intercellular interactions are represented using an appropriate potential function. Following Newman and Grima (2004), we obtain a mean field approximation to our model, this being an integro-partial differential equation. By exploiting the biologically plausible limit of intercellular interactions occurring on infinitesimally small length scales, we derive a system of partial differential equations that can approximate the mean-field behaviour of the original Langevin model and and is amenable to analysis. We will show how the molecular scale details (represented by our choice of interaction potential) are reflected in the PDE approximation. An analysis of the resulting patterns will be given. Relevant applications, such as cell-sorting and chemotaxis, will also be discussed.

MINI-SYMPOSIUM 5

The emergence of resistance in cancer using mathematical modelling

Saturday, July 2, 08:30, *Room*: **AM7**

Organizer: **David Basanta**

08:30–09:10

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Integrated Mathematical Oncology, Moffitt Cancer Centre

Regulating drug resistance: Evolution and the double-bind

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

09:10–09:30

Edward H. Flach
Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, FL, USA
Inna Fedorenko

Molecular Oncology, Moffitt Cancer Center, Tampa, FL, USA
Kim Paraiso
Molecular Oncology, Moffitt Cancer Center, Tampa, FL, USA
Keiran S. M. Smalley
Molecular Oncology, Moffitt Cancer Center, Tampa, FL, USA
Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA
Alexander R. M. Anderson
Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, FL, USA

Cancer drug treatment is unnatural selection

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

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

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

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

09:30–09:50

Jasmine Foo
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Modeling diversity in drug-resistant populations using multitype branching processes

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

discuss implications for treatment strategies. (Joint work w/R. Durrett, K. Leder, J. Mayberry. F. Michor)

09:50–10:10

Heiko Enderling
Center of Cancer Systems Biology, Tufts University School of Medicine
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Emergence of radioresistance through selection for cancer stem cells in solid tumors

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

10:10–10:30

David Basanta
Moffitt Cancer Center
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Tumour heterogeneity and its role in the emergence of resistance

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

MINI-SYMPOSIUM 6

Modeling physiological systems: model validation and experimental design issues

Wednesday, June 29, 11:00, *Room*: **UA2**

Organizers: **Jerry Batzel, Mette Olufsen**

11:00–11:20

Jerry Batel
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Methods of Sensitivity Identifiability Analysis in Modeling Human Physiological Systems

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

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

Orthostatic stress is caused by blood pooling in the lower limbs when standing upright, a consequence of gravity. This pooling removes a percentage of blood from

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

Several aspects and problems of model validation will be discussed. Various tools derived from sensitivity analysis will be applied, including both classical and generalized sensitivities and subset selection [**1, 3**]. Applied jointly, these tools can provide insight into how specific experimental protocols such as HUT and LBNP impact model response and the potential for parameter estimation.

References.

[1] M. Burth, G. C. Verghese, and M. Vélez-Reyes, *Subset selection for improved parameter estimation in on-line identification of a synchronous generator*, IEEE Transactions on Power Systems **14** (1999), no. 1, 218 – 225.

[2] I. Taneja, C. Moran, M. S. Medow, J. L. Glover, L. D. Montgomery, and J. M. Stewart, *Differential effects of lower body negative pressure and upright tilt on splanchnic blood volume*, Am J Physiol Heart Circ Physiol **292** (2007), no. 3, H1420 — H1426.

[3] K. Thomaseth and C. Cobelli, *Generalized sensitivity functions in physiological system identification*, Ann Biomed Eng **27** (1999), no. 5, 607 – 616.

11:20–11:40

Mette Olufsen
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Modeling and parameter estimation in cardiovascular dynamics

The main role of the cardiovascular system is to maintain adequate oxygenation of all tissues. This is accomplished by maintaining blood flow and pressure at a fairly constant level and transporting blood from the heart to the periphery with a minimal loss of energy. In addition, a number of control mechanisms are imposed regulating vascular resistance, compliance, pumping efficiency and frequency. In cardiovascular diseases, both the transport system and its regulation may be compromised, and for a number of diseases it is either not known or difficult to study what mechanism that lead to the breakdown of homeostasis. Typically, some general observations can be made, but these vary significant between individuals. Furthermore, for most patients only a few quantities can be measured, making it difficult to assess essential quantities such as cerebral vascular resistance, cardiac contractility, or the gain and time constants associated with the regulation. This presentation will discuss development of patient specific models obtained by combining models predicting control of blood flow and pressure with parameter estimation

techniques. Models analyzed are composed of systems of nonlinear equations each specified via a set of model parameters. Nominal parameter values are obtained from analysis of populations and data available. Subsequently, sensitivity analysis, correlation analysis, and subset selection, are combined with parameter estimation techniques to obtain a subset of patient specific parameters.

11:40–12:00

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

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

12:00–12:20

Franz Kappel
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Parameter selection in multi-output systems

We present methods for a priori selection of parameters to be estimated in inverse problem formulations for models with multiple measurable outputs. Since in many modeling processes we have to deal with dynamical systems with numerous state variables and an even larger number of parameters, but with limited availability of data, we cannot expect to estimate all parameters with sufficient accuracy. Therefore methods of the type indicated above are becoming increasingly important. In situations with multiple measurable outputs we are also interested to know if the possibility to measure additional outputs would improve parameter estimates. Such questions become important if these additional measurements involve high costs, for instance. We illustrate the results for a model for insulin-glucose dynamics [2] and a model for the reaction of the cardiovascular system to an ergometric workload [1].

References.

[1] F. Kappel and R. O. Peer, *A mathematical model for fundamental regulation processes in the cardiovascular system*, J. Math. Biology **31** (1993), 611 – 631.

[2] M. Munir, *Generalized Sensitivity Functions in Physiological Modelling*, PhD-Thesis, University of Graz, April 2010.

12:20–12:40

Johnny Ottesen
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Patient specific modeling of the heart as a tool for early diagnoses and treatment planning.

The perspective for Patient Specific Modeling (PSM) is to create and develop medical decision system based mathematical modeling of the underlying mechanisms and statistics. We will give an example of PSM of the function of the heart including a discussion of patient specific parameter estimation based on the model in combination with new individual patient data obtained from MR measurements of various relevant blood volumes (and flows). Such parameters will characterize the state of the patients in far more details than clinical investigations unveil today. Thus these parameters will define diagnosed heart illnesses in a refined manner and pinpoint exactly where in the physiological system malfunctioning appears. This opens up for early diagnoses and individual treatments targeting the actual malfunctioning part of the physiological system.

Recently precise and detailed volume data have become assessable by help of MR scanning and imaging technologies. The associated finding confirm earlier results except that atria volumes may show one hump or two hump and all intermediate configurations in between during one heart cycle. These findings are reflected

in the corresponding ventricle volume curves but are not so pronounced. In addition, these curves vary very much with the condition of the contractile strength of the atria and ventricles and thus it become reduced in cicatrical myocardial tissue (after an infarction) and with the condition of the heart valves.

Data from 40 subjects encompass left atria volume, left ventricle volume, right atria volume, right ventricle volume, flow from left ventricle into aorta, and flow from right ventricle into pulmonary aorta versus time during one heart cycle. Data was recorded for objects at rest and for objects given dobutrex and robinul as well.

Our model describe preload to atria, atria itself, ventricle, and afterload for left heart using ordinary differential equations. Based on data, sensitivities on and correlation between the model parameters will be investigated and parameter estimation on a meaningful subset will be performed. Thus various pathologies, including decreased contractile capacities and stenosis, will be categorizes in terms of the model parameters.

12:40–13:00

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Physiological modeling of trace gas exhalation kinetics: a non-invasive window to the body

Exhaled breath contains a plethora of volatile organic compounds (VOCs), resulting from normal metabolic activity as well as from specific pathological disorders. These trace gases can be detected and quantified at concentrations down to the parts-per-billion (ppb) level and hold great promise for medical diagnosis, therapeutic monitoring, and general assessments of physiological function. In particular, exhaled breath can nowadays be measured *on-line*, thus rendering VOC analysis as an optimal choice for gaining continuous and *non-invasive* information on the current metabolic and physiological state of an individual.

The success of using breath VOC concentration profiles for estimating endogenous processes will mainly hinge on the availability of valid mechanistic descriptions for the observable exhalation kinetics of the compound under scrutiny. Within this context, we focus on *real-time* measurements of VOCs during distinct physiological states, e.g., rest, exercise, and sleep [1,2].

An experimental setup for correlating breath-by-breath analyses using proton transfer reaction mass spectrometry (PTR-MS) with the behavior of major hemodynamic and respiratory variables will be presented. Building on the phenomenological findings from studies of normal volunteers, a novel compartmental modeling framework capturing the physiological flow of two prototypic VOCs, isoprene and acetone, is developed and validated [3,4].

Furthermore, several powerful concepts for system and parameter identification will be outlined, including qualitative system analysis, *a priori* identifiability, and numerical schemes based on multiple shooting.

The results discussed are intended as a first step towards employing breath gas analysis as a tool for examining exhalation, storage, transport, and biotransformation processes associated with volatile organic compounds *in vivo*.

References.

[1] J. King, A. Kupferthaler, K. Unterkofler, H. Koc, S. Teschl, G. Teschl, W. Miekisch, J. Schubert, H. Hinterhuber, and A. Amann. *Isoprene and acetone concentration profiles during exercise on an ergometer.* J. Breath Res. **3** 027006 (16pp).

[2] J. King, P. Mochalski, A. Kupferthaler, K. Unterkofler, H. Koc, W. Filipiak, S. Teschl, H. Hinterhuber, and A. Amann. *Dynamic profiles of volatile organic compounds in exhaled breath as determined by a coupled PTR-MS/GC-MS study.* Physiol. Meas. **31** 1169–1184.

[3] J. King, H. Koc, K. Unterkofler, P. Mochalski, A. Kupferthaler, G. Teschl, S. Teschl, H. Hinterhuber, and A. Amann. *Physiological modeling of isoprene dynamics in exhaled breath.* J. Theor. Biol. **267** 626–637.

[4] J. King, K. Unterkofler, G. Teschl, S. Teschl, H. Koc, H. Hinterhuber, and A. Amann. *A mathematical model for breath gas analysis of volatile organic compounds with special emphasis on acetone.* J. Math. Biol. DOI 10.1007/s00285-010-0398-9.

MINI-SYMPOSIUM 7

Ecology and evolution of infectious diseases

Friday, July 1, 14:30, *Room*: **AM9**

Organizers: **Barbara Boldin, Eva Kisdi**

14:30–15:10

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

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

15:10–15:30

Akira Sasaki
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Resistance threshold in spatially explicit epidemic model: Finite size scaling applied to dynamic percolation in epidemic processes with mixed cultivar planting

We examine the fraction of resistant cultivars necessary to prevent a global pathogen outbreak (the resistance threshold) using a spatially explicit epidemiological model (SIR model) in a finite, two-dimensional, lattice-structured host population[1]. Threshold behaviour of this spatially explicit SIR model cannot be reduced to that of bond percolation, as was previously noted in the literature, unless extremely unrealistic assumptions are imposed on infection process. The resistance threshold is significantly lower than that of conventional mean-field epidemic models, and is even lower if the spatial configuration of resistant and susceptible crops are negatively correlated. Finite size scaling applied to the resistance threshold reveals that its difference from static percolation threshold (0.41) is inversely proportional to the basic reproductive ratio of pathogen. Estimated value, 4.7, of critical basic reproductive ratio in a universally susceptible population is much larger than the corresponding critical value (1) in the mean-field model and nearly three times larger than that of SIS model.

References.

[1] Suzuki, S.U. and Sasaki, A. *How does the resistance threshold in spatially explicit epidemic dynamics depend on the basic reproductive ratio and spatial correlation of crop genotypes?* Journal of Theoretical Biology **276** 117–125 (2011).

15:30–15:50

Andy White
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Alex Best
University of Sheffield
Eva Kisdi
University of Helsinki
Janis Antonovics
University of Virginia
Mike Brockhurst
University of Liverpool
Mike Boots
University of Sheffield

The evolution of host-parasite range

Understanding the coevolution of hosts and parasites is one of the key challenges for evolutionary biology. Adaptive dynamics techniques have examined coevolutionary outcomes in classical infectious disease model frameworks in which infection depends on absolute rates of transmission and defence [**1**]. These models typically predict either that one strain dominates or that there is evolutionary

branching, where disruptive selection around a fitness minimum causes the emergence of two distinct strains. This may therefore provide insight into the onset of diversity but does not fully explain the generation and maintenance of the wide range of variation in host and parasite strains observed in natural systems. Here we present a fully coevolutionary host-parasite model using the assumptions of adaptive dynamics, but rather than assuming that transmissibility and defence are absolute we approximate an 'all or nothing' infection process where the success of infection depends upon the relative 'range' of host resistance and parasite infectivity. A parasite that can infect a wide range of host strains will pay a cost in terms of disease transmission compared to parasites that infect a narrower range of hosts. A similar trade-off exists in terms of the range of parasite strains a host can resist and the host reproductive rate. Infection success therefore depends on the specific characteristics of both the parasite and the host. We show that considerable diversity can be generated and maintained due to epidemiological feedbacks, with strains differing in the range of host and parasite types they can respectively infect or resist [**2**]. The patterns of resistance and infectivity are also in close agreement with laboratory results that assess the evolutionary behaviour in a bacteria-phage system.

References.

[1] Best, A., White, A. and Boots, M. 2009. *The implications of coevolutionary dynamics to host-parasite interactions.* American Naturalist, **173**: 779-791.

[2] Best, A., White, A., Kisdi, E., Antonovics, J., Brockhurst, M. A. and Boots, M. 2010. *The evolution of host-parasite range.* American Naturalist, **176**: 63-71.

15:50–16:10

Samuel Alizon
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Within-host parasite cooperation and the evolution of virulence

Infections by multiple genotypes are common in nature and are known to select for higher levels of virulence in some pathogens. It has been argued that for parasites whose virulence is determined by the production of public goods, such co-infections can select for lower levels of virulence. However, this prediction is rooted in a perspective that neglects epidemiological feedbacks. Here, we analyse the case of parasites producing a public good, for example siderophore-producing bacteria, using a nested model that ties together within-host and epidemiological processes. Making the epidemiology explicit with an SI model reveals that the

current prediction that co-infection should select for less virulent strains for public-goods producing parasites is only valid if both parasite transmission and virulence are a linear function of parasite density. If there is a trade-off relationship such that virulence increases more rapidly than transmission, or if virulence also depends on the total amount of public goods produced, then co-infections should select for more virulent strains. This suggests that theoretical or empirical studies that seek to determine optimal virulence within a single host may not be representative of the selection pressures faced by parasites at the population level. At the same time, it underlines the importance of including epidemiological processes when studying the evolution of infectious diseases.

16:10–16:30

Eva Kisdi
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Barbara Boldin
University of Primorska

The curse of the pharaoh hypothesis revisited: Evolutionary coexistence of parasite strains

Several pathogens produce free-living stages that allow the infection to spread from one host to the next indirectly, via an outside environment. Since the reproductive success of pathogens with long-lived spores depends less on the host's survival, it has been hypothesized that such pathogens can afford to exploit their hosts more recklessly and thus evolve higher virulence. We revisit the so called 'curse of the pharaoh' hypothesis and study the evolution of virulence in pathogens that can transmit directly as well as indirectly, via free-living stages. We show that the two transmission routes introduce two environmental feedback variables, which allows for coexistence of two parasite strains one of the two specializes to some extent on direct transmission, while the other makes better use of indirect route of transmission. We give general conditions for coexistence in terms of incidence in host-to-host and host-propagule-host transmission, and discuss the conditions for evolutionary branching leading to coexisting strains in terms of the shape of trade-off functions.

MINI-SYMPOSIUM 8

Game theoretical modelling and optimization in evolution and ecology I

Tuesday, June 28, 11:00, *Room*: **UA2**

Organizers: **Mark Broom, Krzysztof Argasinski**

11:00–11:25

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Evolution of tree architecture

The astounding biodiversity of the Earth's ecosystems is the outcome of competition, cooperation, and migration among species and within-species varieties. The potential for frequency-dependent selection to shape these biodiversity patterns is easily appreciated in plants, where height-asymmetric competition for light has not only driven the evolution of tall trees, but is also responsible for their coexistence with smaller plants. Less is known, however, of how frequency-dependent competition for light has affected other salient aspects of plant architecture. Here, we present a trait-, size-, and patch-structured model of vegetation dynamics to study the evolution of tree-crown architecture. Our study extends a related model by Falster et al. (2011), by incorporating self-shading within tree crowns and a more detailed representation of biomass-allocation to branches. Tree-crown architecture is described by two individual-level traits for crown shape and crown width. Three scenarios are investigated and contrasted for different combinations of sun angle, site productivity, and disturbance frequency. First, we consider optimal tree-crown architectures for solitary trees growing apart from competing trees. Second, we ask the same question for a monoculture of identical trees subject to density-dependent growth. Third, we investigate the coevolution of tree-crown shape and tree-crown width under competition and for potentially polymorphic traits, and determine the

resultant evolutionarily stable state. Finally, we critically reassess the common belief that a low sun angle is a main force driving the conical tree-crown architectures observed in boreal forests.

References.

[1] Falster DS, Brännström Å, Dieckmann U, Westoby M. 2011. *Influence of four major plant traits on average height, leaf-area cover, net primary productivity, and biomass density in single-species forests: a theoretical investigation.* Journal of Ecology. **99**, 148-164.

[2] Shinozaki K, Yoda K, Hozumi K, Kira T. 1964. *A quantitative analysis of plant form - the pipe model theory. I. Basic analyses.* Japanese Journal of Ecology. **14**, 97-105

[3] Shinozaki K, Yoda K, Hozumi K, Kira T. 1964. *A quantitative analysis of plant form - the pipe model theory. II. Further evidence of the theory and its application in forest ecology.* Japanese Journal of Ecology. **14**, 133-139

11:25–11:50

Maciej Jan Ejsmond
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Macrin Czarnołęski
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Jan Kozłowski
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More capital or income breeding optimal strategies for indeterminate growers in the seasonal environment

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

11:50–12:15

Andrei R. Akhmetzhanov
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Dynamic game for optimal resource allocation of annual plants and grazing consumers

In [**1**] authors have formulated a model of optimal resource allocation in annual plants with constant grazing pressure along a season of fixed length. The plant has two choices: either to invest nutrients in the vegetative part of the plant or in the reproductive part. This kind of problem has been stated and solved as a problem of optimal control using Pontryagin's maximum principle.

In our work we consider a similar model but we take into account that the grazing pressure on the plant varies in time and occurs due to the presence of consumers in the system. Consumers are also faced with an allocation dilemma between the investment of time in increasing their internal energy through grazing or in reproduction (see for details [**2**]). Hence we are dealing here with a dynamic game of two players which are known to be fairly advanced mathematical objects [**3**]. Its resolution address interesting questions such as the influence of an adaptive, rather than fixed, grazing pressure on plants phenology.

References.

[1] N. Yamamura, N. Fujita, M. Hayashi, Y. Nakamura, A. Yamauchi, *Optimal phenology of annual plants under grazing pressure* Journal of Theoretical Biology **246** 530–537, 2007
[2] A.R. Akhmetzhanov, F. Grognard, L. Mailleret, *Optimal life-history strategies in seasonal consumer-resource dynamics* In revision for Evolution
[3] T. Basar, G.J. Olsder *Dynamic Non-Cooperative Game Theory*, 2nd ed., SIAM, Philadelphia, 1999

12:15–13:00

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dr Mark Broom
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In which currency are paid payoffs in evolutionary games?

In the standard approach to evolutionary games and replicator dynamics, differences in fitness can be interpreted as an excess from mean malthusian growth rate

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

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

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

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MINI-SYMPOSIUM 9

Game theoretical modelling and optimization in evolution and ecology II

Tuesday, June 28, 14:30, *Room*: **AM8**

Organizers: **Mark Broom, Krzysztof Argasinski**

14:30–14:55

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Evolutionary games on graphs

Evolutionary game dynamics models have been mainly studied on homogeneous infinite populations. However, real populations are neither homogeneously mixed nor infinite. This study investigates the stochastic evolutionary game dynamics in structured populations as represented by graphs. In this talk, we consider analytically the fixation probability and the speed of the evolutionary process (absorption time) when a single mutant individual invades into three simple graphs of finite number of vertices: the star, the circle and the complete graph. Applying the obtained results, it is then shown the significant impact that the structure of the population might have on the evolutionary process. As a specific example, we consider a Hawk-Dove type game. Finally, it is demonstrated that although the update rule (evolutionary dynamics) of the evolutionary process does not significantly affect the evolution of the invader mutants in homogeneous populations, it might cause significant changes in populations with a non-homogeneous structure.

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14:55–15:20

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Mixed Strategies, Evolution and the Tragedy of the Commons in Heterogeneous Populations

The question of sustainability and prevention of the tragedy of the commons, also known as evolutionary suicide, which occurs when extremely efficient consumers exhaust the common resource and eventually harm themselves, is becoming of vital importance in the modern world. In order to investigate it we consider a situation, when consumers can choose different strategies for resource consumption in different proportion, investing primarily in consumption or in sustaining the resource. This is modeled by an infinitely-dimensional system of ODEs, which is then reduced to a finitely-dimensional system using parameter distribution. The population of consumers is then allowed to evolve over time, and the changes in the frequency of different strategies are tracked through changes in the expected value of the parameter that describes the choice of a strategy. We demonstrate that under different parameter values different strategies predominate, leading to either sustained interaction with the resources, or to population extinction, which occurs after a series of transitional regimes.

15:20–15:45

Chaitanya S. Gokhale and Arne Traulsen
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Multiplayer evolutionary games: from selection to mutation

Evolutionary game theory is an abstract and simple, but very powerful way to model evolutionary dynamics. Even complex biological phenomena can sometimes be abstracted to simple two player games. But often, the interaction between

several parties determines evolutionary success. In these cases, one can resort to multiplayer games. Public goods games are a special class of multiplayer games which have been studied in great detail. A general approach to multiplayer games has although has remained limited **[3]**. We extend the replicator analysis to general d player games with n strategies and comment on the maximum number of equilibria possible. Moving on to finite populations we provide general conditions for a strategy to be favoured by natural selection in a d player game with two strategies **[4]**. Another important evolutionary force is mutations, which has only recently yielded to analytical methods **[1, 2]**. We derive the composition of a d player, n strategy system in the mutation-selection equilibrium **[5]**. The average frequencies of the strategies at this equilibrium are obtained via recursions using coalescence theory **[6]**. Multiplayer multi strategy games offer the generality which helps us to apply them to diverse entities like from alleles to behavioural strategies.

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15:45–16:10

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On evolutionary stability in some population games

The classical models of population dynamics (e.g., the Lotka-Volterra predator-prey model) assume that interaction strength is fixed and independent of population densities. However, empirical evidence suggests that both prey and/or predators change their behavior with changes in population numbers. For example, an increase in predator numbers often decreases prey activity. Such plasticity in animal behavior leads to variable interaction strength that can strongly influence population dynamics. As predators and prey often play avoidance game (i.e., prey try to avoid predators while predators try to find prey), to solve this game methods of evolutionarily game theory are often used. In particular, it is assumed that the

optimal solution to such a game corresponds to the evolutionarily stable strategy. By definition, such a strategy cannot be invaded by rare mutants, and from this respect it is the ultimate outcome of evolution. However, the classical theory does not consider changes in population numbers and in such a dynamic setting it is not a priori clear, if evolutionarily stable strategies can be invaded by rare behavioral mutants when population dynamics are considered. In this talk we will show that this can happen, although behavioral mutants cannot replace residents. However, a polymorphism can arise. Whether this happens or not, depends on particular dynamics and food web topology.

16:10–16:35

Mark Broom
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Jan Rychtar
Department of Mathematics and Statistics, University of North Carolina at Greensboro

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

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

MINI-SYMPOSIUM 10

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling I

Saturday, July 2, 08:30, *Room*: **AM4**

Organizers: **Arnaud Chauviere, Haralampos Hatzikirou, John Lowengrub**

08:30–09:10

Dirk Drasdo
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Multi-scale modeling of cells: concepts and open questions

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

talk we discuss different individual-based models to tissue organization including hybrid and multi-scale models.

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

(2) In a second step we show how intra-cellular, molecular core modules can be embedded into a single-cell-based model to a multi-scale model. We consider several examples: the integration of the beta-catenin core module to mimic the epithelial-mesenchymal transition during cancer invasion (Ramis-Conde et. al., Biophys. J. 2008), intravasation, the process by which a tumor cells enters a blood vessel (Ramis-Conde et. al., Phys. Biol. 2009), mesenchymal stem cell differentiation (Krinner et. al., Cell Prol. 2009; BMC Syst. Biol. 2010), and the change of cell metabolism during liver regeneration after drug-induced damage. (3) Finally we show how individual-based models can be used to guide the development of continuum models considering growth of disperse and compact tumor phenotypes (Byrne and Drasdo, J. Math. Biol. 2009).

09:10–09:30

Vitaly Volpert
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Hybrid models of normal and leukemic hematopoiesis

We develop hybrid models of cell population dynamics where cells are considered as individual objects, intracellular regulatory networks are described by ordinary differential equations while biochemical species in the extracellular matrix by partial differential equations. We use this approach to various biological and medical application. In particular, to model normal and leukemic hematopoiesis and leukemia treatment.

09:30–09:50

Yangjin Kim
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The role of the microenvironment in an early development of breast cancer: a hybrid (multiscale) model.

Mathematical modeling and computational analysis are essential for understanding the dynamics of the complex gene networks that control normal development and homeostasis, and can help to understand how circumvention of that control leads to abnormal outcomes such as cancer. Tumor microenvironment (TME) is comprised of various signaling molecules, cell types and the extracellular matrix. We investigate how the local biochemical and mechanical microenvironment can affect the progression of potentially-cancerous cells in an early development of breast cancer. The model deals with the effects of the mechanical properties of the microenvironment on tumor growth, and we report results from a multi-scale model of the signaling pathways and the TME. The results emphasize the complexities of the interactions within the TME and their effect on tumor growth, and show that tumor progression is not solely determined by the presence of a clone of mutated immortal cells, but rather that it is communitycontrolled.

09:50–10:10

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Andrew J. Evans, Alastair M. Thompson
Dept. of Surgical & Molecular Oncology, U. of Dundee, UK

An illustration of patient-specific cancer modelling: from microscopic data to macroscopic, quantitative predictions

Ductal carcinoma in situ (DCIS)—a type of breast cancer whose growth is confined to the duct lumen—is a significant precursor to invasive breast carcinoma. DCIS is commonly detected as a subtle pattern of calcifications in mammograms. Mammograms are also used to plan surgical resection (lumpectomy) of the tumour, but multiple surgeries are often required to fully eliminate DCIS. This highlights deficiencies in current surgical planning. Immunohistochemical measurements have been proposed to assess DCIS and plan treatment, but no standard has emerged to quantitatively predict a patient's clinical progression (i.e., macroscopic measurements such as the growth rate) based upon such microscopic measurements.

We present a mechanistic, agent-based model of solid-type DCIS with comedonecrosis and calcification [1]. Each agent has a lattice-free position and phenotypic state. Cells move by exchanging biomechanical forces with other cells and the basement membrane. Each phenotypic state has a "submodel" of changes in

cell volume and composition. Phenotypic transitions from the quiescent state are regulated by proteomic- and microenvironment-dependent stochastic processes. We combine a model analysis, a mathematically-oriented literature search, and a new patient-specific calibration protocol to fully constrain and calibrate the model to an individual patient's immunohistochemical and morphometric data [3].

The model predicts linear growth at approximately 7–10 mm per year, consistent with mammography [4]. It also predicts a linear correlation between the calcification size (as in a mammogram) and the tumour size (post-operative pathology measurement), in excellent quantitative agreement with 87 clinical data points [4]. These results suggest that hybrid multiscale models can be rigorously calibrated to molecular data by upscaling mechanistic cell-scale models. Such multiscale models can potentially bring mathematics to the clinic to improve patient care.

References.

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10:10–10:30

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Cell Adhesion and Re-organisation in a Multiphase Model Describing Tumour and Tissue Growth

The main aim of the talk is to describe how to embed the experimental results recently obtained studying the detachment force of single adhesion bonds in a multiphase model developed to describe the growth of tumours and tissues in general. In order to do that the microscopic infomation is upscaled to the macroscopic level to describe the dependence of some crucial terms appearing in the PDE model on the sub-cellular dynamics involving, for instance, the density of bonds on the membrane, the probability of bond rupture and the rate of bond formation. In fact, adhesion phenomena influence both the interaction forces among the constituents of the mixtures and the constitutive equation for the stress of the cellular components.

Studying the former terms a relationship between interaction forces and relative velocity is found. The dynamics presents a behaviour resembling the transition from

epithelial to mesenhymal cells or from mesenchymal to ameboid motion though the chemical cues triggering such transitions are not considered here.

The latter terms are dealt with using the concept of evolving natural configurations consisting in decomposing in a multiplicative way the deformation gradient of the cellular constituent distinguishing the contributions due to growth, to cell rearrangement and to elastic deformation. This allows to describe situations in which if in some points the ensemble of cells is subject to a stress above a threshold, then locally some bonds may break and some others may form, giving rise to an internal re-organisation of the tissue that allows to relax exceedingly high stresses.

MINI-SYMPOSIUM 11

Multiscale modeling of biological systems: from physical tools to applications in cancer modeling II

Saturday, July 2, 11:00, *Room*: **AM4**

Organizers: **Arnaud Chauviere, Haralampos Hatzikirou, John Lowengrub**

11:00–11:40

John Lowengrub
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Physical oncology

Cancer models relating basic science to clinical care in oncology may fail to address the nuances of tumor behavior and therapy, as in the case, discussed herein, of the complex multiscale dynamics leading to the often-observed enhanced invasiveness, paradoxically induced by the very antiangiogenic therapy designed to destroy the tumor. Studies would benefit from approaches that quantitatively link the multiple physical and temporal scales from molecule to tissue in order to offer outcome predictions for individual patients. Physical oncology is an approach that applies fundamental principles from the physical and biological sciences to explain certain cancer behaviors as observable characteristics arising from the underlying physical and biochemical events. For example, the transport of oxygen molecules through tissue affects phenotypic characteristics such as cell proliferation, apoptosis, and adhesion, which in turn underlie the patient-scale tumor growth and invasiveness. Here, we illustrate how tumor behavior and treatment response may be a quantifiable function of marginally stable molecular and/or cellular conditions modulated by inhomogeneity. By incorporating patient-specific genomic, proteomic, metabolomic, and cellular data into multiscale physical models, physical oncology could complement current clinical practice through enhanced understanding of cancer behavior, thus potentially improving patient survival.

11:40–12:00

Cristian V. Achim
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Phase Field Crysyal Model for Liquid Crystals

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

References.

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12:00–12:20

Isabell Graf
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Homogenization of a reaction-diusion system modeling carcino- gens inside a human cell

We use a reaction-diusion model to describe the behavior of potentially cancer-causing chemicals inside a human cell. We show how periodic homogenization can be used to upscale rigorously the reaction-diusion equations in the cytosol as well as on the surface of the endoplasmic reticulum. The resulting macromodel is also suitable for direct implementation. Results of numerical simulations will be shown.

12:20–12:40

Applications of phase field models in biological systems

Simon Praetorius
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Shapes of complex geometry are ubiquitous in our natural environment. A few examples are snow flakes, crack patterns, microstructures in materials or th evein network in plant leaves. These shapes have in common that they are created by out-of-equilibrium phenomena and thus evolve in time. The understanding of a diverse array of phenomena involving complex time-dependent shapes in the physical and biological sciences has been greatly enhanced by a theoretical/computational framework rooted in statistical physics, that is commonly refered to as phase-field modeling. The main challenge in this field is to construct models which encompass the complexity of practically relevant materials or biological systems, are capable of making quantitatively accurate predictions and are mathematically simple enough to be solved on physically realistic time and length scales.

We present various applications in biological systems, including cell dynamics, viral capsides and bone remodeling.

12:40–13:00

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Multiscale modeling of biological systems

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

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

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

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

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

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

MINI-SYMPOSIUM 12

Plants, growth and transport processes I

Tuesday, June 28, 11:00, *Room*: **AM9**

Organizers: **Andrés Chavarría-Krauser, Mariya Ptashnyk**

11:00–11:40

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Transport of metal and water in plant roots: Modelling and Analysis

We study the problem of metal and water transport through plant roots. The model equations reflect the complex microscopic structure of a root tissue. We distinguish between apoplastic and symplastic pathways for metal and water transport. The active water transport is modelled by Stokes equations and is defined by the pressure difference between roots and atmosphere and by the osmotic pressure in cells. The transport of metal molecules is specified by reaction-diffusion-convection equations. The ordinary differential equations describe the dynamic of metal transporter concentrations on cell membranes. Using multiscale analysis we derive a macroscopic model for transport processes defined on the scale of a whole root branch. The convergence of nonlinear terms is shown applying the unfolding method.

11:40–12:00

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Anita Roth-Nebelsick

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Dynamics of plant water transport derived from applying an optimisation scheme to Soil-Plant-Atmosphere-Continuum

In Central Europe, plant transpiration injects more than 40% of precipitation back into the atmosphere. Thus, plants play an important role in the exchange of water between soil and atmosphere.

Plants can actively open and close their leaf openings ("stomata"), gateways for incoming carbon dioxide molecules to be processed by photosynthesis as well as for outgoing water vapour. Since both gas species use the same pathways, the majority of terrestrial plants has to compromise between the conflicting tasks of (i) minimising transpiration (in order to avoid water stress and wilting) and (ii) maximising assimilation of carbohydrates (which constitute both building material and energy source of plants).

Plants deal with this conflict by regulating leaf gas exchange (via stomatal aperture) according to soil moisture and the diurnal cycles of temperature, insolation and relative humidity. The (physiological) details of this regulation mechanism are largely unknown. Nonetheless, it is possible, to emulate the actual plant gas exchange by a mathematical optimisation scheme ([1], [2], [3]): Optimum stomatal conductance as a function of time is determined by requiring that the assimilates assembled during one day accumulate to a maximum, being subject to the constraint that the quantity of water transpired during this time span equals a given amount. The diurnal variations of temperature, insolation and relative humidity have to be prescribed.

The calculus of variation subject to constraints introduces a Lagrangian multiplier whose value cannot be determined in the usual way, due to an intractable integral. Application of the continuity equation to the water current through soil, plant roots and xylem allows, however, to express the Lagrangian multiplier in terms of soil properties, tree anatomy and tree physiologic restrictions.

Applications of this model encompass the reconstruction of palaeo-environment from fossilised plant leaves and the predictions of the impact of changing atmospheric CO_2-level on climate ([4]). Redistribution of precipitation between soil (run-off and ground water) and atmosphere (transpiration) due to modified stomatal action caused by changing atmospheric CO_2-content can also be assessed.

References.

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12:00–12:20

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Plant gas exchange: Theoretical considerations on the level of single stomata

Plant gas exchange: Theoretical considerations on the level of single stomata Land plants require gas exchange between leaf interior and atmosphere to obtain sufficient amounts of CO2 for photosynthesis. Stomata, micropores on the leaf surface, are the gateways for plant gas exchange. The stomatal pore is formed by two guard cells whose shape change (caused by changing turgor) controls the aperture width. This in turn controls stomatal conductance. Tight control of stomatal conductance is necessary since diffusional CO2 influx through open stomata is accompanied by water vapour loss (= transpiration). Besides stomatal pore area that is controlled by the guard cells, the actual stomatal conductance is dependent on various other anatomical traits, such as stomatal density and depth and shape of the stomatal pore [1, 2].

The entire diffusion pathway is, however, more complex in reality. In most cases, it is still unclear where evaporation inside the leaf occurs. If cutinization does not reach beyond the stomatal channel, i.e. if internal cuticles are absent, then evaporation should occur close to the stomata [3, 4]. If internal cuticles are present, evaporating sites are seated more deeply within the leaves. Shifting evaporation deeper into the mesophyll by cutinization beyond the stomatal channel can lead to a substantial decrease in stomatal conductance for water vapour (with all other parameters constant) [4].

Details of leaf internal diffusion of water vapour and CO2 are of interest, due to different aspects. For example, measurement of stomatal conductance for water vapour is used also for analyses of photosynthesis, implicitly assuming that diffusion pathways of CO2 and water vapour are mostly identical. In ecophysiology, various modifications of stomata are ascribed to adaptations to environmental conditions. For example, arrangement of stomata in stomatal crypts, that are depressions of the leaf surface in which stomata are seated, should restrict water loss. It is, however, questionable whether this really happens, or if other functional benefits may linked to these kind of structures. Furthermore, variations in stomatal structure and/or arrangement add more parameters to the stomatal pathway, thereby altering the contribution of the controllable stomatal channel to overall conductance.

As a whole, important details of stomatal diffusion are still not well understood. Analyzing gas diffusion on the level of single stomata, and within the mesophyll, can contribute substantial information to various topics in ecophysiology and plant physiology.

References.

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[3] M. T. Tyree and P. Yianoulis, Annals of Botany, 1980, 46, 175-193.
[4] A. Roth-Nebelsick, Annals of Botany, 2007, 100, 23-32.

12:20–12:40

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The interaction of leaves with the environment

Plant leaves are highly specialized organs to facilitate gas exchange, carbon uptake and water loss usually upon illumination. Leaf internal structures have an enormous influence on these processes. For example, heterobaric leaves have bundle sheaths with extensions which reach from the upper to the lower epidermis and create closed compartments. Homobaric leaves, on the other hand lack these extensions and have large interconnected intercellular spaces so that lateral diffusion of CO2 can substantially support photosynthesis in particular, when one part of the leaf is shaded being a CO2 source while the adjacent leaf area is illuminated and a CO2 sink. Light environment also plays a key role for a range of plant processes. A light beam interacting with a leaf penetrates the epidermis with little interaction and the largest part of the energy is absorbed bythe pigments in the mesophyll cells driving off water vapor which in turn affects the epidermis with stomata. This interaction feeds back on stomata and provides a control mechanism for the interaction of stomata with the environment. These processes aim at a mechanistic description of the interaction of plants with the environment. Comprehensive understanding of plant interaction with the environment for a prediction of plant performance requires a measurement of phenotyping variation with a range of genotypes. This approach called plant phenotyping is a rapidly evolving concept that links genomics with ecophysiology and agronomy. The basis of this concept is that the functional plant body (phenotype) originates during plant growth and development from the dynamic interaction between the plant genetic background and the environment in which the plant develops.

12:40–13:00

Konstantinos Zygalakis
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National Soil Resources Institute, Cranfield University

D.L. Jones
School of Environment, Natural Resources & Geography, Bangor University
M. Wissuwa
Crop Production and Environment Division, Japan International Research Center for Agricultural Sciences
T. Roose
Bioengineering, Faculty of Engineering and Environment, University of Southampton

A dual porosity model for the uptake of nutrients by root hairs

Root hairs are thought to play an important role in mediating nutrient uptake by plants. In this talk we develop a mathematical model for the nutrient transport and uptake on the scale of a single root. We treat soil as a double porous material, since nutrients are assumed to diffuse both in the soil fluid phase and within the soil particles, while they can also bind to the soil particle surfaces by reversible reactions. Using homogenization techniques we derive a macroscopic model for nutrient diffusion and reaction in the soil which includes the effect of all root hair surfaces. Various numerical simulations of a simplified version of the macroscopic model highlight the importance of root hairs for the uptake of nutrients by the plant in a variety of different soil moisture scenarios.

MINI-SYMPOSIUM 13

Plants, growth and transport processes II

Tuesday, June 28, 14:30, *Room*: **AM9**

Organizers: **Andrés Chavarría-Krauser, Mariya Ptashnyk**

14:30–15:10

Vitaly Volpert
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Nonlinear dynamics of plant growth

We model plant growth with free boundary problems where the moving boundary corresponds to the mersitem, a narrow layer of proliferating cells. Cell cycle progression and transport of nutrient and metabolites are taken into account. Nonlinear dynamics of plant growth, endogeneous rhythms and branching patterns are discussed.

15:10–15:30

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Modelling hormone-regulated plant root growth

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

15:30–15:50

R.J. Dyson
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The mechanics of plant root growth

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

The relationship between stress and strain-rate is shown to exhibit the characteristic yielding-type behaviour seen experimentally. The model shows how this stress strain-rate relationship is modified in the presence of enzymes and predicts the distribution of crosslinks and stress within the cell wall.

15:50–16:10

Robert Nolet
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J. Hulshof
VU University Amsterdam
G. Prokert
Eindhoven University of Technology

Existence of solutions for the diffusive VSC model.

The concept of a vesicle supply center (VSC), first proposed by Bartnicki-Garcia *et al* lies at the basis for a whole hierarchy of mathematical models which attempt to explain tip growth in fungal hyphae. It assumes that there is a point source in the tip which distributes cell wall material for the tip. Vesicles diffuse out from the VSC to the cell wall, producing growth of the cell wall orthogonal to the wall surface. This yields a geometric evolution equation for the surface of the hypha, in which the normal velocity of the surface is proportional to the flux of new material arriving at the cell wall and the inverse of the mean curvature. In this talk, we shall assume the VSC is given a fixed velocity, we will then show how to prove the existence of surfaces which stay stationary in a coordinate frame moving along with the supply center.

16:10–16:30

Andrés Chavarría-Krauser
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A model of plasma membrane flow and cytosis regulation in growing pollen tubes

In plant sexual reproduction, pollen tubes carry the male genetic information from pollen grains to ovules. These single cells traverse the entire female tissue to

reach the eggs. Astonishing high expansion rates and total lengths are achieved: rates of 1 mm/h in lily flowers and lengths of 30 cm in maize. This extreme growth rates and total lengths demand perfect coordination of cell wall expansion, cell wall material deposition and membrane recycling.

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

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

References.

[1] Zonia and Munnik, *Uncovering hidden treasures in pollen tube growth mechanics*, Trends in Plant Science **14:** 318–327.

MINI-SYMPOSIUM 14

Mathematical Modeling of Mosquito-Borne Diseases

Tuesday, June 28, 11:00, *Room*: **AM8**

Organizer: **Nakul Chitnis**

11:00–11:40

Alun Lloyd
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Modeling Wolbachia-Based Strategies for Controlling Mosquito-Borne Diseases

Mosquito borne infections, most notably malaria and dengue, kill over a million people every year. Traditional control measures (such as insecticides) against these infections in developing countries have had mixed success. A novel avenue of attack involves the production and release of mosquitoes that have been manipulated or genetically engineered to be less able, or even unable, to transmit infection.

Mathematical modelling is playing an important role in several large-scale projects that are currently under way to assess the feasibility of these techniques. In this talk I shall discuss the biology of one approach that uses the bacterial symbiont Wolbachia and the accompanying modelling work, illustrating how a number of different models are being used as the projects move along the path from lab-based studies to field deployment.

11:40–12:00

Carrie Manore
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Nakul Chitnis
Swiss Tropical and Public Health Institute
Mac Hyman
Tulane University

A Model for the Spread of Rift Valley Fever in Livestock with Vertical Transmission

Rift Valley Fever (RVF) is a zoonotic infectious disease spread by mosquitoes and transmitted between several animals species and occasionally humans. We present and analyze a new model for mosquito-transmitted disease that includes vertical transmission mechanisms from an infected mosquito mother to infected offspring. In particular, we model the spread of RVF in cattle and mosquito populations, extending existing models for vector-borne diseases to include vertical transmission and an egg/larvae stage. We analyze the importance of vertical transmission in predicting the spread of RVF and discuss how modeling can reduce the uncertainty of the estimates of disease prevalence. We also make this extended model reactive to environmental changes and demonstrate that even if the endemic equilibrium has a low ratio of infectious vectors and animals, a large pulse of vectors resulting from increased hatch and survival rates due to high rainfall events can result in a large epidemic.

12:00–12:20

Angelina Mageni Lutambi[1,2]
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Nakul Chitnis[1]
Melissa Penny[1]
Tom Smith[1]
[1]Swiss Tropical and Public Health Institute, Socinstrasse 574002 BASEL, Switzerland
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Modelling mosquito dispersal in a heterogeneous environment

Mosquito foraging behaviour for hosts and oviposition sites/habitats is an important aspect for malaria control. Recent studies have highlighted the impact of the presence of habitats on mosquito search for oviposition sites. While others have highlighted the significance of habitat elimination within certain distances from human habitations to prevent mosquitoes using human hosts for blood meals. While minimizing or eliminating the impact of mosquitoes on the spread of malaria has been a concern of current malaria research, mosquito dynamics and mosquito spatial distribution remain a challenge. The goal of this work is to describe and understand mosquito population dynamics in relation to dispersal in spatial environments.

A simple mathematical model based on the mosquito life cycle is formulated to describe the population dynamics of mosquitoes. Dispersal of adult mosquitoes searching either for hosts or oviposition sites is also modelled and its effects incorporated in the population dynamics. The spatial aspect of mosquito dispersal is

described by their movement between patches in a two-dimensional spatial environment. A hexagonal grid with each hexagon representing a patch is used where vital dynamics are allowed to occur. Numerical simulations are carried out to demonstrate the biological application of the model.

The modelled population dynamics of each stage of the mosquito life cycle in space are presented and the links between factors influencing the spatial dynamics are discussed.

12:20–12:40

Susana Barbosa
Liverpool School of Tropical Medicine
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A genetic model for the spread of insecticide resistance in a heterogeneous environment

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

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

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

12:40–13:00

Nakul Chitnis
Swiss Tropical and Public Health Institute
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Diggory Hardy, Nicolas Maire, Amanda Ross, Melissa Penny, Valerie Crowell, Olivier Briët, Thomas Smith
Swiss Tropical and Public Health Institute

Mathematical Modeling to Support Malaria Control and Elimination

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

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

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

MINI-SYMPOSIUM 15

Modeling Dynamics of Complex Biological Systems

Tuesday, June 28, 17:00, *Room*: **UA3**

Organizers: **Ching-Shan Chou, Richard Gejji**

17:00–17:40

German A. Enciso
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Protein scaffolds can enhance the bistability of multisite phosphorylation systems

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

17:40–18:00

Deena Schmidt
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Linking network structure and stochastic dynamics to neural activity patterns involved in sleep-wake regulation

Sleep and wake states are each maintained by activity in a corresponding neuronal network, with mutually inhibitory connections between the networks. In infant mammals, the durations of both states are exponentially distributed, whereas in adults, the wake states yield a heavy-tailed distribution. What drives this transformation of the wake distribution? Is it the altered network structure or a change in neuronal dynamics? What properties of the network are necessary for maintenance of neural activity on the network and what mechanisms are involved in transitioning between sleep and wake states? We explore these issues using random graph theory, specifically looking at stochastic processes occurring on random graphs, and also by investigating the accuracy of predictions made by deterministic approximations of stochastic processes on networks.

References.

[1] D. Schmidt, J. Best, M.S. Blumberg, *Random graph and stochastic process contributions to network dynamics* (submitted).

[2] M.S. Blumberg et al., *Dynamics of sleep-wake cyclicity in developing rats* PNAS **102** 14860–14864.

18:00–18:20

Anna Cai
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Kelly Radtke
Department of Developmental and Cell Biology, University of California, Irvine
Thomas F. Schilling
Department of Developmental and Cell Biology, University of California, Irvine
Qing Nie
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Critical roles for intracellular binding proteins in creating a robust retinoic acid morphogen gradient

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

Cellular retinoic acid binding proteins (Crabps) transport RA intracellularly but their roles in morphogen gradient formation remain unclear. Using a combination of computational and experimental approaches in zebrafish, we show that both positive and negative feedback by Crabps on RA signaling dramatically improves

robustness. Crabps improve robustness within an optimal concentration range and transport of Crabp bound RA to Cyp26 degradation enzymes appears to be critical for these robustness gains. These results suggest that Crabps are essential for modulating the RA signaling gradient in the face of varying levels of dietary vitamin A.

18:20–18:40

Richard Gejji
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Macroscopic model of reversing self-propelled bacteria

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

18:40–19:00

Paul Hurtado
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In-Host Dynamics of Mycoplasma Infections: Conjunctivitis in Wild Passerine Birds

The host-pathogen interaction is at the core of every infectious disease system, and provides an important foundation from which to study infectious disease at the individual, population and community levels. This work uses tools from applied dynamical systems and bifurcation theory to investigate how different aspects of the host immune response affect the progression of a localized bacterial infection caused by small, persistent bacteria known as mycoplasmas. The goal is to better understand observed variation within and between host species in the motivating biological system: infectious conjunctivitis in the house finch (*Carpodacus*

mexicanus) and other passerine birds caused by the novel pathogen *Mycoplasma gallisepticum*.

MINI-SYMPOSIUM 16

Multiscale modelling of reaction kinetics in biology

Tuesday, June 28, 14:30, *Room*: **UA2**

Organizer: **Simon Cotter**

14:30–15:00

Simon Cotter
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A constrained multiscale approach to modelling biochemical systems

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

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

15:00–15:30

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Stochastic simulation of reaction-diffusion processes in living cells on multiple scales

The number of molecules of each chemical species in biological cells is small and the molecules react with each other with a certain probability. A stochastic mesoscopic model of the diffusion and the chemical reactions is therefore more accurate than a deterministic, macroscopic model based on the reaction rate equations. In a computer simulation of a trajectory of the system, the diffusion is often the most computationally expensive part. The diffusion of different species are treated differently in [**1**] in order to reduce the computational cost. Depending on if the copy number is high, intermediate or low the diffusion events are simulated macroscopically, with the tau leap method or with the stochastic simulation algorithm (SSA) by Gillespie in an unstructured mesh covering the cell. The reactions are handled by SSA. Sometimes the mesoscopic model is not sufficiently accurate and a microscopic description is necessary. In such a model, single reacting and diffusing molecules are tracked [**2**]. The molecules move in the unstructured mesh by Brownian motion and are coupled to the mesoscopic model via the reactions [**3**]. Examples from molecular biology will be given.

References.

[1] L. Ferm, A. Hellander, P. Lötstedt, *An adaptive algorithm for simulation of stochastic reaction-diffusion processes*, J. Comput. Phys., 229 (2010), 343-360.

[2] S. Hellander, P. Lötstedt, *Flexible single molecule simulation of reaction-diffusion processes*, J. Comput. Phys., to appear.

[3] A. Hellander, S. Hellander, P. Lötstedt, *Coupled mesoscopic and microscopic simulation of stochastic reaction–diffusion processes in mixed dimensions*, to appear.

15:30–16:00

Konstantinos Zygalakis
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K. Burrage
Computing Laboratory, University of Oxford
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Alternative formulations of the Chemical Langevin Equation

The Chemical Langevin Equation is a Stochastic Differential Equation that describes the time evolution of molecular counts of reacting chemical species D. Gillespie, Journal of Chemical Physics, 113(1), pp 297-306 (2000)). It stands as a bridge between the deterministic ODE model and the discrete probabilistic chemical Master equation.

Suppose n chemical species react through m reaction channels, and the n x m stoichiometry matrix is denoted by S. Gillespie formulated the CLE with m independent standard Brownian motions. In this talk we describe an alternative formulation of the CLE which in general leads to a SDE with a smaller number of Brownian motions. For example if r is the number of pairs of reversible reactions, then in Gillespie's formulation there would be 2r Brownian motions for the reversible reactions, while in our formulation there would only be r. We illustrate that such a reaction leads to significant computational savings.

16:00–16:30

Ovidiu Radulescu
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Guilherme Innocentini
University of Sao Paolo

Timescales of stochastic gene expression

Gene expression exhibits a high degree of stochasticity when studied at the level of individual cells. Even in genetically identical cell populations exposed to a uniform environment, gene activity levels and their phenotypic consequences are subject to random fluctuations that generate cell-to-cell variations and eventually lead to alternative cell fates. This stochastic noise in gene expression is a critical, biologically relevant property of genetic circuits in both microbial and eukaryotic cells.

Many studies underlined the importance of network architecture and of feedback loops for shaping and controlling the gene expression noise. Here we defend a different point of view, according to which in many situations the order relations between different timescales of the biochemical processes are determinant of the expression fluctuations.

In order to cope with network multi-scaleness we developed hybrid stochastic approaches (Crudu et al 2009). These methods distinguish between molecular species according to their abundances. Species in small amounts can be treated as discrete variables, whereas species in large amounts can be considered continuous. For computational ends, hybrid approaches can be used to simplify biochemical mechanisms, accelerate simulation and facilitate model analysis.

Hybrid stochastic approaches can also be used to understand the impact of multi-scaleness on the expression noise in gene networks. We distinguish between two situations referred to as normal and inverted time hierarchies. The noise can be buffered by network feed-back in the first situation, whereas can have rich, often counterintuitive behaviour in the latter.

The theoretical results are supported by recent experimental findings concerning stochastic noise in the bacterium catabolite repression (Ferguson et al).

References.

[1] A.Crudu, A.Debussche, and O.Radulescu, BMC Systems Biology (2009) 3:89.

[2] M.L. Ferguson, D. Le Coq, M. Jules, B. Chun, S. Aymerich, O. Radulescu, N. Declerck, C.A. Royer, submitted.

MINI-SYMPOSIUM 17

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents I

Tuesday, June 28, 17:00, *Room*: **UA1**

Organizers: **Harel Dahari, Avidan Neumann**

17:00–17:40

Avidan U. Neumann
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Tal Olshak
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Deterministic and Stochastic Multi-level Modeling of Hepatitis C Viral Kinetics and Resistance Evolution

Mathematical models of viral dynamics and resistance evolution have brought important insights for understanding the treatment of HIV, HBV and HCV viral infections. However, current models of in vivo anti-viral therapy (CI models) consider only cell to cell infection dynamics, disregarding the impact of intra-cellular replication dynamics. This class of models shows either viral decline with non-resistant viral strains or a permanent viral rebound once a phenotypically resistant strain evolves. Indeed, these are the patterns observed for HIV, where intra-cellular replication has less of an impact because integrated viral DNA is a static replication unit and the various resistance events occur at the time scale of cell infection. However, other patterns of viral evolution kinetics, which are contradictory to the current models, were observed during direct anti-viral therapy against HCV, where intra-cellular dynamics play an important role.

We have therefore developed a novel model (Guedj and Neumann, 2010) for resistance evolution, which includes viral dynamics and evolution in both the intracellular replication level and the cell-infection level (ICCI model). As a consequence of the complex interaction between the two levels of viral dynamics, the ICCI model predicts a rich repertoire of viral kinetics and resistance evolution patterns. In particular, we predict that continuous viral decline is possible even if a phenotypically resistant strain has emerged. Furthermore, we show that a resistance related viral breakthrough could be merely transient and nevertheless resolved. In both cases, counter-intuitively to our experience with HIV, viral eradication may be achieved even with a phenotypically resistant virus.

In addition, the ICCI model allows for rapid emergence of resistance evolution without the need for rapid turnover of infected cells, i.e. new cells are not needed to be available for infection by resistance virus. This is due to the fact that the intra-cellular replication space can be freed for evolution to resistant virus within the cells that are already infected. This theoretical possibility was verified also by stochastic modeling of the intra-cellular resistance evolution with a fixed population of infected cells. Furthermore, stochastic simulation of the ICCI model shows how different patterns of resistance evolution occur as function of the intra-cellular parameters. These results elucidate what the important parameters to measure empirically in order to understand what kind of resistance patterns will occur during treatment.

17:40–18:00

Lior Strauss
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Avidan U. Neumann
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Distributed Intra-Cellular Model of Hepatitis C Viral Replication and Resistance Evolution

The new generation of direct acting anti-viral (DAA) drugs for HCV led to the need for mathematical models that take in consideration the intra-cellular drug effects within clinical virology data. We have recently introduced the ICCI model that integrated the intra-cellular level of replication and resistance evolution processes with the cellular infection level (Guedj and Neumann, 2010). However, the ICCI model used a mean-field approach to treat all infected cell as the same dynamics, which we know is not accurate. Here, we present a new model (DIC) that describes the intra-cellular level dynamics integrated into the cell infection level whle taking into consideration the distribution of infected cells as function of the number of replication complexes in each cell. The DIC model shows that main novel findings of the ICCI model hold even when the mean-field assumption is released. Most importantly, the model allows for 2 modes of viral decline: either the delta model, where long term viral decline slope is governed by the loss of infected cells, or the gamma mode, where the viral decline is more rapid and related to the intra-cellular loss of replication complexes. Furthermore, the DIC model shows that while on the delta mode the distribution of cells with different number of replication complexes is held stable, on the gamma mode the distribution of cells is shifting towards intra-cellular clearance. We have also established the properties of the infected cell distribution at steady state. The model was able to show a good fit for a wide range of results observed in real patients treated either with IFN based therapy or DAA combination therapy. In a second part of the work we have established the various resistance evolution patterns observed with the ICCI model hold also without the mean-field assumption. Furthermore, we show how the distribution of

cells with different number and identity, wild-type versus resistant, of replication complexes follows specific patterns during evolution of resistance. These results are important for our understanding of the DAA therapy effect and allowing us to optimize treatment and prevent resistance evolution.

18:00–18:20

Jeremie Guedj
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Harel Dahari
Uni of Illinois at Chicago
Alan Perelson
Los Alamos National Laboratory, NM, USA

Determinants of the early hepatitis C viral decline after treatment initiation

The standard model of HCV infection and treatment (Neumann et al., 1998, Science 282(5386):103-107) has played an important role in the analysis of HCV RNA decay after the initiation of interferon (IFN)-based therapy. Using this model and assuming that IFN rapidly reduces the average rate of virion production, it has been possible to estimate the antiviral effectiveness of therapy, as well as to estimate the rate of HCV clearance rate. However it will be shown that this model cannot predict the early viral decline observed with some new direct-acting antiviral (DAA) agents if one uses the HCV clearance rate estimated during IFN-based therapy, which hints that the determinants of HCV decline under treatment may not be fully understood.

Indeed one limitation of the standard model is that the intracellular viral replication, which is directly targeted by DAA agents, is not taken into account. In order to provide a more comprehensive understanding of the determinants of the early viral decline after treatment initiation, a new multi-scale model that considers both intra- and extra-cellular level of infection will be introduced. Simulation studies will show that in the framework of this model, the analysis of HCV RNA decay allows to one to dissect the antiviral effectiveness in blocking different stages of viral replication. Based on data from several clinical trials, HCV kinetics under different classes of DAAs will be compared and the implications of this new approach for the estimation of the HCV clearance rate will be discussed.

18:20–18:40

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PK-PD Models for viral kinetics of combination treatments in viral hepatitis

Even in the era of direct anti-viral agents, interferon-based combination treatments are very important. It is well known that serum levels of long-acting interferons can vary considerably and that PK of interferon has an observable influence on viral kinetics also in combination treatment. Therefore, reliable viral kinetic modeling of interferon-based treatments should deal with non-constant treatment efficacies based on PK-PD models.

The first topic of the talk will focus on modeling results which analyze the effect of different PK and treatment schedules of long-acting interferons on the treatment efficacy and the development of resistance. Overall, high or low peak-to-trough levels of the PK of interferon has only minor influence on the development of resistance as long as the overall interferon efficacy is not changed.

Secondly, we will illustrate that modeling PK of direct antivirals can be quite challenging and simple open one-compartment models may be too simplistic to obtain reliable modeling results which fit with observed PK profiles.

Besides some theoretical background and illustration of simulation results, we will also show some clinical data analysis where a full PK-PD approach can give some indications how to optimize treatments.

18:40–19:00

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Paul Panorchan
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The use of viral dynamics modeling to optimize the design of a Phase Ib trial, facilitate its analysis, and inform the decision making for the development of directly acting HCV compounds

Hepatitis C virus (HCV) causes a chronic infection of the liver, and leads to fibrosis, cirrhosis, and in some patients to hepatocellular carcinoma. Current standard of care (pegylated interferon plus ribavirin for 48 weeks) is an arduous regimen for the patient and has a cure rate of only 50 % in genotype 1 (GT 1) patients. Therefore, in recent years there has been significant effort to develop directly acting antivirals that will have a substantially higher rate of cure and require a shorter period of treatment. This presentation will describe how we used pharmacokinetic and viral dynamics modeling to design the duration of treatment in a Phase Ib clinical trial of an HCV NS5B polymerase inhibitor in GT 1a, 1b, and 3 patients, and to determine the optimal sampling times both during and after treatment. Quantitative analysis of the resulting viral load data led to a much clearer understanding of the response across genotypes and supported the decision making process in clinical development.

MINI-SYMPOSIUM 18

Modeling viral hepatitis dynamics in-vivo and in-vitro in the era of direct anti-viral agents II

Wednesday, June 29, 08:30, *Room*: **SP1**

Organizers: **Harel Dahari, Avidan Neumann**

08:30–09:10

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

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

09:10–09:30

Jun Nakabayashi
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Mathematical models of the intracellular replication and within host evolution of HBV and HCV

Hepatitis virus type B (HBV) is a major causative agent of acute and chronic hepatitis. Especially, chronic hepatitis is a major risk factor of liver cirrhosis and hepatocellular carcinoma. During the long time course of chronic hepatitis, severity of hepatitis varies depending on the viral load. It is important to estimate the viral kinetics of HBV for the prediction of the outcome of hepatitis. Though the detailed mechanism of HBV replication is revealed according to the development of molecular biological technique, how reproduction rate of HBV is determined in single cell level had not been clear yet. To investigate the intracellular replication dynamics of HBV, a mathematical model of HBV replication process is constructed. And how the long time course of hepatitis is affected by within host evolution of HBV was investigated by using an evolutionary simulation [1]. From the analysis of our model, the condition for the exacerbation of hepatitis during the chronic hepatitis is obtained. It is shown by our model that the waiting time for release of newly produced virion from infected cell plays critical roles for determining the clinical course of hepatitis. Now, a mathematical model of HCV is additionally constructed to compare with HBV.

In the intracellular replication of virus, the viral genome should play several distinguished roles, as a template of the genome replication, as a component of the viral particle and as a template for the viral gene expression. Because it is impossible to simultaneously play many roles, it is necessary to optimally distribute the viral genome to these roles for the efficient replication. The optimum distribution of genome is common problem for many viruses. HBV is DNA virus, on the other hand, HCV is the positive strand RNA virus, and their replication patterns are quite different. HBV and HCV respectively achieve the optimum distribution of genome by different regulatory mechanism. The intracellular replication dynamics of HBV and HCV are drastically changed by the distribution of genome. I would like to show how the replication dynamics of HBV and HCV is affected by the distribution of their genome. And I would like to discuss how the long time course of chronic hepatitis is affected by the intracellular dynamics and within host evolution of HBV and HCV in this mini-symposium.

References.

[1] Nakabayashi J. and Sasaki A, *A mathematical model of the intracellular replication and within host evolution of hepatitis type B virus: Understanding the long time course of chronic hepatitis.* J Theor Biol. 2011 **269** 318-329.

09:30–09:50

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Modeling Early Events in Hepatitis Delta Virus Infection

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

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

09:50–10:10

Narendra Dixit
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Pranesh Padmanabhan
Indian Institute of Science, Bangalore, India

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

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

10:10–10:30

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

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

treatment duration might be very helpful for decision making after a lead in phase of Peg-IFN+RBV therapy when the direct antiviral agents will be available, thus optimizing the cost-effectiveness of the new antiviral therapies.

MINI-SYMPOSIUM 19

Statistical methods in computational neuroscience II

Wednesday, June 29, 17:00, *Room*: **UA2**

Organizer: **Susanne Ditlevsen**

17:00–17:40

Sonja Grün
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Scales of Neuronal Data and the Problem of Interaction

Cortical information processing was suggested to be performed via functional groups of cells, called cell assemblies [**1**]. Theoretical work supported this idea by indicating that synchronous input to a neuron is much more effective in emitting a spike than uncorrelated input. Although this coding scheme was controversially discussed, first supporting indications for spike synchrony were published, soon after techniques became available to simultaneously record from more than a single neuron. Presence of excess spike synchrony was found to be dynamic and related to behaviorally relevant instances in time. As expressed by different recording techniques (e.g. action potentials, local field potential (LFP)), the brain exhibits interesting phenomena on several spatial and temporal scales. However, the relationship of the various measures of cortical activity now experimentally available is largely unknown. The characterization of the joint signature of cortical processing in functionally meaningful contexts provides insight into the relevant scales and the potentially hierarchical organization of brain processes.

The mechanisms underlying neuronal coding and in particular the role of temporal spike coordination are hotly debated. However, this debate is often confounded by an implicit discussion about the use of appropriate analysis methods. To avoid wrong interpretation of data, the analysis of simultaneous spike trains for correlation needs to be properly adjusted to the features of experimental spike trains. Neuronal spiking activity is typically not stationary in time, but neurons 'respond' by changes in their firing rates to external stimuli or behavioral contexts. Also, data are not stationary across trials, but the statistical features may change during the experiment. Parametric approaches may be applied to experimental data to account for these aspects, however, the data may also contain features (e.g.

deviation from Poisson) that do not allow an analytical treatment or parametric testing. Ignorance of such features present in parallel spike trains are potent generators of false positives, but can be avoided by including those features in the null-hypothesis of the significance test. In this context the usage of surrogate data becomes increasingly important to deal with such complex data [**2**].

The assembly hypothesis implies that entities of thought or perception are represented by the coordinated activity of (large) neuronal groups. However, whether or not the dynamic formation of cell assemblies constitutes a fundamental principle of cortical information processing remains a controversial issue of current research. While initially mainly technical problems limited the experimental surge for support of the assembly hypothesis, the recent advent of multi-electrode arrays reveals fundamental shortcomings of available analysis tools. Although larger samplings of simultaneous recordings from the cortical tissue are expected to ease the observation of assembly activity, it implies on the other hand an increase in the number of parameters to be estimated. It is usually infeasible to simply extend existing methods to such massively parallel data due to a combinatorial explosion and a lack of reliable statistics if individual spike patterns are considered. Due to limitations in the length of experimental data, in particular in respect to stationarity, all parameters of the full system cannot be estimated. Thus new concepts need to be developed and I will give a short review on the methods we developed that allow the analysis of massively parallel (hundred or more) spike trains for correlated activities [**3**].

Alternatively, one may directly observe a measure that reflects the activity of populations of neurons, as does the local field potential (LFP). It has been conjectured that LFP oscillations may represent an alternative network-averaged signature of assembly activations. With the aim to test this hypothesis we study and found that in different species and brain areas spikes are locked to the LFP and the locking may even increase with learning. Furthermore, we found that excess spike synchrony is much better locked to the LFP than chance synchronous events or individual spikes clearly indicating that significant excess spike synchrony reflects coordinated network activity on larger scales as expressed by the LFP [**4**].

In this presentation I will give an overview of the potential obstacles in the correlation analysis of parallel neuronal data and possible routes to overcome them.

References.

[1] Hebb. The organization of behavior. John Wiley, 1949
[2] Grün (2009) Data-driven significance estimation of precise spike correlation. J Neurophysiol, 101, 1126-1140
[3] Grün & Rotter (eds) Analysis of parallel spike trains. Springer, 2010
[4] Denker, Roux, Lindén, Diesmann, Riehle, Grün (2011) Local field potentials reflects surplus spike synchrony. Cerebral Cortex (in press)

17:40–18:00

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Made-to-Order spiking neuron model for a variety of cortical neurons

Information is transmitted within the brain through various types of neurons that respond differently to the same input. The Hodgkin−Huxley model has been revised by including ionic channels that account for typical neuronal firing phenomena. However, estimating parameters of the Hodgkin−Huxley models from experimental data is a notoriously difficult. Furthermore, the computational costs of these models are high, which hinders performing a simulation of massively interconnected neural networks.

Here we introduce a computationally fast spiking neuron model [1] that is capable of accurately predicting a rich variety of spike responses. We also developed a procedure for optimizing model parameters. The key features of the new model are a non-resetting leaky integrator and an adaptive threshold equipped with fast (10 ms) and slow (200 ms) time constants. The model can be easily tailored to various cortical neurons, including regular-spiking, intrinsic-bursting, and fast-spiking neurons, by simply adjusting three parameters. Both the high flexibility and low computational cost would help to model the real brain reliably and examine how network properties may be influenced by the distributed characteristics of component neurons.

References.

[1] R. Kobayashi, Y. Tsubo, S. Shinomoto, *Made-to-order spiking neuron model equipped with a multi-timescale adaptive threshold.* Front. Comput. Neurosci. **3** 9.

18:00–18:20

Susanne Ditlevsen
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Parameter estimation of the stochastic Morris-Lecar model with particle filter methods

Stochastic Morris Lecar model is a well-known two-dimensional stochastic differential equation (SDE) describing neuronal activity by taking into account the random behavior of neurons. Drift and volatility functions of this SDE are non-linear functions of the process and depend on unknown physiological parameters. Statistical estimation of these parameters from neuronal data is very difficult. Indeed, neuronal measurements correspond to discrete observations of only the first coordinate of the system. Furthermore, the SDE has no explicit solution. We propose an estimation method based on a stochastic version of the EM algorithm, the SAEM algorithm, which requires the simulation of the hidden coordinate conditionally to the observations. We propose to perform this simulation step with a Particle Markov Chain Monte Carlo algorithm. We illustrate the performance of our estimation method on simulated and real data.

18:20–18:40

Martin Paul Nawrot
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Exploring the Relation of Interval and Count Variability in Neural Spike Trains

Understanding the nature and origin of neural variability at the level of single neurons and neural networks is fundamental to our understanding of how neural systems can reliably process information. At the level of single neuron spike trains we discern two aspects of variability. The variance of inter-spike intervals (ISIs) reflects intra-trial variability on a relatively fast time scale of tens to hundreds of milliseconds. In contrast, the variance of the number of action potentials counted during repeated experimental observations reflects a variability on a comparably slow time scale of seconds or even minutes. On theoretical grounds, interval and count statistics of stochastic point processes are fundamentally related. Analyzing their empirical relation in neural spike trains thus allows to better characterize the observed neural spiking processes [1].

To estimate inter-spike interval variability I employ the empirical coefficient of variation (CV) defined as the standard deviation of ISIs normalized by the average ISI. The empirical count variability is measured by the Fano factor (FF) defined by the ratio of count variance and mean count as estimated during repeated observations. For general stationary non-renewal processes we obtain the relation

$$\lim_{T\to\infty} \mathsf{FF} = \mathsf{CV}^2\Big(1 + 2\,\xi\Big) \qquad \text{with} \quad \xi = \sum_{i=1}^{\infty} \xi_i\,, \tag{1}$$

where ξ_i denotes the ith-order serial interval correlation coefficient. In the case of a renewal process Eq.(1) simplifies to $\mathsf{FF} = \mathsf{CV}^2$. I will discuss how deviations from this equality can be interpreted with respect to non-renewal properties and non-stationarity of the observed spiking processes [1].

The relation Eq.(1) transfers to the population activity of superimposed point processes, which allows to deduce the average CV^2 and serial correlation ξ of single neuron spike trains from the so-called multi unit activity obtained in extracellular recordings [2].

References.

[1] M.P. Nawrot (2010) *Analysis and Interpretation of Interval and Count Variability in Neural Spike Trains.* In: S. Grün, S. Rotter (eds.), Analysis of Parallel Spike Trains, Springer Series in Computational Neuroscience **7** 37–58.

[2] F. Farkhooi, E. Muller, M.P. Nawrot (2010) *Adaptation Reduces Variability of the Neuronal Population Code.* arXiv: **1007.3490**

18:40–19:00

Klaus Kähler Holst
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A Latent Variable Model for brain serotonin levels as measured by cerebral serotonin transporter and 5-$\mathbf{HT_{2A}}$ receptor binding *in vivo*

Today, it is not possible to non-invasively measure the extracellular levels of serotonin (5-HT) *in vivo*. However, indirect measurements can be obtained by positron emission tomography (PET) techniques. A non-linear structural equation model is proposed for describing the association between 5-$\mathrm{HT_{2A}}$ receptor binding and serotonin (5-HT) transporter binding as measured by PET imaging. The approach is based on a biological model where the 5-$\mathrm{HT_{2A}}$ receptor and serotonin transporter measurements are expressed non-linearly by a common regulator, e.g. the raphe serotonergic output. The proposed model makes it possible to study the association between latent brain 5-HT levels and other end-points, for instance development of mood disorders.

Methods for obtaining approximate maximum likelihood estimates are discussed and new model diagnostic methods based on cumulative residuals are presented.

MINI-SYMPOSIUM 20

Multiscale mathematics of liver: bridging molecular systems biology to virtual physiological human scale

Wednesday, June 29, 11:00, *Room*: **AM4**

Organizers: **Dirk Drasdo, Stefan Hoehme**

11:00–11:40

Peter Hunter
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Modelling infrastructure for the VPH/Physiome project

This talk will describe the model and data encoding standards and their associated databases and tools that are being developed as part of the VPH/Physiome project.

11:40–12:05

Hermann-Georg Holzhuetter
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Mathematical modelling of liver metabolism — do we need a multi-scale approach?

The liver is the central metabolic organ of the human organism authoritatively involved in the detoxification of xenobiotics (drugs), the homeostasis of numerous blood compounds and production of anti-inflammatory agents. Most of these metabolic functions are accomplished by hepatocytes comprising about two thirds of liver cells. Therefore, mathematical modelling of liver metabolism hitherto has widely focused on the single hepatocytes. However, hepatocytes arranged along the same supporting vessel have different access to oxygen, nutrients and hormones in the blood and therefore differ in their functional capacities. Irregularities of the vascular tree and regional partial occlusions of blood vessels (e.g. caused by swollen

cells due to lipid accumulation) may entail that within the organ normoxic and partly ischemic regions coexist. Furthermore, the molecular processes underlying complex physiological liver functions proceed at different time scales: Seconds for the hormonal initiation of glycogen degradation, some weeks for liver regeneration after partial hepatectomy and several months or even years for the development of a non-alcoholic fatty liver. Finally, the metabolic state of hepatocytes is affected by cellular contacts with each other and signals received from other hepatic cells, e.g. endothelial cells or macrophages. These are aspects that necessitate to study the metabolism of the liver on the basis of a multi-scale model that covers different spatial and temporal scales. This talk outlines the basic structure of such a liver model and presents some first results.

12:05–12:30

Stefan Hoehme
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Dirk Drasdo
University of Leipzig, INRIA Paris
Jan Hengstler
IfADo Dortmund

Regeneration after partial hepatectomy: from cell to organ scale

The liver is a vital organ with a wide range of functions. It plays a key role in detoxification of the blood and is essential for most metabolic functions of the body. One of the outstanding features of the liver is its capacity to regenerate a loss of large parts of its mass within days. This rapid regeneration is of utmost importance for patient survival for example after partial hepatectomy, a process where parts of the liver are surgically removed for example during liver transplantation or the treatment of liver cancer. In liver, function and architecture are tightly coupled. Therefore, a deep understanding of liver regeneration requires an understanding of how functional components like hepatocytes or blood vessels and their spatial organization together affect the regeneration process. In order to study regeneration after partial hepatectomy, we advanced the single-cell based spatial-temporal model in 3D established in [1]. The model is constructed based on experimental data, in particular confocal laser scans and whole slide scans, that were quantified by a novel image processing and analysis chain. It now spans from cellular scale up to organ scale.

The talk introduces the model along with the methods developed to construct it and presents first results obtained by model simulations.

References.

[1] Hoehme, S., Brulport, M., Bauer, A., Bedawy, E., Schormann, W., Gebhardt, R., Zellmer, S., Schwarz, M., Bockamp, E., Timmel, T., G. Hengstler, J.G., and Drasdo, D. (2010). Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration. Proc. Natl. Acad. Sci. (USA), 107(23), 10371-10376.

12:30–12:55

Tim Ricken
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Uta Dahmen
University Hospital of Essen
Olaf Dirsch
German Heart Institute Berlin

A biphasic Finitee-Element-Model for Sinusoidal Liver Perfusion Remodeling

Liver resection can lead to focal outflow obstruction due to transection of hepatic veins. Outflow obstruction may cause additional damage to the small remnant liver. Drainage of the obstructed territories is reestablished via dilatation of sinusoids. Subsequently sinusoidal canals are formed draining the blood from the obstructed territory to the neighboring unobstructed territories. We raised the phenomenological hypothesis that the blood pressure gradient is the main driving force for the formation of sinusoidal vascular canals. Based on the theory of porous media we generated a biphasic mechanical model to describe this vascular remodeling process in relation to the variable pressure gradient. Therefore, we introduced a transverse isotropic permeability relation as well as an evolutional optimization rule to describe the relationship between pressure gradient and the direction of the sinusoidal blood flow in the fluid phase. As a next step, we developed a framework for the calculation concept including the representation of the governing weak formulations. The governing equations of the model are developed on the basis of a consistent thermo-mechanical approach including the momentum and mass balances of both solid and fluid phases. The mathematical concept describes the motion of the solid phases coupled by the fluid transport due to pressure development. The theoretical formulations are implemented into the finite element code FEAP. Then, we examined a representative numerical example with simulation of the blood flow under both conditions, the physiological situation as well as after outflow obstruction. We based our simulation on the concept of mechanical-induced remodeling. We incorporated the fluid directly into the model as a mixture together with the solid. We hypothesized that the reorientation of the sinusoidal flow and the remodeling of the sinusoidal structure depends mainly on the fluid pressure and the fluid pressure gradient caused by the outflow obstruction. We tested this hypothesis with a numerical simulation and compared the results to the experimental findings. As we did not implement liver resection in the mathematical model presented here, but concentrated on focal outflow obstruction only, liver growth (=regeneration) was not addressed. Doing so, we were able to reproduce numerically the experimentally

observed process of reestablishing hepatic venous drainage via redirection of blood flow and formation of new vascular structures in respect to the fluid flow. The calculated results support the hypothesis that the reorientation of blood flow mainly depends on the pressure gradient. Further investigations are needed to determine the micromechanical influences on the reorientation of the sinusoids.

MINI-SYMPOSIUM 21

Bridging the Divide: Cancer Models in Clinical Practice

Thursday, June 30, 11:30, *Room*: **AM4**

Organizers: **Marisa Eisenberg, Harsh Jain**

11:30–12:10

Avner Friedman
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Therapeutic approaches to brain cancer

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

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

12:10–12:30

Michael Meyer-Hermann
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Harald Kempf
Department of Systems Immunology, Helmholtz Centre for Infection Research

Optimised cancer treatment using cell cycle synchronisation with heavy ion irradiation

Cancer is a leading cause of death worldwide. As a consequence a multitude of experimental and mathematical studies on cancer growth and a diversity of treatments are being developed. Among these is tumour irradiation with heavy ions. While this novel methodology was restricted to research institutes for a long time, this treatment became a full part of clinical reality now.

We present an agent-based approach to the modelling of cellular dynamics within tumour spheroids that is based on experimentally accessible parameters and thus is able to take advantage of experimental data from irradiation experiments. As the model architecture is lattice-free and average-free, it can be considered to be a realistic representation of tumours. The model grows a tumour from a single malignant cell and the dynamics of tumour growth in response to irradiation protocols can be tracked. As the model is single cell based we are able to provide an in depth analysis of all possible observables ranging from the cell cycle phase, pressure inside the spheroid, nutrient supply and limitations, up to genetic expression profiles for the intracellular network. Target of our study is a detailed examination of the dynamical reaction of tumours to heavy-ion irradiation treatment.

It is found that irradiation treatment induces a variety of dynamical reactions within a tumour. Reoxygenation of the tumour volume and a decrease in pressure due to cell death lead to excessive regrowth after irradiation. As expected fractionation of the radiation dose changes the degree of tumour control considerably depending on the applied fractionation scheme. A pronounced resynchronisation of the cell cycle within the tumour after irradiation is found which could be exploited in order to administer follow-up treatments in accordance to the cell's most radiosensitive phases. This result has direct implications for experimental studies and eventually for clinical trials.

12:30–12:50

Marisa Eisenberg
Mathematical Biosciences Institute, The Ohio State University
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Modeling Remnant Ablation Protocols in Thyroid Cancer

Thyroidectomy of pediatric and adult patients with differentiated thyroid cancer is typically followed by radioactive iodine treatment to ablate thyroid remnants. A common protocol for this followup treatment is to give replacement thyroid hormone T_4 after surgery as the patient recovers, and then withdraw replacement hormone for 2-3 weeks to raise TSH levels to 30 mU/L or higher, as radioiodine uptake is improved when TSH levels are high. Patients may be quite sick and impaired during these several weeks, due to the severe clinically hypothyroid condition generated. To explore whether this protocol can be improved, we adapted a physiologically based ODE model of adult hypothalamic-pituitary-thyroid axis regulation to incorporate severe hypothyroid effects, as well as adjusting the parameters to model pediatric

thyroid cancer using pediatric clinical data. We simulated a range of replacement protocols to establish withdrawal times needed to raise TSH levels > 30 mU/L, each for a range of tissue remnant percentages based on typical clinical remnants after thyroidectomy. We found that use of T_3-only after thyroidectomy, rather than T_4, can substantially reduce the withdrawal time needed prior to radioiodine ablation therapy, thereby decreasing patient morbidity.

12:50–13:10

Harsh Jain
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Avner Friedman
Mathematical Biosciences Institute, Ohio State University
Steven Clinton
Comprehensive Cancer Center, Ohio State University
Arvinder Bhinder
Comprehensive Cancer Center, Ohio State University

The Impact of Androgen Ablation on Mutation Acquisition in Prostate Cancer

Prostate cancer (CaP) is the second most common cancer in American men. Although the majority of patients diagnosed with CaP are cured with primary treatment, it remains the second lead cause behind only lung cancer, of male cancer-related deaths in the western world. A few features set it apart from other cancers; it develops slowly over a period of years; CaP cells are dependent on male sex hormones for growth; treatment in the form of continuous androgen ablation fails due to the emergence of castrate-resistant CaP cells. Therefore, it has been proposed that intermittent androgen ablation therapy might be a better strategy for treating CaP. I present a model of prostate growth in humans, which can simulate the onset of CaP, as well as explain the emergence of resistance in response to therapy. Our model shall incorporate a variety of cell types such as healthy and CaP cells, as well as detailed biochemical pathways crucial to the growth of these cells. Fits to individual patient data will also be presented. By being able to distinguish between various drug actions, and being fitted to individual patient data, we hope to develop a truly prescriptive tool to aid physicians in treatment choices for CaP patients.

13:10–13:30

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Modelling the Spatio-Temporal Distribution of Drugs in Tumours

The distribution of drugs in tumours is studied in a multiscale modelling framework. On the molecular scale we analyse the random walk of drug molecules through subsystems of the vascular network, from which molecules extravasate into the tissue, diffuse in the interstitial space, bind to receptors on the surfaces of tumour cells and finally induce apoptosis. Knowledge gained on the molecular scale, like diffusion coefficients and reaction rates, is then incorporated in a multiscale model of vascular tumour growth and angiogenesis. The model combines blood flow, angiogenesis, vascular remodelling, interactions between normal and tumour cells and diffusive nutrient / VEGF transport as well as cell-cycle dynamics within each cell. To study the effects of therapies, the model enables us to include a drug specific intracellular response (modelled by ordinary differential equations) and link it to an extracellular drug concentration that is described by reaction-diffusion equations. Drugs are supplied by the vascular system and adsorbed by normal and cancer cells, as well as decomposed by natural decay.

The numerical simulations let us analyse how the heterogeneity of the tumour structure influences the drug distribution and lead to predictions of therapeutic efficacy.

MINI-SYMPOSIUM 22

Bridging Time Scales in Biological Sciences

Saturday, July 2, 14:30, *Room*: **AM8**

Organizers: **Konstantin Fackeldey, Susanna Röblitz, Marcus Weber**

14:30–15:10

Konstantin Fackeldey
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Efficient Simulation in Protein Modelling and Non-equilibrium Processes

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

15:10–15:35

Volkmar Liebscher
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Stephan Thober
Helmholtz-Centre for Environmental Research Leipzig

The Quasi-steady state hypothesis for stochastic models of enzyme kinetics

In a stochastic version of the Briggs-Haldane equations, we show that the classical quasi-steady state hypothesis corresponds to a averaging principle or local ergodic theorem for the fast enzymatic reaction. This way, we obtain a more natural explanation of the Michaelis Menten kinetics on the slow time scale. Some more detailed estimates are presented, too.

15:35–16:00

Iris Antes
Technical University of Munich
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Hierarchical approaches for the investigation of biomolecular recognition

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

16:00–16:25

Susanna Röblitz
Zuse Institute Berlin (ZIB)
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Rare events in chemical reaction systems

Chemical kinetics can usually be described by a deterministic system of ordinary differential equations. However, when the concentrations of certain species become small, stochastic fluctuations play an important role, which can be modeled by the chemical master equation (CME). For some systems, the steady state solution of the CME is a multimodal distribution with small transition rates (rare events), a situation comparable to metastable molecular conformations. In this talk we will present a mesh-free discrete Galerkin method for the solution of the CME, which allows for an efficient computation of transition rates. In particular, we will discuss the future potential of this method for the simulation of endocrinological networks.

MINI-SYMPOSIUM 23

Delay Differential Equations and Applications I

Friday, July 1, 14:30, *Room*: **AM4**

Organizers: **Urszula Foryś, Monika Joanna Piotrowska**

14:30–15:10

Michael C. Mackey
McGill University
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Using mathematical modeling to tailor the administration of chemotherapy and G-CSF

In this talk I will briefly describe recent work that we have carried out using a mathematical model for the regulation of human hematopoiesis to investigate optimal delivery strategies for granulocyte colony stimulating factor (G-CSF) in the treatment of patients with cyclical neutropenia, and to aid patients in the post-chemotherapy phase. Additionally I will discuss optimal ways to deliver chemotherapy.

15:10–15:30

Alberto d'Onofrio
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Malay Banerjee
Department of Mathematics and Statistics Indian Institute of Technology Kanpur, India

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

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

15:30–15:50

Yukihiko Nakata
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Philipp Getto
BCAM-Basque Center for Applied Mathematics
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Analysis of a characteristic equation for a Delay Equation from cell population dynamics

We present Delay Equations describing age-structured cell population dynamics where the cell population is divided into proliferative and quiescent cells. We derived a characteristic equation for an interior equilibrium and analyzed the model in the framework of [**1, 2**]. We will show how to use the characteristic equation to determine stability boundaries for the interior equilibrium in two-parameter space.

References.

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[2] O. Diekmann, Ph. Getto, M. Gyllenberg (2007) Stability and bifurcation analysis of Volterra functional equations in the light of suns and stars. SIAM J Math Anal 39:1023-1069

15:50–16:10

Jacek Miekisz
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Delayed protein degradation does not cause oscillations

It is well known that time delays may cause oscillations in solutions of ordinary differential equations. We would like to point out that the presence of oscillations depends on particular causes of a time delay.

Models with time delays may be divided into two families [1,2]. In social-type models, where individuals react to the information concerning the state of the population at some earlier time, we should expect oscillations. On the other hand, in biological-type models, where some changes already take place in the population at an earlier time, oscillations might not be present for any time delay. We will briefly review two specific examples of evolutionary games - replicator dynamics with time delay [1].

Our main goal is to show that delayed degradation does not cause oscillations as it was recently argued [3]. To do so we propose a new methodology to deal with time delays in biological systems and apply it to simple models of gene expression with delayed degradation [4].

We develop a systematic analytical treatment of stochastic models of time delays. Specifically, we take into account that some reactions, for example degradation, are consuming, that is once molecules start to degrade they cannot be part in other degradation processes. It follows from our rigorous analysis that one should look for different mechanisms than just delayed protein degradation to explain causes of oscillations observed in certain biological experiments.

References.

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16:10–16:30

Philipp Getto
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A differential equation with state-dependent delay from cell population dynamics

The aim of this research is an analysis of the maturation process of stem cell populations. The regulation of this process leads to a description of the population dynamics as a differential equation with state-dependent delay, i.e., an object of great mathematical challenge. We show for this system well-posedness and give some results on the existence of equilibria.

MINI-SYMPOSIUM 24

Delay Differential Equations and Applications II

Saturday, July 2, 08:30, *Room*: **CP3**

Organizers: **Urszula Foryś, Monika Joanna Piotrowska**

08:30–09:10

M.L. Hbid
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Delay in Structured Population Models.

The aim of this work is to put in evidence the onset of delays, distributed delays and state-dependent delays in models, especialy in threshold models for structured population dynamics. A unified approach to these models is provided, based on solving the corresponding balance law (hyperbolic P.D.E.) along the characteristic lines and showing the common underlying ideas. Size and age-structured models in different fields are presented: fish populations, insect populations, cell proliferation and epidemics. Existence and uniqueness results related to such models will be discussed as well as some results of semigroup's properties , of stability, and bifurcation results.

09:10–09:30

Samuel Bernard
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Distributed delays stabilize negative feedback loops

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

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

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

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

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

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

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

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

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

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

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

References.

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09:30–09:50

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Delay can stabilise: population and love affairs dynamics.

It is well known that time delay may lead to destabilisation of a steady state and oscillations may arise due to the Hopf bifurcation. We show that for the system of two equations with one delay the unstable steady state can be stabilised by time delay. Namely, if for delay equal to 0 the steady state is an unstable node or unstable spring, then the steady state may gain stability for larger time delays. We

give a condition which guarantees this kind of behaviour and we illustrate it with some linear and non-linear sociological models of romantic relationship.

09:50–10:10

Monika Piotrowska
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Urszula Foryś
University of Warsaw, Faculty of Mathematics, Informatics and Mechanics

Gompertz model with time delays

We study the influence of time delays on the dynamics of the classical Gompertz model. First we consider the models with one discrete delay introduced in two different ways and next the models with two delays. We present the basic properties of investigated models including the asymptotic behaviour of solutions, the examination of Hopf bifurcation occurrence and stability switches. We also show results for the types of occurring bifurcations. The analytical results are illustrated and completed by numerical simulations.

10:10–10:30

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Mathematical model of bioenergetic process in green plants with delayed argument

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

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

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

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

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

References.

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MINI-SYMPOSIUM 25

Reports from US - African BioMathematics Initiative: Conservation Biology

Saturday, July 2, 14:30, *Room*: **AM4**

Organizer: **Holly Gaff**

14:30–14:50

Holly Gaff
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Sadie Ryan
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Overview: Reports from US - African BioMathematics Initiative: Conservation Biology

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

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

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

This mini-symposium is a product of the initiative that was not part of the original prospectus for funding. The initiative funded a follow-up institute to the originally planned single combined institute and workshop. Faculty who would otherwise not have met each other have been inspired to collaboratively apply for funding to continue teaching these institutes, and to conduct joint research in the future. A minimum of three publications and 5 talks are resulting from student projects formed at these institutes, so far, and established connections to the South African Wildlife College (SAWC) and Kenya Wildlife Services Training Institute (KWSTI) at Naivasha are spawning new ideas and project bases.

14:50–15:10

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Canine Distemper Virus (CDV): Methods for modeling spillover infections for African Wild Dogs (Lycaon pictus) in a multi-host community

Canine Distemper Virus (CDV) is a potentially lethal morbillivirus spread via aerosol. It is common in domestic dogs and also affects many wild carnivores, including lions, hyenas, jackals and African wild dogs (AWDs). The AWD is a critically endangered canid that is known to experience high mortality from epizootics of CDV. AWDs are only known to survive in protected areas in Africa, which they share with lions, hyenas and jackals. Inter-species interactions at shared kill sites provide an opportunity for CDV to spill over from one infected species to another susceptible species. We aim to examine how CDV is transmitted between four different host species (lions, jackals, hyenas and AWDs) within a reserve.

We constructed a heterogeneous deterministic SEIR model to establish a disease-free equilibrium for each species. We then introduced stochasticity to our model to

understand how CDV spreads through multispecies metapopulations. Stochasticity was introduced in the infection process and in the inter-species contact process. Due to variation in collection techniques for demographic data in the literature, our model was compromised since data for some species may already reflect the endemic state of the disease while other species are potentially disease-free. Nevertheless, our model demonstrates a valid method for determining the sources and sinks of disease in a multi-host metapopulation. We also plan to build a contact network model to avoid the issue of mixing endemic host populations with disease-free host populations. These models could be applied to other metapopulation systems to study or prevent disease spillovers between neighboring populations.

15:10–15:30

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Sharon Baruch-Mordo

Using individual-based movement models to investigate mechanism of emergent herding behavior in African buffalo

Ungulate species worldwide have been observed to aggregate into variable-sized temporary or permanent herds. One important thread of research in ecology has been to try to understand why such aggregations occur, and what mechanisms control the dynamics of herding. Most research to date has focused on population-level herding dynamics, and evidence exists for both bottom-up control, wherein herds form as a result of patchy resource distribution, and top-down control, in which predator avoidance controls aggregation dynamics. In this study we used an individual-based model (IBM) to test whether population-level herding patterns emerge from individual-level movement decisions, and to examine the influence of bottom-up mechanisms on this emergent phenomenon. We used African buffalo (Syncerus caffer) in Kruger National Park, South Africa as our focal population, and simulated individual movement based on rules in which each buffalo attempts to meet its daily resource requirements. Our model did not incorporate birth or death processes but focused solely on spatial dynamics. To validate our model we compared herd size distribution observed in our IBM to herd size distributions observed in Kruger National Park between 1985 and 2001. Using IBM we found that herding behavior was an emergent property. We were able to emulate empirical herd size distributions when resources were available at low levels in large parts of the study area but abundant in small scattered areas. Our study demonstrates that empirically-based patterns of herding behavior can emerge from bottom-up mechanisms alone. Our continued research will attempt to elucidate whether predator avoidance behavior can produce similar empirically-validated herding patterns and how a combination of top-down and bottom-up mechanisms might change population-level herding dynamics.

15:30–15:50

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Adel Ferchichi
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The effects of disturbance, fire, and elephants on savanna woodlands

The extent to which ecological systems are experiencing disturbance and change in function and structure is critical for the long-term conservation of biological diversity. The savanna, the dominant ecosystem of sub-Saharan Africa, is characterized by the coexistence of a variety of woody plants and grasses. Vegetation modification from woodland to grassland has most often been attributed to the coupled effects of elephant herbivory and fire. Therefore, to better inform management strategies for woodland savanna ecosystems, the objective of our study was to model the impact of fire and herbivory on tree survival. We used density-dependent, stochastic Lefkovitch matrix models to simulate the population dynamics of woody plants in Kruger National Park, Mpumalanga, South Africa. Our model was run on biannual time steps, including wet and dry seasons, for 50 years. Elephant herbivory was assumed to occur every dry season, while the occurrence of fire was stochastic. We tested different frequencies and intensities of fire and herbivory in our model, and also altered the variance of the fire parameters. Preliminary results indicated an average fire return interval of 3-4 years produced an approximately stable population growth. Our sensitivity analysis showed that under baseline conditions adult tree survival was the most important factor affecting population growth rates. We also found that different fire regimes, varying intensities of disturbance, and even altering the variance of these parameters can profoundly affect the pattern of savanna structure over time. Therefore, our results indicate that savanna woodland structure is sensitive to both the frequency and intensity of disturbance which has important management implications.

15:50–16:10

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

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

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

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

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

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

16:10–16:30

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Looking to the future: how to progress to success from the US-Africa Biomathematics Initiative

In this session, we have heard reports from the US-Africa Biomathematics Initiative's two Advanced Studies Institutes (ASIs) for Conservation Biology. The question remains, what happens next? The original goals of the initiative were to bring together US and African students to examine questions in conservation biology in Africa, using a combination of mathematical and biological approaches. This goal has been achieved and has produced results beyond original expectations. In this talk, we will address how to progress from here: the process of publication, the potential for future work, communicating results back to conservation biologists. We will also discuss how participants will take this experience back to their home institutions, and avenues for sharing the benefits of the experience. We hope that this will enable us all to distill important lessons in both collaboration and higher education pedagogical and communication abilities.

MINI-SYMPOSIUM 26

Mathematical models of gene regulation

Tuesday, June 28, 11:00, *Room*: **AM1**

Organizer: **Tomas Gedeon**

11:00–11:40

Michael C. Mackey
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Marta Tyran-Kamińska
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Molecular distributions in gene regulatory dynamics

Extending the work of Friedman et al.(2006), we study the stationary density of the distribution of molecular constituents in the presence of noise arising from either bursting transcription or translation, or noise in degradation rates. We examine both the global stability of the stationary density as well as its bifurcation structure. We have compared our results with an analysis of the same model systems (either inducible or repressible operons) in the absence of any stochastic effects, and shown the correspondence between behaviour in the deterministic system and the stochastic analogs. We have identified key dimensionless parameters that control the appearance of one of two stable steady states in the deterministic case, or unimodal and bimodal densities in the stochastic systems, and detailed the analytic requirements for the occurrence of different behaviours. This approach provides, in some situations, an alternative to computationally intensive stochastic simulations. Our results indicate that, within the context of the simple models we have examined, bursting and degradation noise cannot be distinguished analytically when present alone.

11:40–12:00

Dagmar Iber
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From Gene Networks to Tissue Engineering: Computational Models of Pattern Formation

Limb bud development has long served as a paradigm of organogenesis and pattern formation. Decades of genetic and biochemical studies provide us with a wealth of information about the molecular circuits that control cell expansion and position-dependent cell differentiation in the developing limb bud. In spite of much detailed biological knowledge and much theoretical work a detailed mechanistic understanding of how the genes and regulatory circuits interact to control limb organogenesis is still lacking. In collaboration with the Zeller group at the Department of Biomedicine of the University of Basel we are developing detailed computational models for limb development in mice. By combining mathematical modeling with experimentation we seek to understand how key processes at the microscopic level interact to give rise to patterning at the macroscopic level.

The signaling pathways (Fgf, Shh, Bmp, Gremlin) that regulate limb bud development are strikingly similar to those that regulate lung morphogenesis. Based on the model for limb development we have also developed a mechanistic model for the regulatory network that governs lung branching. The branching of the bronchi in the lungs is highly stereotyped and results from a highly regulated process that restricts the types and sequence of branching modes.

In the long run we seek to use our mechanistic insights in the engineering of tissue and bone.

12:00–12:20

Thomas Höfer
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A recruitment-reaction model for chromatin-associated regulatory processes

Computational frameworks for gene regulation have focused on the sequence-specific binding of transcription factors and the subsequent recruitment of cofactors to DNA. Combining mathematical modeling and quantitative experimentation, we have developed kinetic models for gene regulation and DNA repair in mammalian cells. The experimental data forced the inclusion of biochemical reaction steps executed by the recruited proteins. I will show how the resulting recruitment-reaction models make testable predictions on rate, fidelity and memory in chromatin-associated regulatory processes.

12:20–12:40

Tomas Gedeon

Montana State University
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Lisa Davis
Montana State University

Modelling delays induced by transcription and translation

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

12:40–13:00

Felix Naef
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Calibrating stochastic models of transcriptional bursting in single mammalian cells

In both prokaryotes and eukaryotes, stochasticity in the dynamics of mRNA and protein expression has important consequences on gene regulation and on non-genetic cell-to-cell variability. Here, we show how discontinuous transcription of mammalian genes leads to broad spectra of temporal bursting in mRNA synthesis. To monitor transcription at high temporal resolution, we designed chromosomally-integrated vectors encoding a very short-lived luciferase in combination with ultra-sensitive bioluminescence microscopy. These data enabled us to develop and calibrate a probabilistic model of gene expression to estimate gene-specific transcription burst sizes and switching rates. The model was further used to deconvolve the time traces, which showed that rapid bursting at timescales of tens of minutes may be an intrinsic property of transcription in mammalian cells, and lead to the characterization of refractory periods of variable duration in the inactive state. Experiments in which the regulatory elements were modified showed that the bursting kinetics was markedly altered by sequence modifications of cis-regulatory sequences. This high temporal resolution monitoring of transcription is readily applicable to many systems; including the circadian oscillator in which we show that increased bursting frequency precede maximal burst sizes by few hours.

MINI-SYMPOSIUM 27

Heart rate dynamics: models and measures of complexity (part I)

Wednesday, June 29, 14:30, *Room*: **CP2**

Organizers: **Grzegorz Graff, Beata Graff**

14:30–15:10

Jose Amigó
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An overview of permutation entropy

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

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

References.

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15:10–15:30

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Entropy-based measures of complexity in the assessment of heart rate variability: a theoretical approach

Recently, in a study of heart rate variability and other physiological data, growing attention has been paid to entropy-based complexity measures, among which are Approximate Entropy, Sample Entropy, Fuzzy Entropy, local entropies and some others. Mathematical components of their definitions will be presented with the stress on the problems of vulnerability to noise, loss of data, relative consistency, dependence on sample length and sensitivity to the input parameters. The usefulness of the above methods to distinguish time series with respect to their irregularity and unpredictability will be discussed and tested on various kinds of stochastic, nonlinear and physiological data.

15:30–15:50

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Entropy-based measures of complexity in the assessment of heart rate variability: a clinical approach

Non-linear dynamics is a powerful approach to understanding physiological data but non-linear methods usually require long data sets. In 1991, Pincus et al. introduced Approximate Entropy, a measure of complexity which can be applied to short and noisy time series of clinical data [**1**]. Subsequently, other entropy-based methods with some improvements were added and presently there are many examples of their successful application in medicine. An overview of the most promising applications

in heart rate variability assessment will be presented. Advantages and limitations of these methods from the physician's point of view will be discussed based on recently published papers and our own results.

References.

[1] S. Pincus, *Approximate entropy as a measure of system complexity* Proc Nati Acad Sci. USA **88** (6) 2297–2301.

15:50–16:10

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Generalized multifractal analysis of heart rate variability recordings with a large number of arrhythmia

The regulation of human heart rate is the result of many inputs e.g. the activity of the sympathetic and parasympathetic nervous system, respiration and its control or such pathologies as ectopic activity or delayed conduction of cardiac tissue - each having its own characteristic time scale and magnitude. The MF-DFA (MultiFractal Detrended Fluctuation Analysis) method used by us allows to assess the effect of the different controls systems and pathologies. Because it requires stationarity the method is applied in the literature to heart rate variability recordings with less than 5% of arrhythmia.

We analyzed the published MF-DFA method, using synthetic data and chosen RR intervals series. We developed an original, generalized version of the MF-DFA method - multiscale multifractal analysis MMA. We found that the calculation of the $f(\alpha)$ curve is a major source of artifacts. We thus focused on the dependence of the local Hurst exponent h on the multifractal parameter q: $h(q)$ and we allowed it to depend on the scale s. In the standard MF-DFA the time scale s is fixed, somewhat arbitrarily (usually from 50 intervals up to 500). Thus, we obtained the $h(q, s)$ dependence - a surface - the shape of which tells us what is the magnitude of the fluctuations the RR intervals have in different time scales (different frequency bands). MMA was found to be immune to noise contamination of the data (we tested up to 50% of noise). It also allows to study heart rate variability with an arbitrary level of arrhythmia required for clinical applications.

We analyzed 51 24-hour recordings of heart rate variability (36 males age 16-64, 15 females age 11-57: 42 healthy persons, 9 cardiac arrest cases including 5 without organic heart disease). We did not remove arrhythmia from the recordings. We limited the study to the night hours to avoid arbitrary daytime activity. Our

mathematical criterion was able to distinguish, in a blind test, healthy subjects from the high risk cardiac arrest cases including those without organic disease. The different peculiarities of each recording have a unique effect on the results of the multiscale MF-DFA analysis e.g. the occurrence of arrhythmia may readily be identified from the results. Thus, the new method allows to recognize and assign a complexity measure to features of the heart rate variability which hitherto went unnoticed when using standard, linear diagnostic methods and MF-DFA.

References.

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[2] A. Saichev, D. Sornette, *Generic multifractality in exponentials of long memory processes* Physical Review E **74** 011111.

16:10–16:30

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Healthy aging by multifractal analysis of heart interbeat intervals

Heart rate responds dynamically to various intrinsic and environmental stimuli. The response is supposed to be mediated by autonomic nervous system. Multifractal analysis offers a novel method to assess this response. Fractal properties of the power spectra in VLF (and ultra-low-frequency (ULF: $\leq$ 0.0033Hz)) have being analyzed for more than 20 years and they were found to have prognostic significance in cardiac patients [1] though also they were questioned when they were used for an individual [2]. Therefore the reliability of the approach has to be carefully validated.

The method of effective reading of multifractal properties will be described. The method consists of two way analysis pertaining each signal. In parallel, a given signal analysis and integrated signal analysis are performed. Differences between the multifractal spectra received from the same signal are found important in discriminating monofractality from multifractality.

The method is used in study 24-hour ECG recordings of RR interbeat intervals of 48 elderly volunteers, 40 middle-aged persons and 36 young adults in order to assess the effect of aging on autonomic regulation during normal activity in healthy adults. The variability of heart interbeat intervals was evaluated in the VLF band (32-420 RR intervals) to preserve links to standard measures of heart rate variability [1]. The nocturnal and diurnal multifractality was considered separately.

The switch from multi- to monofractality is observed between diurnal and nocturnal series in the group of young adults. That change can be directly related to the circadian alternation in the central mechanisms controlling the temporal organization of cardiovascular system — nocturnal dominance of the vagal tone versus sympathetic main drive during daily activities. With aging the multifractal structure of nocturnal signals declines. Our observations are consistent with [3] that imbalance in the autonomic control due to healthy aging should be related to changes that are emerging from the vagal tone, what in consequence results in increasing activity of sympathetic modulation.

References.

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[2] Task Force of the European Society of Cardiology the North American Society of Pacing and Electrophysiology 1996 *Heart rate variability. Standards of measurement, physiological interpretation, and clinical use* Eur. Heart J. **17** 354–81

[3] Struzik Z R, Hayano J, Soma R, Kwak S and Yamamoto Y *Aging of complex heart rate dynamics* IEEE Transactions on Biomededical Engineering **53** 89

MINI-SYMPOSIUM 28

Heart rate dynamics: models and measures of complexity (part II)

Wednesday, June 29, 17:00, *Room*: **CP2**

Organizers: **Grzegorz Graff, Beata Graff**

17:00–17:20

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Modeling of the human atrium using Liénard equations

Liénard systems can be used for modeling oscillatory behaviour of many phenomena - starting from chemical reactions, through neuron excitability [1], up to the action potential in the heart muscle. The universality of the Liénard systems and the rather well-established mathematical knowledge about them creates a flexible framework for designing simple models. Such models are very robust and computationally efficient. On the contrary, the existing physiological ionic channel models of cardiac cells are too complex to allow an investigation of long time dynamical properties of the heart. As a consequence, very rarely do they address the problem of heart rate variability comparable with portable ECG recordings.

We focus on the simulation of human atria, where the dynamics of action potential propagation affects the sinus rythm the most. In the model of the right atrium proposed here, we describe the various anatomical parts of the atrium by means of different equations but all of the same class of Liénard equations. The two nodes - the sinoatrial and the atrioventricular node are modeled by diffusively coupled modified van der Pol-Duffing oscillators while the atrial muscle tissue is currently represented by a diffusively coupled modified FitzHugh-Nagumo system.

Models of the sinoatrial and atrio-ventricular nodes were developed taking into account physiologically important properties such as the phase response curve, the refraction period and threshold potential. Several modifications of the models presented in [2] allowed to achieve a more physiological behaviour of the model. The

effect of the autonomous nervous system activity is incorporated into the model in a simple way.

We performed a series of simulations of the atrium, with differing anatomical simplifications varying from a simple 1 dimensional chain of oscillators to a two-dimensional mapping of the atrium with chosen anatomical details included. The simulations allowed to reconstruct such effects as the AV node reentry tachycardia - both in an extended one dimensional model and in the 2D simulation, the phase relations between sinus rhythm and the location and properties of an ectopic source and their effects on the resultant rhythm.

References.

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17:20–17:40

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Correlation in human heart rate variability from a stochastic model

The extraction of Kramers-Moyal coefficients [1] from measurement data was applied to human heart rate variability. The expansion truncated at the second element is known as the Fokker-Planck equation. The Langevin equation is equivalent to a model of the system dynamics consisting of two parts: a deterministic one and a stochastic term. The necessary assumption is that the noise term be due to δ-correlated noise [2,3]. For heart rate variability, we found that such a description is valid only for daytime recordings of heart rate variability. Nighttime heart rate variability is characterised by non-negligible higher order Kramers-Moyal coefficients [4]. This effect can be explained by the correlation properties of heart rate variability. Correlations may be related to both deterministic and stochastic components of the heart rate. Using Kramers-Moyal expansion the drift (deterministic) and diffusion (stochastic) terms are calculated. Deterministic term coresponds to regulatory processes in the cardiorespiratory coupling. The stochastic one is a measure of the noise amplitude.
We will present the analysis of shortterm correlations. Especially a particular,

asymmetric form of the dependence of the diffusion coefficient on the heart rate will be discussed. This is a measure of the ability of the system to lengthen and shorten the RR intervals [5]. Moreover, for different recordings we obtained a different ranges and shapes of the slow-varing diffusion term as a function of the heart rate close to its minimum. This property can be related to arrhytmic RR intervals. To ilustrate this, several recordings from patients with hypertrophic cardiomyopathy will be compared with time series from healthy men.
We will also focus on the occurence of higher order Kramers-Moyal coefficients and their meaning in terms of correlations [4]. We will discuss the variability of heart rate (mechanisms of increasing and of decreasing of the heart rate) including the effect of recorded pathology on the obtained Kramers-Moyal expansion.

References.

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[5] M. Petelczyc, J. J. Żebrowski, R. Baranowski and L. Chojnowska Physiol. Meas. **31**, 1635 (2010)

17:40–18:00

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Oscillations and synchronization in human circulatory system

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

Another source of complex oscillations, crucially important for homeostasis is the respiratory system. All the systems are interrelated in a complex way and give rise to the complex cardiovascular dynamics. One of interesting phenomena that

arises in such a system is the cardiorespiratory synchronization and the related phenomenon of the interdependence between short-term dynamics of blood pressure, heart rate and breathing. Both problems will be addressed in the talk.

18:00–18:20

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Structure of heart rate asymmetry

Heart rate asymmetry (HRA) is a physiological phenomenon reflecting the fact that heart rate decelerations contribute more to short-term HRV than accelerations, and accelerations contribute more to long-term and total HRV than decelerations. These HRA methods are variance-based, and can be called macrostructural. Recently, a methods based on a counting statistics which depends on fast- and slow- changing rate of microstructure of the RR intervals time series was defined. In this study we show that the related entropic parameters H_{AR} (dependent on accelerations) and H_{DR} (dependent on decelerations) are asymmetric. The nature of this asymmetry is exactly the same as with the variance-based descriptors: it is unidirectional and consistent.

Materials and methods: 24-hour Holter ECG recordings were obtained from 50 healthy subjects, including 27 women. The microstructure related to decelerations and accelerations was calculated from the resulting RR time series and the H_{AR} and H_{DR} were computed. This was repeated for the same recordings in shuffled order, for which the shuffling distribution of microstructure is known for theoretical considerations. The H_{AR} and H_{DR} were compared with the t-test after establishing normal distribution with the Shapiro-Wilk test. The presence of asymmetry in the studied group was established with the binomial test.

Results: The value of H_{AR} was 1.08 ± 0.021 and H_{DR} 1.01 ± 0.18. This difference is statistically significant with $p<0.001$. There were 43 cases with $H_{AR} > H_{DR}$, and the binomial test for equality of both of proportions being equal gives a statistically significant result $p<0.001$. No differences were observed for shuffled data.

Discussion: Heart rate asymmetry understood as a consistent and unidirectional difference between patterns of accelerations and decelerations is an inherent property of the RR intervals time series. It is visible both in macrostructural, variance-based descriptors and microstructural counting based entropic parameters.

18:20–18:40

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Heart rate asymmetry and its reflection in HRV complexity measures

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

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

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

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

18:40–19:00

Krystyna Ambroch
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Time series models for healthy people and patients with LVSD

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

MINI-SYMPOSIUM 29

Applications of nonnegative Radon measure spaces with metric structure to population dynamic models

Wednesday, June 29, 17:00, *Room*: **AM9**

Organizers: **Piotr Gwiazda, Anna Marciniak-Czochra**

17:00–17:40

Jose A. Carrillo
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On some kinetic models of swarming

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

17:40–18:00

Piotr Gwiazda
Institute of Applied Mathematics and Mechanics, University of Warsaw, Banacha 2, 02-097 Warszawa
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Mertics on the space of the measures and transport equation

The talk will be a short introduction to the issue of abstract methods of Wasserstein and related metrics in the context of the their applications to solutions in the space of Radon measures for linear and nonlinear PDEs. However the topic was studied in many aspects of PDEs coming from mathematical physics, but in the context of mathematical biology it is not very well understood. As an introductory talk to the mini-symposium we will give some survey of the most important facts, to give some general feeling of the topic.

18:00–18:20

Gael Raoul
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Structured population models for evolution

We are interested in an integro-differential model that describe the evolution of a population structured with respect to a continuous trait. Those model are able to capture various biological phenomena, and in particular the speciation process, that is the concentration of the population around a finite number of traits. We analyse this property, and relate it to other theoretical tool used by theoretical biologists. We are also able to analyse some cases pointed out by biologists, where the concentration phenomena does not occur.

18:20–18:40

Agnieszka Ulikowska
University of Warsaw
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Two-sex, age-structured population model

The subject of the presentation is a two-sex, age-structured population model introduced first by A.Fredrickson and F.Hoppensteadt. The model consists of a system of three PDE's describing the evolution of males and females populations and the process of couples formation. The age structure plays here a crucial role, because individuals of different ages usually have different preferences for entering into a

marriage. Also environmental limitations and influences are taken into consideration - a birth rate, death rate, divorce rate and marriage function depend on the state of the whole system.

Existence and uniqueness of the weak solutions in the space of nonnegative finite Radon measures equipped with a flat metric is proved. The proof bases on the operator splitting algorithm. Splitting transport terms (which describe aging and death) and boundary terms (which describe an influx of the new individuals) allows for obtaining necessary estimates. Hence, the continuous dependence with respect to time, initial data and model coefficients is proved.

References.

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18:40–19:00

Grzegorz Jamróz
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Measure-transmission conditions - a powerful tool in modeling bimodal dynamics

Differentiation of cells may be subject to two paradigms. Either a cell is in a state of inevitable alteration of its characteristics or the state is quasi-stationary, meaning that for a certain period of time the biochemical characteristics remain the same. A cell in the former, transient state usually originated in and heads towards the latter, reaching it in a finite time. On the other hand, a cell in a quasi-stationary state may stay there arbitrarily long and is typically capable of both self-renewal (by division) and differentiation (with or without division). Incidentally, all these scenarios may coincide in a single system, as e.g. in the case of neurogenesis, and lead to interesting bimodal dynamics. These two types of dynamics can be modeled by transport equations or (a system of) ordinary differential equations, respectively. Nonetheless, the two approaches can be unified in a purely continuous setting of measure-valued solutions of the transport equation with additional transmission conditions. In the simplest case, this leads to the following problem ([1]):

$$\begin{aligned}
\partial_t \mu(t) + \partial_x (g(v(t)\mathbf{1}_{x\neq x_i}(x)\mu(t)) &= p(v(t),x)\mu(t),\\
g(v(t))\frac{d\mu(t)}{d\mathcal{L}^1}(x_i^+) &= c_i(v(t))\int_{\{x_i\}} d\mu(t), \quad i=0,\dots,N,\\
\mu(0) &= \mu_0,\\
v(t) &= \int_{\{x_N\}} d\mu(t).
\end{aligned}$$

In the talk, we present this new setting and discuss how it allows to capture in an elegant way a wealth of effects, promising interesting applications well beyond its original motivation.

References.

[1] Piotr Gwiazda, Grzegorz Jamróz, Anna Marciniak-Czochra, *Models of discrete and continuous cell differentiation in the framework of transport equation.* Submitted.

MINI-SYMPOSIUM 30

Modeling and analysis of tumor invasion I

Tuesday, June 28, 11:00, *Room*: **AM4**

Organizers: **Haralampos Hatzikirou, Andreas Deutsch, Arnaud Chauviere**

11:00–11:30

Vittorio Cristini
University of New Mexico
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Multiparameter Computational Modeling of Tumor Invasion

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

11:30–12:00

Haralampos Hatzikirou
University of New Mexico
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Mechanisms of glioma tumor invasion

Invasion of malignant glioma tumors is typically very aggressive and a highly complex phenomenon involving molecular and cellular processes at various spatiotemporal scales, whose precise interplay is still not fully understood. By means of a mathematical modeling, we compare theoretical results to the experimental data

and deduce microscopic interactions (cellular mechanisms) from microscopic and macroscopic observables (experimental data). In particular, using multicellular spheroid data, we exhibit the key role of migration/proliferation in tumor invasion dynamics. Finally, we study the influence of vascularization on tumor growth with the help of a combination of in vivo data from implanted xenografts of U87 MG in nude mice brain and a mathematical model.

12:00–12:30

Caterina Guiot
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Antonio S. Gliozzi
Politecnico di Torino, Italia
Pier Paolo Delsanto
Politecnico di Torino, Italia

Lumped models for tumor progression

(Primary)tumors have been described mainly as localized entities which grow by mitotic duplication (with a given intrinsic maximal growth rate) in restricted conditions. Such restrictions will slow tumor growth rate until a proper value of carrying capacity is reached.

Some of the most popular scenarios, reflecting tumor growth in specific phases of development (avascular phase, 'multipassage'syngenic transplant in mice, development of the necrotic core, angiogenesis, invasive phase,..)can be satisfactorily described by means of the Phenomenological Universality (PUN) method, which assumes that the tumor volume V depends on the growth rate c(t), whose effective time derivative can be approximated by a series expansion in the variable c(t) itself:

dV/dt = c(t) V; dc/dt = -alpha c - beta c2 +...

Retaining only the constant term we get the unlimited growth U(0), while by considering the linear term the Gompertz law U(1) is obtained, accounting for a time-varying growth rate and a constant carrying capacity.U(2), which is the following term, corresponds to the so called West law, whose main characteristics is that of accounting for tumor vascularization through an 'optimal' fractal network. As a matter of fact, U(2) entails a variation in the overall tumor carrying capacity, that in a more general sense becomes not only dependent from the limiting volume for tumor development, but on the overall environmental conditions, including nutrients availability, switch to different metabolic pathways, hormonal influences and so on.

Provided the two main parameters, i.e. growth rate and carrying capacity, are modulated in time to properly account for the internal metabolism and the relationship between the tumor and its environment respectively, a full description of the 'natural history' of the tumor can finally be obtained. Comparison with available data and clinical description (e.g. for the case of prostate cancer) will help in finely modulating the model parameters. Even more interestingly, such a general model is

suitable for 'theoretical' validation of therapeutic efficiency. The effect of therapy t(t), whose functional form can be expressed in terms of tumor radiosensitivity, drug resistance, etc., can be incorporated into Eqn. 1 by substituting c(t) with the difference c(t) - t(t). Spatially inhomogeneous tumor patterns can be included provided different 'clones' of cells are accounted for.

In conclusion, by retaining the tumor biological complexity in the progressively changing values of the growth rate and carrying capacity of the tumor-host system, a easy-to-handle lumped-model can be worked out, which can prove useful to further stimulate and improve cooperations between theoreticians and clinicians.

12:30–13:00

Georgios Lolas
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Avner Friedman
Michael Pepper

The Lymphatic Vascular System in Lymphangiogenesis, Invasion and Metastasis: A Mathematical Approach

There are two distinct categories of tumors: benign and malignant. Benign tumors remain confined to the tissue in which they arise and although they may continue to grow, they do not spread to other parts of the body. Unlike benign tumors, malignant tumors grow rapidly, invade and destroy the surrounding tissues and, by exploiting the blood or the lymphatic systems, establish new colonies, a process called metastasis. Metastasis is the predominant cause of cancer death. There are four major routes of neoplastic dissemination: (1) local invasion; (2) direct seeding to body cavities; (3) hematogenous spread; and (4) lymphatic spread, preferentially to regional lymph nodes and later to distant sites.

For a primary tumor to grow, it needs a supply of nutrients, delivered by the blood. The tumor therefore secrets growth factors which induce the formation of new blood vessels, sprouting them from preexisting vessels and directing them toward. the tumor. This is the process of tumor angiogenesis. Targeting angiogenesis, namely, cutting of blood supply, is one off the strategies for blocking tumor growth and dissemination.

A similar, although far less well studied process, also occurs in the lymphatic system and is referred to as lymphangiogenesis or lymphagenesis. Surprisingly, almost all of the published literature focuses on the correlations between angiogenesis, microvessel density, metastatic spread, and tumor prognosis, leaving a missed link between primary tumor and nodal metastases: the lymphatic system.The lymphatic system comprises a vascular network of one-way, open-ended, thin-walled complex network of capillaries and larger vessels, collecting vessels, lymph nodes, trunks, and ducts that transport lymph and cells from body tissues back to the circulatory system.

Various studies have shown that angiogenesis is important for solid tumour growth and, presumably, also in hematogenous metastasis. By contrast, the role of lymphatic vessels and the relevance of lymphangiogenesis to tumor pathology is less clear. Until recently only limited information concerning the molecular mechanisms and pathways involved in tumor lymphangiogenesis and tumor lymphatic invasion have been obtained

Although intensive research in tumor angiogenesis has been going on for the past four decades, experimental results in tumor lymphangiogenesis began to appear only in the last five years. In this paper we propose the first mathematical model of lymphangiogenesis, and obtain numerical results that qualitatively agree with experimental results. In conclusion, we propose the possibility to use the mathematical model presented as a possible lymphangiogenesis assay for better understandingand preventing tumor invasion and tumor lymphangiogenesis

MINI-SYMPOSIUM 31

Modeling and analysis of tumor invasion II

Tuesday, June 28, 14:30, *Room*: **AM4**

Organizers: **Haralampos Hatzikirou, Andreas Deutsch, Arnaud Chauviere**

14:30–15:10

Sergei Fedotov
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Migration-Proliferation Dichotomy in Tumor Cell

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

15:10–15:30

Kevin Painter
Heriot-Watt University
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The impact of a heterogeneous environment on invasive processes

The invasion or migration of cells in tissues, either during embryonic development, normal physiological processes such as tissue repair or as a result of pathologies such as cancer, can be highly variable according to cellular and tissue type. In this talk I will present a variety of results, based on both indivudual and continuous level models, that examine the impact of the extracellular matrix environment on invasion. Specifically, I will examine the impact of both a heterogeneous adhesive environment surrounding cells and varying degrees of anisotropy resulting from the oriented structure of matrix fibres.

15:30–15:50

Miguel A. Herrero
IMI and Departamento de Matematica Aplicada, Universidad Complutense , Madrid, Spain
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On the determination of the optimal radiation dose on a target tissue volume

A key problem in radiotherapy consists in determining the appropriate dose to be delivered to a clinical target in order to achieve maximum efficiency over malignant tissue on the one hand, while at the same time sparing healthy tissue and organs at risk as much as possible. In this lecture a model problem will be presented and discussed to address that issue , and a number of consequences of the behaviour of the corresponding solutions will be discussed

15:50–16:10

Chiara Giverso
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Modeling the mechanical behavior of cell aggregates and their invasion of mesothelial linings.

The transmigration across the mesothelial lining is a fundamental step in the process of cancer invasion and formation of metastasis. We reproduce in vitro trans-mesothelial migration of ovarian cancer cells, through a mathematical model that integrates: (a) an Extended Cellular Potts Model (CPM), that captures mechanisms of cellular adhesion, shape constraints, motion in response to chemo-attractants and degradation of extracellular matrix (ECM); (b) a continuous model for the diffusion and uptake of chemo-attractants, and for the release of matrix metalloproteinases (MMPs). Simulations are in good agreement with biological experiments (provided by N. Lo Buono and A. Funaro, Laboratory of Immunogenetics of the Molinette Hospital in Turin), showing that the overall process is strongly regulated by the activity of matrix metalloproteinases (MMPs) and by the interplay of adhesive properties between cells. In particular in the case of cellular aggregates the process is more destructive.
Indeed the ability of cells to form aggregates is fundamental in many biological processes and it seems promising to study spheroid mechanical behavior, because the response of soft biological tissues may serve as a parameter in the diagnosis of tumor metastatic potential. We study the mechanical behavior of multicellular aggregates, treated as porous materials, composed of cells and filled with water, to derive an elasto-visco-plastic model. The cellular constituent is responsible for the elastic and the plastic behavior (due to the rearrangement of adhesive bonds

between cells). On the other hand, the liquid constituent is responsible of the viscous-like response during deformation. The model is used to describe the uniaxial homogeneous compression both when a constant load is applied and when a fixed deformation is imposed and subsequently released. Results are compared with the dynamics observed in mechanical experiments found in literature.

References.

[1] C. Giverso, M. Scianna, L. Preziosi, N. Lo Buono and A. Funaro. *Individual cell-based model for in-vitro mesothelial invasion of ovarian cancer*. Mathematical Modelling of Natural Phenomena, Vol. 5, 2010, pp. 203–223.

16:10–16:30

Andreas Deutsch
Centre for Information Services and High Performance Computing, Technical University of Dresden
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Analyzing emergent behaviour in cellular automaton models of cancer invasion

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

References.

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[2] GIESE, A., BJERKVIG, R., BERENS, M. AND WESTPHAL, M. (2003) Cost of migration: invasion of malignant gliomas and implications for treatment. J. Clin. Oncol., 21, 16241636.

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MINI-SYMPOSIUM 32

Epidemic models: Networks and stochasticity I

Wednesday, June 29, 14:30, *Room*: **AM5**

Organizers: **Thomas House, Istvan Kiss**

14:30–15:10

Thomas House
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István Kiss
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Overview of Networks and Stochasticity in Epidemic Models

Two areas of much recent work in modelling epidemics are contact networks and population stochasticity. These concepts are closely related, since the existence of a small, finite neighbourhood of contacts around each individual (or simple demographic stochasticity) make chance events important at the local level, which can then scale up to significant population-level effects.

This talk will introduce the concepts of network structure and stochasticity, and by focusing on network models, will provide an overview of different mathematical, computational and empirical tools used to address these issues. In particular, the relationship between exact models, approximations based on heuristic arguments, and the results of Monte Carlo simulation will be discussed.

15:10–15:30

David Sirl
Loughborough University
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Household epidemic models with variable infection severity

We explore SIR (Susceptible → Infective → Removed) epidemic models with household structure and the feature that infectives can be either mildly or severely

infective. We analyse two different models which describe such behaviour, one where individual's severities are pre-determined (perhaps due to prior partial immunity) and one where the an individual's severity is influenced by the severity of the individual that infects it and whether this infection resulted from a within- or between-household contact. The aim is to determine whether it is possible to find which of the two models best explains the varying response when given final size household outbreak data containing mild and severe cases. We conduct numerical studies from which we conclude that this discrimination usually is possible.

This is joint work with Frank Ball (University of Nottingham) and Tom Britton (Stockholm University).

15:30–15:50

Kieran Sharkey
The University of Liverpool
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Towards understanding the correlations in epidemic dynamics on contact networks via the master equation

It is well-known that deterministic epidemic models such as mean-field or pair-approximation models can fail on contact networks because they ignore correlations that occur between populations. While there is a substantial amount of intuition about these correlations, the literature lacks a more analytic approach to these effects.

Here, by directly relating these epidemic models to the underlying master equations we can understand precisely where and why these models fail. In particular, common models such as mean-field and pair-approximation models are shown to contain implicit anomalous terms describing unbiological processes whereby individuals can be both susceptible and infectious at the same time. This contradicts the assumption of a compartmental model. It is these implicit terms which lead to the observed inaccuracies in the models.

Analysis of these terms enables us to gain a more analytic perspective on correlations in epidemic models and on the role of network clustering on epidemic propagation.

15:50–16:10

Ken Eames
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Measuring and modelling changing social contact patterns

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

16:10–16:30

Peter Simon
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Exact and approximate epidemic models on networks

The rigorous linking of exact stochastic models to mean-field pair and triple approximations is studied. Using a continuous time Markov Chain, we start from the exact formulation of a simple epidemic model on a completely connected network and rigorously derive the well-known mean-field pair approximation that is usually justified under the hypothesis that infected nodes are distributed randomly.

In addition, we propose a new approach that is based on deriving a countable system of ordinary differential equations for the moments of the distribution of the number of infected nodes. We show how the usual mean-field pair approximation can be derived from this countable system, and prove that this converges to the exact solution given by the Kolmogorov equations as order 1/N. We discuss how our new approach relates to the generally cited results by Kurtz.

Finally, the performance of the triple closure approximation is investigated numerically. It will be shown that the usual triple closure yields a solution that also converges as order 1/N to the exact solution, and we propose a novel triple closure where the rate of convergence is of order 1/N2.

MINI-SYMPOSIUM 33

Epidemic models: Networks and stochasticity II

Thursday, June 30, 11:30, *Room*: **AM9**

Organizers: **Thomas House, Istvan Kiss**

11:30–12:10

Tom Britton
Stockholm University
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Dynamic networks in dynamic populations

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

12:10–12:30

Alan McKane
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Stochastic amplification in an epidemic model with seasonal forcing

In this talk I will discuss, using the formalism of master equations, the nature of the stochastic dynamics which appears in models of population biology, and in particular childhood epidemics. When they contain a large number of constituents, the behaviour of these models may be analysed using an expansion in the system size. To leading order the deterministic analogues of the models can be compared to the equations which are normally written down on phenomenological grounds, for

example the SIR (Susceptible-Infected-Recovered) differential equations. At next-to-leading order a simplified stochastic description is obtained. Attention will focus on systems for which the deterministic description fails to predict cycles, but where large cycles are found at next-to-leading order. These cycles have their origin in fluctuations due to the discrete nature of the system components, and are much larger than would naively be expected because they are amplified by a resonance phenomenon. The application of these ideas to the SIR model with term-time forcing will be described.

12:30–12:50

Michael Taylor
Universuty of Sussex
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From Markovian to pairwise epidemic models and the performance of moment closure approximations

Many if not all models of disease transmission on networks can be linked to the exact state-based Markovian formulation. However the large number of equations for any system of realistic size limits their applicability to small populations. As a result, most modelling work relies on simulation and pairwise models. In this paper, for a simple SIS dynamics on an arbitrary network, we formalise the link between a well known pairwise model and the exact Markovian formulation. This involves the rigorous derivation of the exact ODE model at the level of pairs in terms of the expected number of pairs and triples. The exact system is then closed using two different closures, one well established and one that has been recently proposed. A new interpretation of both closures is presented, which explains several of their previously observed properties. The closed dynamical systems are solved numerically and the results are compared to output from individual-based stochastic simulations. This is done for a range of networks with the same average degree and clustering coefficient but generated using different algorithms. It is shown that the ability of the pairwise system to accurately model an epidemic is fundamentally dependent on the underlying large-scale network structure. We show that the existing pairwise models are a good t for certain types of network but have to be used with caution as higher-order network structures may compromise their effectiveness.

12:50–13:10

Adam Kleczkowski
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Savi Maharaj
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Controlling epidemic spread by responding to risk: Do it well or not at all

Disease outbreaks change people behaviour. This change can be used to control epidemics but it comes at a cost. We describe results from using simulation to study the costs and benefits of using social distancing as a form of control. Our model consists of a standard SIR model superimposed on a simple spatial network. Disease spread is controlled by allowing susceptible individuals to temporarily reduce their social contacts in response to the presence of infection within their local neighbourhood. We ascribe an economic cost to the loss of social contacts, and weigh this against the economic benefit gained by reducing the attack rate of the epidemic. Our first result is that, depending on the characteristics of the epidemic and on the relative economic importance of making contacts versus avoiding infection, the optimal control is one of two extremes: either to *panic*, that is, to adopt a highly cautious control, thereby suppressing the epidemic quickly by drastically reducing contacts as soon as disease is detected; or else to *relax* by forgoing control and allowing the epidemic to run its course. The worst outcome arises when control is attempted, but not cautiously enough to cause the epidemic to be suppressed. Our second result comes from comparing the size of the neighbourhood of which individuals are aware to that of the neighbourhood within which transmission can occur. We see that control works best when these sizes match, and that it is particularly ineffective when the awareness neighbourhood is smaller than the infection neighbourhood. These results have implications for the design of control strategies using social distancing. An important message is that a weak control, or one based upon inaccurate knowledge, may give a worse outcome than doing nothing.

References.

[1] A. Author, *Title of paper* Journal Name **1** 1–10.

13:10–13:30

Christel Kamp
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Following epidemic spread: how epidemics travel and trim their network of infectious contacts

Epidemics of infectious diseases are ubiquitous, however, their patterns vary depending on the course of disease and the transmission network established by infectious contacts. Therefore, strategies to maintain public health cannot be applied

uniformly but have to be adjusted to the specific epidemic scenario. Network models have proven to be a helpful tool to infer time scales of epidemic expansion and prevalence from the structure and dynamics of the underlying transmission network. We extend the existing mathematical framework to also quantify the reverse effect: epidemics impact on the way contacts are made among susceptible and infected hosts. A set of partial differential equations links the structure and dynamics of the transmission network to the epidemic process. It allows to study epidemics on dynamic transmission networks with arbitrary degree distributions and under demographic change [1,2]. The framework will be used in epidemic case studies including multi-staged HIV epidemics. These studies show how epidemics do not only travel but also trim their transmission networks and allow for an exploration of intervention strategies.

References.

[1] C. Kamp *Untangling the Interplay between Epidemic Spread and Transmission Network Dynamics* PLoS Comput Biol **6(11)**: e1000984.

[2] C. Kamp *Demographic and behavioural change during epidemics* Proc Comp Sci **1**: 2247–2253.

MINI-SYMPOSIUM 34

From one to many: Cell-based modeling of collective, emergent behaviors in biology -I

Tuesday, June 28, 11:00, *Room*: **SP1**

Organizer: **Yi Jiang**

11:00–11:25

Dirk Drasdo
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Helen Byrne
Nottingham
Jan G. Hengstler
IFADO
Stefan Hoehme
Leipzig

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

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

a mechanism, the experimentally observed regeneration and proliferation pattern cannot be reproduced. The models of regeneration of liver after drug induced damage and after partial hepatectomy made predictions that could subsequently be validated.

References.

[1] Drasdo, D., Hoehme, S. and Block, M. (2007) On the Role of Physics in the Growth and Pattern Formation of Multi-Cellular Systems: What can we Learn from Individual-Cell Based Models? Journal of Statistical Physics, Volume 128, Numbers 1-2, pp. 287-345(59)

[2] Hoehme, S., Brulport, M., Bauer, A., Bedawy, E., Schormann, W., Gebhardt, R., Zellmer, S., Schwarz, M., Bockamp, E., Timmel, T., G. Hengstler, J.G., and Drasdo, D. (2010). Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration. Proc. Natl. Acad. Sci. (USA), 107(23), 10371-10376.

[3] Hoehme and Drasdo, (2010) Biomechanical versus nutrient control: what determines the growth dynamics of mammalian cell populations? Mathematical Population Studies, Volume 17, Issue 3, 2010, 166187.

[4] Byrne and Drasdo, (2009) Individual-based and continuum models of growing cell populations: a comparison. J. Math. Biol. Apr;58(4-5):657-87.

11:25–11:50

C. Anthony Hunt
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Program in Bioengineering , University of California, San Francisco

Emergent patterns of hepatic zonation of xenobiotic clearance and hepatotoxicity: a plausible role for cell learning

Hepatic zonation is conspicuous periportal (afferent) to perivenous (efferent) attribute gradients within lobules. Zonal differences occur in the clearance of a variety of endogenous compounds and xenobiotics, and are evident for a number of normal hepatic functions. However, no concrete, causal, mechanistic theory is available to explain how, for example, different hepatic zonation patterns of P450 isozyme levels and hepatotoxicity emerge following dosing with different compounds. We used the synthetic method of modeling and simulation to discover, explore, and experimentally challenge concrete mechanisms that show how and why biomimetic zonation patterns emerge and change within agent-based analogues. Synthetic methods enable teasing apart complex systems in contrast to inductive methods, which target prediction. Following an iterative Refinement Protocol enabled construction of real (not conceptual), strictly defined, biomimetic mechanisms while also accounting for considerable uncertainty. Even though abstract, the mechanisms and their spatial context are flexible and sufficiently concrete to instantiate mechanistic hypotheses and test their plausibility experimentally. Our working hypothesis was that those mechanisms have counterparts in rats. Mobile objects map to compounds. One

analogue is comprised of 460 identical, quasi-autonomous functional units called sinusoidal segments (SSs). SSs detect and respond to compound-generated response signals and the local level of an endogenous gradient. Each SS used a learning algorithm to adapt to new information with the objective of improving efficiency. Upon compound exposure, analogues developed a variety of patterns that were strikingly similar to those reported in the literature. A degree of quantitative validation was achieved against data on hepatic zonation of CYP1A2 mRNA expression caused by three different doses of TCDD (2,3,7,8-tetracholorodibenzo-p-dioxone).

11:50–12:15

Roeland M. H. Merks
Centrum Wiskunde & Informatica (Amsterdam, The Netherlands)
Netherlands Consortium for Systems Biology (Amsterdam, The Netherlands)
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Cell-based modeling of plant tissues using VirtualLeaf

Plant organs, including leaves and roots, develop by means of a complicated, multi-level cross-talk between gene regulation, patterned cell division and cell expansion, and tissue mechanics. In contrast to the cells in many animal tissues, plant cells cannot migrate and, with very few exceptions, they cannot slide past each other. Consequently, plant morphogenesis depends entirely on patterned cell division, cell expansion, and cell differentiation. Thus plant development requires different cell-centered models than those developed for animal development, in which cell migration and tissue folding play a primary role. We will present a cell-centered computer-modeling framework for plant tissue morphogenesis that we named *VirtualLeaf* [**1**]. We will illustrate the current use of VirtualLeaf with examples of auxin-driven vasculature development, determination of leaf shape, and meristem growth. VirtualLeaf defines a set of biologically intuitive C++ objects, including cells, cell walls, and diffusing and reacting chemicals, that provide useful abstractions for building biological simulations of developmental processes. VirtualLeaf-based models provide a means for plant researchers to analyze the function of developmental genes in the context of the biophysics of growth and patterning. VirtualLeaf is an ongoing open-source software project (http://virtualleaf.googlecode.com) that runs on Windows, Mac, and Linux.

References.

[1] R. M. H. Merks, M. Guravage, D. Inzé, G.T.S. Beemster. *VirtualLeaf: an Open Source framework for cell-based modeling of plant tissue growth and development* Plant Physiology **155** 656–666, 2011.

12:15–12:40

Katarzyna A. Rejniak
Moffitt Research Institute
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Contribution of Individual cells to homeostatic balance and imbalance in epithelia

Epithelial tissues (simple or stratified) form multicellular systems of well defined topology and function. In order to maintain such a fine tissue microarchitecture individual cells must act collectively and respond to signals from their neighbors and from the environment. I will present a mathematical model and computational simulations addressing the questions of individual contributions of epithelial cells to tissue homeostatic balance during its development and turnover. In contrast, the disruption of tissue structure is often associated with the initiation and progression of abnormal tissue states, such as tumors. Specific local cell-cell interactions that can lead to the emergence of abnormalities on tissue scale will be also discussed.

12:40–13:05

James Glazier
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Abbas Shirinifard
Indiana University

Multi-scale, Multi-cell Computational Modeling of Choroidal Neovascularization in Age-Related Macular Degeneration

Choroidal neovascularization (CNV) of the macular area of the retina is the major cause of severe vision loss in patients with age-related macular degeneration (AMD) and the major cause of vision loss in adults in the developed world. In CNV, after choriocapillaries initially penetrate Bruch's Membrane (BrM), the invading vessels may regress or expand (CNV initiation). After initiation, during early and late CNV, the expanding vasculature usually spreads in one of three distinct patterns: in a layer between BrM and the retinal pigment epithelium (sub-RPE, occult or Type 1 CNV), in a layer between the RPE and the photoreceptors (subretinal, classic or Type 2 CNV) or in both loci simultaneously (combined pattern or Type 3 CNV). The factors determining both CNV initiation and progression are poorly understood. While most previous studies of CNV have assumed that it is primarily related to growth factor effects or to local holes in BrM, our simulations of a three-dimensional (3D) multi-cell model of the maculae of normal and pathological retinas successfully recapitulate the three clinically observed types of CNV, under the hypothesis that initiation and early and late CNV result from combinations of impairment of: 1) RPE-RPE epithelial junctions (i.e. the outer blood-retinal barrier), 2) the adhesion of the basement membrane of the RPE (BaM) to BrM, and 3) adhesion of the RPE to the photoreceptor outer segments (POS). Our key findings

are that when an endothelial tip cell or immune cell penetrate BrM: 1) RPE with normal epithelial junctions and basal attachment to BrM and apical attachment to POS resists CNV, showing that higher rates of EC activation due to excess vascular growth factors by themselves are insufficient to produce CNV. 2) Similarly small holes in BrM do not, by themselves, initiate CNV. 3) RPE with normal epithelial junctions and normal apical RPE-POS adhesion, but weak adhesion of BaM to BrM (e.g. due to lipid accumulation in BrM) initially results in Type 1 CNV. 4) Normal adhesion of BaM to BrM, but reduced apical RPE-POS and epithelial RPE-RPE binding (e.g. due to inflammation) initially results in Type 2 CNV. 5) Simultaneous reduction in RPE-RPE epithelial binding and BaM-BrM adhesion results in early Type 1 or 2 CNV which often progresses to Type 3 CNV as neovascularization further perturbs RPE-RPE adhesion and BaM-BrM attachment. These findings suggest that previously neglected changes in adhesion rather than the more often hypothesized excess production of vascular growth factors dominate both CNV initiation and progression.

MINI-SYMPOSIUM 35

From one to many: Cell-based modeling of collective, emergent behaviors in biology -II

Tuesday, June 28, 14:30, *Room*: **CP1**

Organizer: **Yi Jiang**

14:30–14:55

Hans G Othmer
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Multiscale Modeling in Biology — The Mathematical and Computational Challenges

New techniques in cell and molecular biology have produced a better understanding of cell-level processes that has in turn led to better cell-level models for problems ranging from biofilm formation to embryonic development and cancer. However this raises the problem of how to incorporate detailed descriptions of individual-level behavior, be it at the cell, tissue or organ level, into population level descriptions. We will illustrate the mathematical and computational challenges involved with an f example from pattern formation in bacteria, and will discuss some of the open problems in this area.

14:55–15:20

Heiko Enderling
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Emerging tumor morphologies from cancer cell interactions

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

15:20–15:45

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Multiscale modelling of vascular tumour growth and angiogenesis

A three-dimensional multiscale model of vascular tumour growth is presented. In our model, cells are modelled as individual entities (agent-based approach) each with their own cell cycle and subcellular-signalling machinery. Nutrients are supplied by a dynamic vascular network, which is subject to remodelling and angiogenesis.

The model is formulated on a regular grid that subdivides the simulation domain into lattice sites. Each lattice site can be occupied by several biological cells whose movement on the lattice is governed by reinforced random walks, and whose proliferation is controlled by a subcellular cell cycle model. The vascular network consists of vessel segments connecting adjacent nodes on the lattice, with defined inflow and outflow nodes with prescribed pressures. We also specify the amount of haematocrit entering the system through the inlets. The vessel network evolves via sprouting of tip cells with a probability that increases with the local VEGF concentration, tip cell movement is described by a reinforced random walk, and new connections forming via anastomosis. In addition, vessel segments with low wall shear stress may be pruned away. Elliptic reaction-diffusion equations for the

distributions of oxygen and VEGF are implemented on the same spatial lattice using finite difference approximations, and include source and sink terms based on the location of vessels (which act as sources of oxygen and sinks of VEGF) and the different cell types (e.g. cells act as sinks for oxygen and hypoxic cells as sources of VEGF).

In our simulations we demonstrate how our model may be combined with experimental data, to predict the spatio-temporal evolution of a vascular tumour together with angiogenesis.

15:45–16:10

Charles Reichhardt
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Guided Motion of Individual and Collective Swimmers in Funnel Arrays

We generalize a model of swimming bacteria in asymmetric arrays of obstacles [1] to include different rules of motion, including various rules for collective behvaiors. For individual noninteracting swimmers, we observe guided motion and rectification by the asymmetric barriers when the particles align with the walls they contact, but we find no rectification if the particles are reflected by the walls or bounce off the walls. For collectively interacting swimmers, it is possible for the particles to form large swimming clumps that can move against the normal rectification direction of the asymmetric barrier array. In general, the rectification by the barriers is lost when the length scale of the swarms of collectively moving particles is significantly larger than the length scale of the funnel shaped barriers. A particle swarm can become trapped inside a funnel; however, individual strings of particles that follow each other can escape from the trap and move against the funnel direction. [1] M.B. Wan, C.J. Olson Reichhardt, Z. Nussinov, and C. Reichhardt, Phys. Rev. Lett. 101, 018102 (2008).

16:10–16:35

Yi Jiang
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Yilin Wu
Harvard
Mark Alber
Notre Dame
Dale Kaiser
Stanford

Bacterial behavioral principles: Learning from Myxobacteria

Many bacteria are able to spread rapidly over surfaces by the process of swarming. Bacterial swarms are model systems for the study of multicellularity and biological self-organization. Swarming bacteria have rod-shaped cells, and are observed to move smoothly even when they are packed together at high density. Why dont swarming cells interfere with each others movements? Using a cell-based biomechanical model, we show that periodic reversals of moving direction in populations of rod-shaped bacteria can lead to extensive ordering of cells, thus enabling them to effectively resolve traffic jams formed during swarming. We also show that an optimal reversal period and an optimal cell length exist for producing such order. The optimal reversal period and the optimal cell length are connected by a simple relation. We suggest that basic behavioral principles exist for bacterial swarming that are independent of detailed motility mechanisms.

MINI-SYMPOSIUM 36

Epidemics of Neglected Tropical Diseases

Wednesday, June 29, 11:00, *Room*: **CP2**

Organizer: **Roberto Kraenkel**

11:00–11:40

Lourdes Esteva
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Modelling transmission of Chagas' disease

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

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

11:40–12:10

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Modelling the dynamics of dengue real epidemics

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

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

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

12:10–12:40

Roberto Kraenkel
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A model for malaria with ecological components

We present a model for malaria epidemics which takes into account, besides humans and anopheles mosquitoes, the existence of other mosquitoes species which are not vectors for plasmodium but which create a competition effect that can reduce the basic reproductive number. Further, we consider the occurrence of other species that can provide blood meals for mosquitoes but are immune to malaria, creating a dilution effect. These effects are meant to model observed situations in which almost no malaria cases are observed, although the anopheles mosquito is abundant.

MINI-SYMPOSIUM 37

Models in Spatial Ecology

Tuesday, June 28, 17:00, *Room*: **UA2**

Organizer: **Roberto Kraenkel**

17:00–17:40

Roberto Kraenkel
Institute for Theoretical Physics, São Paulo State University, Brazil
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Diffusion in fragmented landscapes: habitat split

This talk gives an overview of some recent results concerning stage-structured species in fragmented habitats. It focus on amphibians, which need two distinct habitats in different life stages. We discuss the particular case where the habitat is split: the terrestrial habitat of the adults is separated from the aquatic habitat of the larvae. A central question is how the distance between the two required habitats affects population size and persistence in isolated fragment. We find a condition for persistence in a simple model based on diffusion equations supplemented with boundary conditions encompassing population regulation. The habitat split model improves our understanding about spatially structured populations and has relevant implications for landscape design for amphibian conservation.

17:40–18:00

, R.M.
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Connectivity and diffusion for *Heliconius* species in a seasonally dry fragmented habitat

In a fragmented landscape, the capability of populations to move between habitat patches, called functional connectivity, is influenced by the nature of the intervening matrix and how organisms respond to it. Models usually treat the matrix as a fixed category and fail to appreciate the possibility of dynamic matrix types. We studied the role of seasonal changes in matrix quality, given that it differs between dry and wet seasons in the seasonal tropics. The duration of the favorable period for dispersal, the species' ability to disperse and the distance between patches could be important factors determining patch connectivity. We explored these connections by employing a diffusion model to a one-dimensional landscape subjected to periodical fluctuations in matrix quality; diffusion was curtailed in the dry season and permitted in the wet season. Our model predicts that, given a particular organism's lifetime and diffusion constant, connectivity will depend on the relation between the duration of the dispersal season and the time for the population to fully extend into the matrix. We parameterize our model with demographic data from *Heliconius* butterflies, finding that the model successfully describes connectivity between habitat patches and so it could be used to model dispersal of other organisms in seasonal environments and to help guide restoration efforts and design of protected areas in the tropics.

18:00–18:20

Franciane Azevedo
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The spatial dynamics of the diphenic planthopper

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

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

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

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

18:20–18:40

Erin Dauson
Dartmouth College
Ben Bier
Dartmouth College
Clyde Martin
Texas Tech University

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

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

MINI-SYMPOSIUM 38

Cell migration during development: modelling and experiment

Saturday, July 2, 08:30, *Room*: **CP4**

Organizers: **Paul Kulesa, Ruth Baker**

08:30–09:10

Paul Kulesa
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Experimental analysis of neural crest migration during development

Experimental analysis of neural crest migration during development Cell migration and cell fate decisions are strongly influenced by microenvironmental signals during embryonic development and cancer. Yet, it is largely unclear how cells receive and interpret microenvironmental signals that influence their fate and choice of direction. To address these questions, we use the neural crest (NC) as our model system. NC cells are a highly invasive, multipotent embryonic cell population that are sculpted into discrete migratory streams and patterned into multiple derivatives by the microenvironments cells travel through. We have developed an in vivo imaging platform in chick that permits single cell resolution and behavior analysis

of fluorescently labeled NC cells. By combining molecular intervention with time-lapse imaging, we have discovered a role for NC cell chemotaxis and how cells may respond to distinct microenvironmental signals and navigate to precise locations. We will show recent tissue transplantation and ablation experiments that alter the position of NC cells along a migratory route and discuss how cells respond to local microenvironmental signals. These data provide the basis for close collaboration with mathematical modellers and offer insights into the underlying mechanisms of embryonic pattern formation.

09:10–09:30

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Models of neural crest cell migration during development

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

09:30–09:50

Matthew Simpson
Queensland University of Technology
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Modelling cell invasion with proliferation mechanisms motivated by time-lapse data

Cell invasion involves a population of cells which are motile and proliferative. Traditional lattice-based discrete models of cell proliferation involve agents depositing daughter agents on nearest neighbour lattice sites. Our new work is motivated by time-lapse images of cell invasion associated with the development of the enteric nervous system where a population of precursor neural crest cells invades the developing gut tissues. Using time-lapse data, we show that the traditional proliferation model is inappropriate and we propose a new proliferation model consistent with time-lapse observations. Using simulation and analysis, we show that the discrete model is related to a family of reaction-diffusion equations and can be used to make predictions over a range of scales appropriate for interpreting experimental data

09:50–10:10

Michelle Wynn
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Paul M. Kulesa
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A computational model of neural crest chain migration provides mechanistic insight into cellular follow-the-leader behavior

Follow-the-leader chain migration is a striking cell migratory behavior observed during vertebrate development, adult neurogenesis, and some cancer metastases. An example of chain migration is found in the embryonic neural crest (NC), a multipotent, invasive cell population. Although some aspects of chain migration have been well described, the mechanisms involved in the persistence of NC cell chain migration are unclear. We developed a quantitative agent based modeling framework to investigate three distinct model mechanisms of chain migration. The models relied on biological data from the NC and involved extracellular matrix and cell contact mediated promotion of chain migration. Sensitivity analysis revealed specific criteria for high chain migration persistence and suggested possible mechanism that may sustain follow-the-leader behavior. Our approach offers a means to test mechanistic hypotheses of collective NC cell chain migration in an in silico framework that is applicable to studying collective chain migration in other biological systems.

10:10–10:30

Kevin Painter
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Richard L. Mort
MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh
Ian J. Jackson
MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh

An integrated experimental/theoretical approach to explore cell migration during embryonic development

Cell migration is critical to multiple developmental processes, from early embryonic reorganisation to the intricate wiring of the nervous system. Neural crest cells (NCCs) form a highly motile population characterised by an epithelial to mesenchymal transformation that allows their migration to various remote target tissues, where they differentiate into multiple cell types. Failure to migrate, proliferate or differentiate leads to a plethora of birth defects. Melanoblasts, a subtype of NCC and the embryonic precursors of melanocytes, serve as a model system for cell migration during development and in pathologies such as cancer cell metastasis. Melanoblasts migrate out of the neural crest into the developing skin before localising into the developing embryonic hair follicles. A variety of factors may contribute to their colonisation of the embryonic skin, including tissue growth, melanoblast motility, melanoblast proliferation and extracellular signaling factors. In this talk I will discuss our integrated experimental/theoretical approach to understanding melanoblast invasion, in which data obtained in an ex vivo system for live imaging of melanoblast migration in embryonic skin is incorporated into mathematical models which, in turn, are used to test distinct hypotheses for colonisation and formulate experimentally testable predictions.

MINI-SYMPOSIUM 39

Biofluids, Solute Transport, and Hemodynamics

Wednesday, June 29, 11:00, *Room*: **AM9**

Organizers: **Anita Layton, S. Randall Thomas**

11:00–11:20

Harold E. Layton
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Countercurrent Multiplication in the Kidney: Is it Real?

A fundamental function of the mammalian kidney, when blood plasma osmolality is too high, is to produce a urine that is more concentrated than blood plasma and thereby reduce blood plasma osmolality to a normal level. Urine is concentrated in the renal medulla by means of a concentration gradient that promotes osmotic water withdrawal from the kidney's collecting ducts. It has become widely accepted that the osmolality gradient along the cortico-medullary axis of the mammalian outer medulla is generated and sustained by a process of countercurrent multiplication: active NaCl absorption from thick ascending limbs is coupled with a counter-flow configuration of the descending and ascending limbs of the loops of Henle to generate the axial gradient. However, aspects of anatomic structure (e.g., the physical separation of the descending limbs of short loops of Henle from contiguous ascending limbs), recent physiologic experiments (e.g., those which suggest that the thin descending limbs of short loops of Henle have a low water permeability), and mathematical modeling studies (e.g., those which predict that water-permeable descending limbs of short loops are not required for the generation of an axial osmolality gradient) suggest that countercurrent multiplication may be an incomplete, or perhaps even erroneous, explanation. We propose an alternative explanation for the axial osmolality gradient: we regard the thick limbs as NaCl sources for the surrounding interstitium, and we hypothesize that the increasing axial osmolality gradient along the outer medulla is primarily sustained by an increasing ratio, as a

function of medullary depth, of NaCl absorption from thick ascending limbs to water absorption from thin descending limbs of long loops of Henle and from collecting ducts.

11:25–11:45

Roger Evans
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Bruce S. Gardiner
University of Western Australia
David W. Smith
University of Western Australia
Paul M. O'Connor
Medical College of Wisconsin

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

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

may reduce the oxygen content of blood destined for the medullary circulation. Conclusions: Cortical AV oxygen shunting limits oxygen delivery to cortical tissue and stabilizes tissue PO2 when arterial PO2 changes, but renders both the cortex and medulla susceptible to hypoxia when oxygen delivery falls or consumption increases. The model also predicts how much kidney oxygen consumption must change, in the face of altered renal blood flow, to maintain cortical tissue PO2 at a stable level.

References.

[1] Nordsletten DA et al. Structural morphology of renal vasculature. Am J Physiol Heart Circ Physiol 291: H296-309, 2006.

[2] Welch WJ et al. Nephron pO2 and renal oxygen usage in the hypertensive rat kidney. Kidney Int 59: 230-237, 2001.

11:50–12:10

Anita Layton
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Myogenic Response of the Afferent Arteriole

We have formulated a mathematical model of the rat afferent arteriole (AA). Our model consists of a series of arteriolar smooth muscle cells, each of which represents ion transport, cell membrane potential, cellular contraction, gap junction coupling, and wall mechanics. Blood flow through the AA lumen is described by Poiseuille flow. Model results suggest that interacting calcium and potassium fluxes, mediated by voltage-gated and voltage-calcium-gated channels, respectively, give rise to periodic oscillations in cytoplasmic calcium concentration, myosin light chain phosphorylation, and crossbridge formation with attending muscle stress mediating vasomotion. The AA model's representation of the myogenic response is based on the hypothesis that the voltage dependence of calcium channel openings responds to transmural pressure so that vessel diameter decreases with increasing pressure. With this configuration, the results of the AA model simulations agree well with findings in the experimental literature, notably those of Steinhausen et al. (J Physiol 505:493, 1997), which indicated that propagated vasoconstrictive response induced by local electrical stimulation decayed more rapidly in the upstream than in the downstream flow direction. The model can be incorporated into models of integrated renal hemodynamic regulation. This research was supported in part by NIH grants DK-42091 and DK-89066, and by NSF grant DMS-0715021.

12:15–12:35

Niels-Henrik Holstein-Rathlou

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Synchronization of nephrons in vascular networks

Tubuloglomerular feedback (TGF) has an important role in autoregulation of renal blood flow and glomerular filtration rate (GFR). Because of the characteristics of signal transmission in the feedback loop, the TGF undergoes self sustained oscillations in single nephron blood flow, GFR and tubular pressure and flow. Nephrons interact by exchanging electrical signals conducted electrotonically through cells of the vascular wall, leading to synchronization of the TGF mediated oscillations. To study the extent of synchronization we have used laser speckle contrast imaging to measure the blood flow dynamics of 50 – 100 nephrons simultaneously on the renal surface of anesthetized rats. Synchronized TGF oscillations were detected in pairs or triplets of nephrons. The amplitude and the frequency of the oscillations changed with time, as did the patterns of synchronization. Synchronization may take place among nephrons not immediately adjacent on the surface of the kidney. Nephrons are organized in a vascular network, and the interaction between them takes place across the network. To investigate the significance of the network structure, we modeled two alternative network configurations: a linear serial network, and a branching fractal structure. Although synchronization among nephrons was observed in both configurations, the tendency was for in phase synchronization among nephrons in the linear, serial network; whereas more complex in- and out of phase patterns of synchronization was observed in the branching model of the vascular network.

12:40–13:00

S. Randall Thomas
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Towards integrative multiscale models of whole kidney structure and function

Existing models of renal function have generally focused on open questions of 'local' (i.e., intrarenal) physiology rather than on providing an overall description of renal function relevant to its role in the body and incorporating sufficient detail to address the roles of transporters and channels in each nephron segment We will present our current efforts towards a multi-organ systems model of blood pressure regulation. The resulting open-source platform will be oriented towards interactive exploration of targeted pathologies and their pharmacology. Our approach will be: (1) to complete an integrated endocrine/paracrine RAAS (renin-angiotensin-aldosterone system) model, (2) to build a whole-kidney model representing essential nephrovascular relationships in the three kidney zones and operational descriptions of specific transport processes in each nephron segment and to build up a multi-nephron model capable of addressing progressive renal failure, (3) to combine the renal and RAAS models in our modular core-model (based on the classic Guyton model), (4) to calibrate and validate the models on the basis of pre-clinical and clinical data related to physiological and pathological conditions, and finally (5) to produce a large population (>100 000) of 'virtual individuals' with randomized model parameters (analogous to genetic polymorphisms) for comparison with data from cohorts of real patients from our partner clinicians (and published clinical trials). These new tools, based on virtual physiopathological models of the kidney and RAAS, will be useful to investigate dysfunctions at the clinical level as well as at the level of scientific research and education.

MINI-SYMPOSIUM 40

Analysis of mathematical models for cancer growth and treatment, Part I

Tuesday, June 28, 11:00, *Room*: **AM3**

Organizers: **Urszula Ledzewicz, Alberto d'Onofrio**

11:00–11:40

Avner Friedman
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Bei Hu
Department of Mathematics, University of Notre Dame, Notre Dame, USA

The development of fingers in solid tumors

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

11:40–12:00

Miguel A. Herrero
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A. Fasano

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Departamento Académico de Matemáticas, Instituto Tecnológico autonomo de México, Rio Hondo 1, San Angel, México.

Wave propagation and tumour growth

Travelling waves (TWs), a particular type of solutions of Reaction-Diffusion systems which move with constant speed, have been widely employed to model various aspects of tumour invasion. In this lecture, I shall deal with some TWs that have been recently used to describe particular types of tumour growth. More precisely, their capability to reproduce some observed morphological features will be addressed, and the relation between their dynamical properties and the underlying biological processes will be discussed.

12:00–12:20

Anna Marciniak-Czochra
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Dynamics of pattern formation in the models of early cancerogenesis

In this talk we will explore a mechanism of pattern formation arising in the processes described by a system of a single reaction-diffusion equation couples with ordinary differential equations. Such models are very different from classical Turing-type models and the spatial structure of the pattern emerging from the destabilisation of the spatially homogeneous steady state cannot be concluded based on linear stability analysis. The models exhibit qualitatively new patterns of behaviour of solutions, including a strong dependence of the emerging pattern on initial conditions and quasi-stability followed by rapid growth of solutions. In numerical simulations, solutions having the form of periodic or irregular spikes are observed. Recently we have proposed models of spatially-distributed growth of clonal populations of precancerous cells, which remained under control of endogenous or exogenous growth factors diffusing in the extracellular medium and binding to the cell surface. We found conditions for emergence of growth patterns, which took the form of spike-type spatially inhomogeneous steady states. This multifocality is as expected from the field theory of carcinogenesis.

In this talk we approach the question of stability of spike solutions, which is essential for their observability in experiments. We study existence and stability of

regular spatially inhomogeneous stationary solution of periodic type and of discontinuous patterns.

The talk is a based on a series of joint works with Marek Kimmel (Rice University), Kanako Suzuki (Tohoku University), Grzegorz Karch (University of Wroclaw) and Steffen Härting (University of Heidelberg)

12:20–12:40

Alberto d'Onofrio
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The noisy life of tumors

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

References.

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

12:40–13:00

Mary Ann Horn
Program in Applied Mathematics & Mathematical Biology, Division of Mathematical Sciences, National Science Foundation, Arlington, USA
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Hannah L.
University of Portland, and H. Alex Brown and the Brown Laboratory at Vanderbilt University, Nashville, USA

Using mathematical modeling to understanding the role of diacylglycerol (DAG) as a second messenger

Diacylgylcerol (DAG) plays a key role in cellular signaling as a second messenger. In particular, it regulates a variety of cellular processes and the breakdown of the signaling pathway that involves DAG contributes to the development of a variety

of diseases, including cancer. We present a mathematical model of the G-protein signaling pathway in RAW 264.7 macrophages downstream of P2Y6 activation by the ubiquitous signaling nucleotide uridine 5'-diphosphate. Our primary goal is to better understand the role of diacylglycerol in the signaling pathway and the underlying biological dynamics that cannot always be easily measured experimentally. The model is based on time-course measurements of P2Y6 surface receptors, inositol trisphosphate, cytosolic calcium, and with a particular focus on differential dynamics of multiple species of diacylglycerol. When using the canonical representation, the model predicted that key interactions were missing from the current pathway structure. Indeed, the model suggested that to accurately depict experimental observations, an additional branch to the signaling pathway was needed, whereby an intracellular pool of diacylglycerol is immediately phosphorylated upon stimulation of an extracellular receptor for uridine 5'-diphosphate and subsequently used to aid replenishment of phosphatidylinositol. As a result of sensitivity analysis of the model parameters, key predictions can be made regarding which of these parameters are the most sensitive to perturbations and are therefore most responsible for output uncertainty.

MINI-SYMPOSIUM 41

Analysis of mathematical models for cancer growth and treatment, Part II

Tuesday, June 28, 14:30, *Room*: **AM3**

Organizers: **Urszula Ledzewicz, Alberto d'Onofrio**

14:30–15:10

Vincenzo Capasso
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Daniela Morale
ADAMSS (Interdisciplinary Centre for Advanced Applied Mathematical and Statistical Sciences) and Department of Mathematics, Universita' degli Studi di Milano, Italy

An hybrid analysis of multiscale models for angiogenesis

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

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

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

Thus our main goal is not in providing additional models for the angiogenic phenomenon but in addressing the mathematical problem of reduction of the complexity of such systems by taking advantage of their intrinsic multiscale structure. A satisfactory mathematical modelling of angiogenesis and of many other fiber processes requires a geometric theory of stochastic fibre processes. We present here a

simplified stochastic geometric model, largely inspired by current literature, both mathematical and biological ones, for a spatially structured angiogenic process, strongly coupled with a family of relevant underlying fields.

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

15:10–15:30

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Alberto d'Onofrio
European Institute of Oncology, Milan, Italy

Vascularization and chemotherapy: inferences from a simple model

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

References.

[1] A. d'Onofrio and A. Gandolfi: Chemotherapy of vascularised tumours: role of vessel density and the effect of vascular "pruning", J. Theor. Biol. 2010, 264, 253-265.

15:30–15:50

K. Renee Fister
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Optimal control scenarios in cancer treatment strategies

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

15:50–16:10

Urszula Ledzewicz
Southern Illinois University Edwardsville
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Heinz Schaettler
Washington University

Optimal protocols for chemo- and immunotherapy in a mathematical model of tumor-immune interactions

In this talk, a classical model for the interactions between tumor and the immune system under treatment is considered as an optimal control problem with multiple controls representing actions of cytotoxic drugs as well as of agents that give a boost to the immune system. In the objective, a weighted average of several quantities that describe the effectiveness of treatment is minimized. These terms include (i) the number of cancer cells at the terminal time, (ii) a measure for the immunocompetent cell densities at the terminal point (included as a negative term), (iii) a measure for the side effects and cost of treatment in form of the overall amount of agents given and (iv) a small penalty on the terminal time that limits the overall therapy horizon which is assumed to be free. This last term is essential in obtaining a well-posed problem formulation. The form of the objective is motivated by the dynamics of the system without treatment and models the goal to move the state of the system from a region of malignant cancer growth into a benign region. Employing a Gompertzian growth model for the cancer cells, for various scenarios optimal controls and their corresponding system responses are calculated. Both the cases of mono- and combination therapies will be considered.

16:10–16:30

Jan Poleszczuk
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Optimal and suboptimal treatment protocols for anti-angiogenic therapy

In 1971 Judah Folman discovered that growth of any tumour is strongly dependent on the amount of blood vessels that it induces to grow. He surmised that, if a tumour could be stopped from growing its own blood supply, it would wither and die. Anti-angiogenic therapy is a novel treatment approach that aims at preventing a tumour from developing its own blood supply system.

On the basis of the biologically validated model proposed by Hahnfeldt, Panigrahy, Folkman and Hlatky in 1999, with the usage of the optimal control theory,

some protocols of anti-angiogenic treatment were proposed. However, in our opinion the formulation of that model is valid only for the anti-vascular treatment, that is treatment that is focused on destroying endothelial cells. Therefore, we propose a modification of the original model which is valid in the case of treatment which is focused on blocking angiogenic signaling.

We propose also a new mathematical description of the anti-angiogenic treatment goal. In current studies it is assumed that the main goal of anti-angiogenic treatment is to minimize the tumor volume at the end of treatment. On the other hand, chemotherapy is still the main kind of cancer treatment, while anti-angiogenic treatment is only a supplement. The efficient treatment with chemotherapy is possible only when the drug can be distributed evenly, that is when vessels penetrate most of the tumour regions.

Therefore, we assume that the main goal of anti-angiogenic treatment, despite the minimization of the tumour volume, is to maintain high ratio of vessels volume that support the tumour to the actual tumour volume. We analyze it as an optimal control problem and a solution of the problem is given in some cases.

MINI-SYMPOSIUM 42

Analysis of mathematical models for cancer growth and treatment, Part III

Tuesday, June 28, 17:00, *Room*: **AM3**

Organizers: **Urszula Ledzewicz, Alberto d'Onofrio**

17:00–17:20

Arnaud Chauviere
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Andreas Deutsch
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The "Go-or-Grow" hypothesis in glioma growth: mathematical modeling and analysis

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

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

In a second part, we formulate continuum models to investigate the influence of quiescence phases on the dynamics of a population of glioma cells. We propose a "Go-or-Rest" model and describe cell migration as a velocity-jump process including resting phases. We derive the corresponding macroscopic model and show that anomalous diffusion arises from the switch between motile and quiescent phases. In particular, sub- and super-diffusion regimes can be observed and are governed by a parameter describing intrinsic migratory properties of cells [**2**]. We show that our results are in excellent agreement with *in vitro* data of glioma tumor expansion [**1**]

when the switch to quiescence is regulated by the cell density. We furthermore show how this density-regulation allows for the the formation of immotile aggregates in the context of the Turing instability. We use a combination of numerical and analytical techniques to characterize the development of spatio-temporal instabilities and traveling wave solutions generated by our model. We demonstrate that the density-dependent Go-or-Grow mechanism can produce complex dynamics similar to those associated with tumor heterogeneity and invasion.

References.

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[4] K. Pham et al., *Density-dependent quiescence in glioma invasion: instability in a simple reaction-diffusion model for the migration/proliferation dichotomy*, J. Biol. Dyn. (2011, in review).
[5] M. Tektonidis et al., *Identification of intrinsic in vitro cellular mechanisms for glioma invasion*, J. Theor. Biol. (2011, in review).

17:20–17:40

C. Gerin[1], M. Badoual[1], C. Deroulers[1], B. Grammaticos[1], J. Pallud[2,3], E. Mandonnet[4]
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When do a low-grade glioma appear?

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

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

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

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

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

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

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17:40–18:00

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

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

eliminate residual or eventual newly arising tumor cells, providing thus protection from further cancer development.

18:00–18:20

S. Benzekry
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Optimal schedules for therapies in metastatic cancers.

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

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

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

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18:20–18:40

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A control approach for ODE cancer models

In this talk, we investigate cancer by using a control approach based on set-valued analysis and viability theory, given a class of ODE tumor dynamics. We show how adequate selection procedures can lead to feedback protocols with which cancer cells are eradicated. In contrast to the optimal control approach, our set-valued framework allows of highlighting the well known connection between the initial cancer stage and its curability, as well as the minimality and smoothness of a protocol and their impact on the patient quality of life. Examples from the literature are studied in order to illustrate the approach.

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MINI-SYMPOSIUM 43

Analysis of mathematical models for cancer growth and treatment, Part IV

Wednesday, June 29, 08:30, *Room*: **AM3**

Organizers: **Urszula Ledzewicz, Alberto d'Onofrio**

08:30–09:10

Antonio Fasano
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Alberto Gandolfi
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Evolution of tumor spheroids: adopting a Bingham scheme for the cell component

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

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

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

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

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

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

Thus our model is in the context of the two-fluid approach. The inspiring criterion was to incorporate some physically relevant feature (as it can be the presence of intercellular links providing a stress threshold for flow), but introducing the minimum possible number of constitutive quantities. Formulating a Bingham-like scheme proved to be not so simple, since some classical models are not compatible with velocity fields that have necessarily to occur in the case of a growing spheroid. Thus this aspect of the analysis is particularly delicate. The spheroid evolution is followed from the initial fully proliferating phase, to the stage which includes a necrotic liquid core, possibly reaching an asymptotic equilibrium (the existence of steady states has been studied in the same framework in the paper [2]). Despite the many simplifications (to which we add some less important assumptions, like the existence of interfaces separating the various classes of cells), the problem turns out to be considerably complicated. An existence theorem and numerical simulations will be presented.

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09:10–09:30

Leonid Hanin
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The End of Linear-Quadratic Era in Radiation Biology

We review mathematical and biological grounds for the linear-quadratic (LQ) model of irradiated cell survival. The LQ model was a tool of choice in quantitative radiation biology for more than 60 years. We show that some of the premises of the LQ model are unrealistic, especially for intermediate and high doses of radiation. Furthermore, we develop a more realistic cell survival model based on rigorous accounting for microdosimetric effects [1]. The new model is applicable to low, intermediate, and high acute doses of radiation, and unlike the LQ model, it does not assume that the distribution of the number of primary lesions is Poisson. For small doses, the new model can be approximated by the LQ model. However, for high doses, the best fitting LQ model grossly underestimates cell survival. The same is also true for the conventional LQ model, only more so. It is shown that for high doses, the microdosimetric distribution can be approximated by a Gaussian distribution, and the corresponding cell survival probabilities are compared.

This is a joint work with Dr. Marco Zaider from the Memorial Sloan-Kettering Cancer Center, New York.

References.

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09:30–09:50

Mirosław Lachowicz
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Macroscopic limits of a model of alignment

The macroscopic limits of the kinetic model for interacting entities are studied. The kinetic model is one–dimensional and entities are characterized by their position and orientation (+/-) with swarming interaction controlled by the sensitivity parameter. The macroscopic limits of the model are considered for solutions close either to the diffusive (isotropic) or to the aligned (swarming) equilibrium states for various sensitivity parameters. In the former case the classical linear diffusion equation results whereas in the latter a traveling wave solution does both in the zeroth ("Euler") and first ("Navier–Stokes") order of approximation.

09:50–10:10

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Markov model of cancer development – survival time prediction

We will present a newly developed [1] Markov model of cancer development. This is a compartmental model which allows one to separately consider different stages of the disease's progress. The model assumes that the distribution of waiting times between stages is exponential with the rate depending linearly on an arbitrary number of predictors. We apply this model to a breast cancer data set of women from the Pomerania region (1987–1992) [2]. We use the medical data in conjunction with a modified Bloom grading system to assign patients to different states of the Markov chain and explore what clinical predictors (which include amongst others age, tumour size, number of infected nodes, presence of estrogen and proestrogen receptors) best describe the state dependent transition probabilities and whether they have detrimental effects via a regression analysis. We also explore the possibility of survival time prediction under this Markov model of disease and consider extensions of the assumption of exponentially distributed waiting times.

References.

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10:10–10:30

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Mathematical Model of Doxorubicin Transport within Solid Tumours

The efficacy of treating tumours with chemotherapeutic agents, such as doxorubicin, is dependent on how much drug reaches the regions most distant from drug supply in sufficient concentrations. Primerau et al. [1] show that the concentration of doxorubicin decreases exponentially with the distance from the nearest

blood vessel. It is therefore important to understand how drug penetrates through cancerous tissue and how the penetration depends on treatment constraints, such as the pharmacokinetic profile or the dose of the injection.

Evans et al. [2] develop a mathematical model for the drug penetration through a multicellular layer, incorporating the "flip-flop" mechanism as a form of transport to and from cells and a Pgp-pump mechanism, which is thought to be the leading mechanism for the increased drug resistance of cancer cells. Because the model is bespoke to a transwell geometry, it has been successfully validated by experiments and important transport rates have been estimated.

Building on the work of Evans et al. [2], a model is presented for a geometry closer to that encountered *in-vivo*: a cylindrical blood vessel surrounded by multiple layers of cancerous cells. Moreover, the limited amount of membrane proteins that facilitate the transport of the drug is incorporated into the model, leading to Michaelis-Menten transport terms. Using this model, the effect of different pharmacokinetic profiles representing bolus injections, repeated bolus injections of lower concentration and infusions over several hours are assessed for their ability to deliver drug to the outer layers in the most efficacious manner.

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MINI-SYMPOSIUM 44

Analysis of mathematical models for cancer growth and treatment, Part V

Wednesday, June 29, 11:00, *Room*: **AM3**

Organizers: **Urszula Ledzewicz, Alberto d'Onofrio**

11:00–11:40

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

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

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

are both physiologically (by circadian clocks) and pharmacologically controlled. Differences between healthy and tumour cells are here modelled as different synchronisations between cell cycle phases, since healthy cell populations are assumed to be more synchronised, i.e., with steeper transition functions between cell cycle phases, than tumour cell populations.

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

11:40–12:00

Heinz Schaettler
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Urszula Ledzewicz
Southern Illinois University Edwardsville, USA

Optimal protocols for chemo- and immunotherapy in a mathematical model of tumor-immune interactions

In this talk, a classical model for the interactions between tumor and the immune system under treatment is considered as an optimal control problem with multiple controls representing actions of cytotoxic drugs as well as of agents that give a boost to the immune system. In the objective, a weighted average of several quantities that describe the effectiveness of treatment is minimized. These terms include (i) the number of cancer cells at the terminal time, (ii) a measure for the immunocompetent cell densities at the terminal point (included as a negative term), (iii) a measure for the side effects and cost of treatment in form of the overall amount of agents given and (iv) a small penalty on the terminal time that limits the overall therapy horizon which is assumed to be free. This last term is essential in obtaining a well-posed problem formulation. The form of the objective is motivated by the dynamics of the system without treatment and models the goal to move the state of the system from a region of malignant cancer growth into a benign region. Employing a Gompertzian growth model for the cancer cells, for various scenarios optimal controls and their corresponding system responses are calculated. Both the cases of mono- and combination therapies will be considered.

12:00–12:20

Evans Afenya
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Cancer Modeling: Frameworks, Approaches, and Insights

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

12:20–12:40

A. Nowakowski, A. Popa
The University of Lodz, Faculty of Math & Computer Sciences

Hamilton-Jacobi analysis for cancer treatment

Tumor anti-angiogenesis is a cancer therapy approach that targets the vasculature of a growing tumor. In the last fifteen years tumor anti-angiogenesis became an active area of research not only in medicine (see e.g. [**2**], [**3**]) but also in mathematical biology (see e.g. [**1**], [**6**], [**7**]) and several models of dynamics of angiogenesis have been described e.g. by Hahnfeldt et all [**1**], d'Onofrio [**6**], [**7**]. In a sequence of papers [**4**], [**5**] Ledzewicz and Schaettler completely decribed and solved from optimal control theory point of view the following or similar free terminal time T problem (P): minimize

$$J(p,q,u) = p(T) + \kappa \int_0^T u(t)dt \tag{1}$$

over all Lebesgue measurable functions $u : [0,T] \to [0,a] = U$ subject to

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_{0,} \tag{2}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq, \qquad q(0) = q_0. \tag{3}$$

The term $\int_0^T u(t)dt$ is viewed as a measure for the cost of the treatment or related to side effects. The upper limit a in the definition of the control set $U = [0,a]$ is a maximum dose at which inhibitors can be given. The time T is the time when the maximum tumor reduction achievable with the given overall amount A of inhibitors is being realized. The state variables p and q are, respectively, the primary tumor

volume and the carrying capacity of the vasculature. Tumor growth is modelled by a Gompertzian growth function with carrying capacity q, by equation (2), where ξ denotes a tumor growth parameter. The dynamics for the endothelial support is described by (3), where bp models the stimulation of endothelial cells by the tumor and the term $dp^{\frac{2}{3}}q$ models endogenous inhibition of the tumor. The coefficients b and d are growth constants. The terms μq and Guq describe, respectively, loss to the carrying capacity through natural causes (death of endothelial cells etc.), and loss due to extra outside inhibition. The variable u represents the control in the system and corresponds to the angiogenic dose rate while G is a constant that represents the anti-angiogenic killing parameter. Ledzewicz and Schaettler analysed the above problem using first-order necessary conditions for optimality of a control u given by the Pontryagin Maximum Principle, the second order: the so-called strengthened Legendre-Clebsch condition and geometric methods of optimal control theory.

In most of the mentioned papers the numerical calculations of approximated solutions are presented. However in any of them there are not proved assertions that calculated numerically solutions are really near the optimal one.

The aim of this paper is an analysis of the porblem (1)-(3) from Hamilton-Jacobi-Bellman point of view i.e. using dynamic programming approach and to prove that for calculated numerically solutions the fuctional (1) takes an approximate value with a given accuracy $\varepsilon > 0$.

References.

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12:40–13:00

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Existence and Asymptotic Behaviour of Solutions to Nonlinear Evolution Equations Arising in Mathematical Models of Tumour growth

In this talk we investigate the global existence in time and asymptotic profile of the solution of nonlinear evolution equations with strong dissipation. Applying the above result to some models of mathematical biology and medicine, we discuss mathematical properties of them.

For this purpose we first show the solvability and the asymptotic profile of the solution to the intial boundary value problem of non linear evolution equations:

$$(\mathrm{NE})\begin{cases} u_{tt} = D\nabla^2 u_t + \nabla\cdot(\chi(u_t, e^{-u})e^{-u}\nabla u) & in\ \mathbf{\Omega}\times(0,T) \quad (1.1)\\ \dfrac{\partial}{\partial\nu}u\,|_{\partial\mathbf{\Omega}} = 0 & on\ \partial\mathbf{\Omega}\times(0,T) \quad (1.2)\\ u(x,0) = u_0(x),\quad u_t(x,0) = u_1(x) & in\ \mathbf{\Omega} \quad (1.3)\end{cases}$$

where Ω is a bounded domain in R^n and $\partial\Omega$ is a smooth boundary of Ω and ν is the outer unit normal vector and we denote

$$\frac{\partial}{\partial t} = \partial_t,\ \frac{\partial}{\partial x_i} = \partial_{x_i},\ i = 1\cdot\cdot, n,\ \nabla u = \mathrm{grad}_x u = (\partial_{x_1}u, \cdots, \partial_{x_n}u)$$

$$\nabla^2 u = \nabla\cdot\nabla u = \Delta u = \partial^2_{x_1}u + \cdots + \partial^2_{x_n}u.$$

(1.1) includes the nonlinear evolution equations considered in **[4]**-**[6]** to show the global existence in time and the asymptotic profile of the solution of the corresponding mathematical models. We improve our mathematical approach and obtain the solution of (NE), which is in general form of one obtained in them. Next we apply our result to mathematical models of tumour growth, tumour induced angiogenesis and tumour invasion, proposed by Chaplain and Anderson(see **[1]**-**[3]**).

References.

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MINI-SYMPOSIUM 45

Turing !! Turing?? on morphogenesis via experimental and theoretical approaches

Wednesday, June 29, 17:00, *Room*: **UA3**

Organizer: **S. Seirin Lee**

17:00–17:20

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Gene Expression Time Delays and Turing Pattern Formation

There are numerous examples of morphogen gradients controlling long range signalling in developmental and cellular systems. The prospect of two such interacting morphogens instigating long range self-organisation in biological systems via a Turing bifurcation has been explored, postulated or implicated in the context of numerous developmental processes. However, modelling investigations of cellular systems typically neglect the influence of gene expression on such dynamics, even though transcription and translation are observed to be important in morphogenetic systems.

The investigations of our study demonstrate that the behaviour of Turing models profoundly changes on the inclusion of gene expression dynamics and is sensitive to the sub-cellular details of gene expression. These results also indicate that the behaviour of Turing pattern formation systems on the inclusion of gene expression time delays may provide a means of distinguishing between possible forms of interaction kinetics, and also emphasises that sub-cellular and gene expression dynamics should not be simply neglected in models of long range biological pattern formation via morphogens. We present results mainly for Gierer-Meinhardt systems but our results are observed more universally in many Turing pattern formation systems. Exploring the dynamics of these systems suggests that the basic Turing mechanism should be reconsidered or would generally require a novel and extensive secondary mechanism to control reaction diffusion patterning.

***This work has already been extended in several papers. The works have been collaborated with E.A. Gaffney (University of Oxford), R.E. Baker (University of Oxford) and N.A.M. Monk (University of Nottingham).** Papers related with this work are given in the following References.

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[4] S. Seirin Lee, E.A. Gaffney, R.E. Baker *The dynamics of Turing patterns for morphogen-regulated growing domains with cellular response delays.* (Submitted in Bull.Math.Bio.).

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17:20–17:40

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The Mechanism To Establish Robust Left-Right Asymmetry

A development of animal body proceeds under the intrinsic noise (gene expression, protein interaction, cell migration etc.) and the extrinsic noise (environment). In spite of existence of so much noise, an animal development proceeds robustly and C.H.Waddington called a stability of a development, "Canalization". Of course, left and right determination in the mouse is not exception and canalization of L-R development attains 99.99 %.

Our body has many internal organs that show asymmetric morphologies about left-right axis and these morphologies play important roles in its function, such as the heart, liver, stomach and intestine. Recently, mechanisms to establish L-R asymmetry in the mouse embryo have been elucidated by using genetics and molecular approaches. In the mouse embryo, the small leftward fluid flow in the node produces first asymmetric information along L-R axis and the left-side specific genes are expressed in the left lateral plate mesoderm subsequently.

Although some cascades of gene expressions were studied, it is unknown how robust expressions of left side specific genes are established from the small asymmetric water flow in the node. Nodal and Lefty, two members of the transforming growth

factor-β super family of proteins and are expressed in the lateral plate mesoderm, have been implicated in Turing system. Turing system is a mathematical model that consists of two diffusible molecules and may underlie pattern formation during development. We have now examined the potential role of Turing system in left-right patterning both by experimentally manipulating Nodal and Lefty gene expression in the mouse embryos and by constructing a mathematical model.

Our results suggest that an initial small difference in the level of an activating signal between the left and right sides of the embryo is amplified and converted into robust asymmetry by Turing system involving Nodal and Lefty.

References.

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17:40–18:00

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Periodic patterning across heterogeneous fields: insights from embryonic feather development

Vertebrate skin is characterized by its patterned array of pigments and structural appendages such as feathers, hairs and scales. A number of lines of evidence point to the action of a Turing type mechanism in laying out the periodic pattern of feathers and hairs in the developing skin. Several candidate Activator and Inhibitor pathways which act during this process have been identified, though the full set of interactions between them remains to be defined. Bone morphogenetic proteins (BMPs) act as key Inhibitors during feather formation, and we have uncovered different sensitivities to this Inhibitor in different regions of the skin. We then focused on combining mathematical modeling and experimental approaches to explore the pattern outcomes and propensity for pattern change arising from the operation of a Turing type system across a field with unequal Inhibitor sensitivities.

18:00–18:20

Eamonn A. Gaffney
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Aspects of Turing's Pattern Formation Mechanism On Growing Domains

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

18:20–19:00

Shigeru Kondo
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How experiment and mathematics can cooperate in the study of Turing patterns of real biological systems?

It was 60 years ago that Turing presented his outstanding idea about the biological pattern formation. Since then, many theoretical studies have been suggesting the RD mechanism could be one of the principles of biological morphogenesis. Such theoretical studies seem to be enough for the mathematicians to believe the biological relevance of the theory. However, majority of the developmental biologists still feel that the idea of RD is not so much related to their study in spite of the several empirical evidences.

We guess this problem comes from the gap of complexity between the simple differential equations and the complex real biological phenomena. Through the 15 years of experiment on the pigmentation stripe of fish skin, we recently found that many kinds of cellular events, migration, differentiation, dendrite elongation, and gap junctions, are involved in the pigment pattern formation. The whole system is not similar to any of simple model proposed before. After presenting our newest data, I would like to discuss the possible way for the cooperation between the theoretical and experimental sides.

MINI-SYMPOSIUM 46

Statistical Analysis of Biological Signals I

Saturday, July 2, 08:30, *Room*: **CP1**

Organizer: **Jacek Leśkow**

08:30–09:10

Modeling mass spectrometry proteomics data using nonparametric regression methods

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The amount and complexity of the data collected from the mass spectrometry instruments has outpaced the methodological developments in their processing. We propose a number of approaches to address the issues arising in modeling such data. The methods used include local polynomial kernel regression with adaptive bandwidth selection and wavelet methods. We address the issues of non-stationarity in the variance process and correlated errors. In this talk, we provide the results of preliminary simulation studies and apply the methods to a lung cancer SELDI-TOF MS data set.

09:10–09:30

Christiana Drake
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Travis Loux
Department of Statistics, University of California, Davis

Not Missing at Random and Combined Odds Ratios from Mixture Models

Longitudinal studies and surveys often deal with incomplete observations. The validity of inference depends on the missingness mechanism [Little J.A, and Rubin, D.B., 2002]. When the missing data mechanism depends on observed data only, estimation of means and/or regression coefficients requires adjustment but is possible

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

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Glynn, R., Laird, N., and Rubin, D.B. (1993), The Performance of Mixture Models for Nonignorable Nonresponse With Followups. Journal of the American Statistical Association, 88: 984-993.

09:30–09:50

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Dynamic Information and the Meaning of Biological Signs

The communication between cooperating and adversary organisms is central to the understanding of biological ecosystems. Commonly, this communication is formalized in terms of Claude E. Shannon's *Mathematical Theory of Communication* [4]. In this theory, information is represented as a measurable quantity arising from statistics on the underlying vocabulary. There have been several works addressing the application of Shannon information to biological systems [1,3,5].

Here, I argue that Shannon information encompasses significant shortcomings, which limit the applicability to communication in the life sciences. Since Shannon information is a purely statistical quantity, it treats only syntactic aspects of the communication process. In contrast, the levels of semantics, pragmatics, and dynamics [1] are not under consideration. Clearly, a message has always an impact

on living systems, because it leads to a certain adaptive response. Yet this active response is part of the pragmatic-dynamic level and integral part of biological communication.

In this talk, I present an alternative concept of information [2]. The so-called *Dynamic Information* rates incoming signals with a relative importance depending on the internal state of an agent [1,2]. The bigger the induced change in the agent's behavior, the bigger are relative importance and the resulting dynamic information.

First, I introduce the mathematical framework modeling elementary biological communication by means of dynamical systems with input and output. In this approach, agents are represented by nonlinear coupled systems of ODEs with input terms. Next, the concept of dynamic information is developed as a bridge between the theory of dynamical systems and Shannons's theory of communication. Finally, I apply the developed framework to task allocation in ant colonies.

References.

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[3] Drew Rendall, M. J. Owren, M. J.Ryan. *What do animal signs mean?*, Animal Behaviour, **78**, 233-240

[4] Claude E. Shannon, *A Mathematical Theory of Communication*, Bell System Technical Journal, **27**, 379-423

[5] Robert M. Seyfarth, Dorothy L. Cheney, Thore Bergman, Julia Fischer, Klaus Zuberbühler, Kurt Hammerschmidt. *The central importance of information in studies of animal communication*, Animal Behaviour, **80**, 3-8

09:50–10:10

T. Kozubowski
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Krzysztof Podgorski
Centre for Mathematical Sciences, Mathematical Statistics, Lund University, Sweden

Skew Laplace Distributions: Theory and Some Applications in Biology

Skew Laplace distributions, which naturally arise in connection with random summation and quantile regression settings, offer an attractive and flexible alternative to the normal (Gaussian) distribution in a variety of settings where the assumptions of symmetry and short tail are too restrictive. In particular, this model has been recently found useful for gene selection and classification methods in analysis of microarray data sets. In another application, it was observed that the Laplace distribution adequately represents the size distribution of microbial cells. We shall

present fundamental properties of this model, which give insight into its applicability in these areas, and discuss its extensions to multivariate models, time series, and stochastic processes.

10:10–10:30

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Analysis and Understanding of Fungal Tip Growth

Fungi cause devastating plant and human diseases. There is considerable evidence that much of the cellular machinery driving growth of invasive fungal hyphae is common across all fungi, including plant and mammalian pathogens, and involves localized tip growth. Furthermore, successful fungal infection is critically dependent on accurate perception of the host surface at the tip to control morphogenesis and trigger host invasion. This suggests that detailed investigation of these early morphogenetic and signalling events is crucial to a thorough understanding of virulence.

We are therefore developing high-throughput automated microscope-based multidimensional image analysis systems to segment and characterize fungal growth, and characterize the patterns of protein localization within the tip that control development. We propose a curvature-based approach to identify fungal cell tip and determine the growth direction, based on segmentation using local thresholding

and mathematical morphology methods. The curvature of cell boundary is calculated and the boundary point with the highest curvature value defines the tip cell position. For cell expressing key GFP-tagged regulatory proteins, the image intensity profiles on the left and right side of the tip position are recorded to provide a map of the plasmamembrane protein distribution, and to determine the relationship between growth vector and asymmetric localization. This procedure is repeated for all images in the time-lapse.

We tested the performance of the proposed concept on fluorescence images of Neurospora crassa germlings expressing GFP-CRIB and GFP-tagged MAK2 kinase during hyphal avoidance responses and conidial anastomosis tube fusion, respectively.

References.

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MINI-SYMPOSIUM 47

Statistical Analysis of Biological Signals II

Saturday, July 2, 11:00, *Room*: **CP1**

Organizer: **Jacek Leśkow**

11:00–11:40

Aleksander Weron
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Identification of fractional subdiffusive dynamics of mRNA molecules

Identification of fractional subdiffusive dynamics of mRNA molecules

Krzysztof Burnecki and Aleksander Weron

Hugo Steinhaus Center, Institute of Mathematics and Computer Science, Wroclaw University of Technology, Wyspianskiego 27, 50-370 Wroclaw, Poland

In this talk we propose a statistical methodology how to distinguish between three mechanisms leading to single molecule subdiffusion, [1-2]. Namely, fractional Brownian motion, fractional Levy stable motion and Fractional Fokker-Planck equation. We illustrate step by step that the methods of sample mean-squared displacement and p-variation can be successfully applied for infinite and confined systems. We already identified fractional subdiffusive dynamics on biological data describing the motion of individual fluorescently labeled mRNA molecules inside live E. coli cells [3-5], but it may concern also many other biological experimental data.

References.

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11:40–12:00

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

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

References.

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12:00–12:20

Jacek Leśkow
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Resampling with Applications to Neurophysiological Time Series

Resampling with Applications to Neurophysiological Time Series

Jacek Leskow Department of Quantitative Methods in Management The Polish-American Graduate School of Business WSB-NLU Nowy Sacz

One of the fundamental tools in the analysis of biosignals including functional magnetic resonance imaging (fMRI) is a time series model and corresponding set of parameters. Such time series are known to exhibit temporal autocorrelation which is one of the fundamental characteristic for such fMRI observations (see e.g. Bullmore et al (2001)). In the presentation, a general survey of resampling methods for time series will be presented and consistency issues will be addressed. The focus of the presentation will be application-oriented toward fMRI signals that exhibit non-gaussian behavior and are non-stationary. The statistical results presented e.g in Leskow et al (2008) will be accompanied by applications to neurophysiological time series.

References.

[1] Bullmore E., Long, C., Suckling, J. ,Fadili, J. Calvert, G., Zelaya. F., Carpenter, T.A, Brammer, M. (2001), Colored Noise and Computational Inference in Neurophysiological (fMRI)

Time Series Analysis: Resampling Methods in Time and Wavelet Domains. Human Brain Mapping, 12:61-78.
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12:20–12:40

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Level crossings in biological time series

Kedem in his research [**1**] made use of zero crossings theory in time series analysis. Zero crossings are remarkably simple and effective tool to examine the autocorrelation structure of time series. The application of nonlinear binary transformation of time series allows to retain information contained in the autocorrelation function of the original data. Kedem (1989) found relation between first order autocorrelation and the expected zero crossings rate. In the case of zero mean stationary Gaussian time series there exist explicit formula (*cosine formula*), connecting the first order autocorrelation ρ_1 and the expected number of zero crossings $E[D]$. The relationship looks as follows

$$\rho_1 = \cos(\frac{\pi E[D]}{n-1}).$$

Cosine formula is therefore very useful for the estimation purposes. Having given the number of zero crossings, we can estimate first order autocorrelation in a very simple and fast way. Using Electroencephalogram (EEG) signal we ilustrate how accurate the cosine formula is. We also answer the question how far precisely we can compute the first order autocorrelation using zero crossings.

References.

[1] B.Kedem, *Time Series Analysis by Higher Order Crossings* IEEE Press New York 1993.
[2] S.Y.Tseng, R.C.Chen, F.C.Chong, T.S.Kuo, *Evaluation of parametric methods in EEG signal analysis* Medical Enginiering and Physics **17** 71–78.
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12:40–13:00

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The joint distribution of the sum and maximum of exponential random variables with applications to biology

We consider the joint distribution of the maximum Y and sum X of n iid exponential random variables. We present the exact joint distribution of the vector (X, Y) together with its marginals and conditionals. Further, we extend our result to stochastic number of terms, and present the exact joint distribution of the random vector (N, X, Y), when N has a geometric distribution. Then, X is the random sum and Y is the random maximum of N iid exponential random variables. We illustrate the modeling potential of these distributions using applications in biology.

MINI-SYMPOSIUM 48

Fluid-structure interaction problems in biomechanics

Saturday, July 2, 08:30, *Room*: **AM6**

Organizer: **Sookkyung Lim**

08:30–09:10

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Yung Sam Kim
Chung-Ang University
Wanho Lee
Konkuk University

A heart model in the whole circulatory system

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

09:10–09:30

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Excitable tissues in fluids

A wide range of numerical, analytical, and experimental work in recent years has focused on understanding the interaction between fluids and elastic structures in the context of cardiovascular flows, animal swimming and flying, cellular flows, and other biological problems. While great progress has been made in understanding such systems, less is known about how these excitable tissues modulate their mechanical properties in response to fluid forces and other environmental cues. The broad goal of this work is to develop a framework to integrate the conduction of action potentials with the contraction of muscles, to the movement of organs and organisms, to the motion of the fluid, and back to the nervous system through environmental cues. Such coupled models can then be used to understand how small changes in tissue physics can result in large changes in performance at the organ and organism level. Two examples will be discussed in this presentation. The first example considers how active contractions generated by the cardiac conduction system can enhance flows in tubular hearts, particularly at low Reynolds numbers. The second example considers how the interactions between pacemakers in the upside down jellyfish can alter feeding currents generated by the bell pulsations. In both cases, the ultimate goal is to simulate the electropotentials in the nervous system that trigger mechanical changes in 1D fibers representing the muscular bands. The muscular contractions then apply forces to the boundaries that interacts with the fluid modeled by the Navier-Stokes equations. The computational framework used to solve these problems is the immersed boundary method originally developed by Charles Peskin.

09:30–09:50

Karin Leiderman
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A Mathematical Model of Thrombus Formation Under Flow

To explore how blood flow affects the growth of thrombi (blood clots) and how the growing masses, in turn, feed back and affect flow, we have developed a spatialtemporal mathematical model of platelet deposition and coagulation under flow. The model includes detailed descriptions of coagulation biochemistry, chemical activation and deposition of blood platelets, as well as the two-way interaction between the fluid dynamics and the growing platelet mass. In this talk, I will present the mathematical model and use it to explain what underlies the threshold behavior of the production of an important enzyme within the coagulation system. I will then show how the wall shear rate of flow and a near-wall enhanced platelet concentrations affect the development of growing thrombi. Since we account for the porous nature of thrombi, I am also able to demonstrate how advective and diffusive transport to and within thrombi affects their growth at different stages and spatial locations.

09:50–10:10

Sarah Olson
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Susan Suarez
Cornell University
Lisa Fauci
Tulane University

Coupling biochemistry, mechanics, and hydrodynamics to model sperm motility

Calcium (Ca2+) dynamics in mammalian sperm are directly linked to motility. These dynamics depend on diffusion, nonlinear fluxes, Ca2+ channels specific to the sperm flagellum, and other signaling molecules. The goal of this work is to couple Ca2+ dynamics to a mechanical model of a motile sperm within a viscous, incompressible fluid. We will first discuss a model of the CatSper mediated Ca2+ dynamics relevant to hyperactivated motility. The method of regularized Stokeslets is used to investigate the hydrodynamics of swimming sperm. Results showing emergent waveforms, swimming speeds, and trajectories will be compared to experimental data.

10:10–10:30

Katarzyna A. Rejniak
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Interactions between interstitial fluid and tumor microenvironment in chemotherapy

Interstitial fluid, a solution filling the space between stromal cells, provides a means of delivering various molecules (such as nutrients, oxygen or drugs) to the cells, as well as removal of metabolic waste. In tumorous tissues, the transport of anticancer drugs is moderated by differences in interstitial fluid pressure that varies in different tumors and at different tumor sides, as well as by changes in stromal tissue structure. I will discuss computational simulations showing how tumor tissue metabolic state (its oxygenation and acidity) become modified due to actions of chemotherapeutic drugs leading to the emergence of tumor zones with potentially drug-resistant cells and/or to tumor areas that are not exposed to drugs at all. Both of these phenomena can contribute to the moderate clinical success of many anticancer drugs.

MINI-SYMPOSIUM 49

Modeling of immune responses and calcium signaling I

Tuesday, June 28, 17:00, *Room*: **AM8**

Organizers: **Tomasz Lipniacki, Bogdan Kaźmierczak, Marek Kimmel**

17:00–17:40

Markus Covert
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Heterogeneous cellular responses via noisy paracrine signals

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

17:40–18:00

Marta Iwanaszko
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The dependence of expression of NF-B dependent genes: Statistics and evolutionary conservation of control sequences in the promoter and in the 3 UTR

Background: NF-B family plays a prominent role in innate (early) immune response and has impact on other processes such as cell cycle activation or cell apoptosis. Upon stimulation by pathogens such as viral RNA a kinase cascade is activated, which eventually strips the NF-B of its inhibitor IB molecule and allows it to translocate into the nucleus. Once in the nucleus, it activates transcription of approximately 90 genes, some of which trigger further stages of the immune response. NF-B-dependent genes can be categorized, based on the timing of their activation counted from NF-B translocation into the nucleus, as Early, Middle and Late genes. It is not obvious what mechanism is responsible for segregation of the genes timing of transcriptional response. Results: It is likely that the differences in timing are reflected in differences in the structure of promoter regions of genes in different categories. Specifically, this might concern differences in number and type of transcription factor binding motifs, required for NF-B itself as well as for the putative cofactors. Using this approach we analyzed if genes assignment to the Early, Middle or Late group based on expression pattern, is connected with special features in promoter structure. This connection may be one of the mechanisms underlying the different patterns of gene expression control. This issue is best considered in the evolutionary framework, first, since functional binding sites are likely to be conserved in evolution and second, since the patterns of evolutionary change of promoter regions are not very well-known and are of serious interest. Another control sequences are AU - rich elements (ARE) located in 3UTR. AREs target mRNA for rapid degradation and inflict mRNA instability. Latest studies show that genes transcribed with unstable mRNA have different transcription dynamic. We have found that there are significant differences between the Early and the Late genes promoter and 3UTR regions and many similarities are observed among the Early genes even between distant species, while the Late genes promoter regions are much more diversified. Conclusions: Wider phylogenetic analysis of NF-B dependent genes provides insight into the degree of cross species similarity found in the Early genes, opposed to many differences in promoter structure that can be found among the Late genes. This suggest that activation and expression of the Late genes is much more species specific than in the Early genes. Based on the promoter structure and ARE content Middle genes can be divided into two subgroups: Early like and Late like.

18:00–18:30

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Prof. Michael White
University of Manchester

Oscillations and feedback regulation in the NF-B signalling

Time-lapse cell imaging showed that in response to Tumour Necrosis Factor alpha (TNF) Nuclear Factor kappa B (NF-B) transcription factor oscillates between the cytoplasm and nucleus (Nelson et al., (2004) Science 306: 704). Treatment with repeat pulses of TNF at different intervals enabled frequency-dependent encoding of target gene expression (Ashall et al., (2009) Science 324: 242). Development of a highly constrained mathematical model suggested that cellular variation in NF-B dynamics arises from a dual-delayed negative feedback motif (involving stochastic transcription of IB and IB). We suggest that this feedback motif enables NF-B signalling to generate robust single cell oscillations by reducing sensitivity to key parameter perturbations. Enhanced cell heterogeneity may represent a mechanism that controls the overall coordination and stability of cell population responses by decreasing temporal fluctuations of paracrine signalling (Paszek et al., (2010) PNAS 107: 11644). We have also shown that the cell to cell heterogeneity is profoundly increased following low-dose stimulation. Low doses of TNF resulted in stochastic delays in single cells, but once the first translocation occurs the typical 100 min period was maintained (Turner, et al., (2010) J. Cell Sci. 15: 2834). Our analyses demonstrate a fundamental role of oscillatory dynamics in control of inflammatory signalling at different levels of cellular organisation.

18:30–19:00

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

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

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

Three kind of experiments were performed:

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

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

MINI-SYMPOSIUM 50

Modeling of immune responses and calcium signaling II

Wednesday, June 29, 14:30, *Room*: **AM8**

Organizers: **Tomasz Lipniacki, Bogdan Kaźmierczak, Marek Kimmel**

14:30–15:10

James R. Faeder
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Rule-Based Modeling of Molecular and Cellular Processes

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

The need to simplify the development of signal transduction models and to expand their scope has motivated the development of rule-based modeling languages, such as BioNetGen [2] and Kappa [3], which provide a rich and yet concise description of signaling proteins and their interactions. Their success is demonstrated by the growing community of users and the substantial number of models that have been developed and published. While greatly facilitating the translation of knowledge about signaling biochemistry into models, however, rule-based languages do not directly address the combinatorial challenges involved in the simulation of such models, which arise from the size of the reaction network implied by the rules. For these, new agent-based stochastic simulation methods have been developed for rule-based models with computational requirements that are independent of the number of possible species (i.e., complexes) and proportional to the number of molecules (e.g., proteins) being simulated. In addition, general and efficient implementations

are now available that enable the rapid simulation of rule-based models of virtually any complexity. NFsim is one such simulator that stands out because of its efficiency and the ability to course-grain complex interactions through the incorporation of high-level functions into the rate laws that govern rule application [4]. The use of stochastic simulations, however, exacerbates the already difficult problems common to all complex models of relating model parameters to model behavior and of estimating parameter values based on experimental observations and data. For these, new statistical model checking algorithms and tools have been developed that allow model properties to be determined from a minimal number of simulation runs [5]. Taken together, rule-based modeling languages and their associated tools address the issue of combinatorial complexity in cell regulatory networks, allowing the development, simulation, and analysis of models with unprecedented scope and detail and, we hope, predictive capability.

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15:10–15:30

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Dimerization Effects in MAPK cascade

The MAPK (Mitogen-Activated Protein Kinase) cascades are among the most important signal transduction pathways in eukaryotic cells. The core of a MAPK pathway comprises a series of sequentially activated kinases, generically referred to as MAP3Ks, MAP2Ks, and MAPKs. Of particular importance are Raf/MEK/ERK and MEKK/MEK/JNK cascades due to their role in stress response, proliferation, differentiation, and the development of cancer. Consequently, these pathways have been extensively modeled. However, the models developed so far ignore homo- and heterodimerization events occurring between kinases within each tier of the cascade. The significance of dimerization of Raf and MEK proteins is especially well documented. In particular, the dimerization of RAF proteins appears critical for their activation - its dysregulation due to mutations or experimental chemotherapeutic inhibitors can lead to oncogenesis [1] or paradoxical activation [2], respectively. The

dimerization of MEK1 and MEK2, on the other hand, introduces a novel regulatory mechanism of controlling the pathway's output via feedback phosphorylation by ERK [3]. Lastly, three-member scaffold proteins such as KSR, which assemble signalling complexes, have themselves been shown to dimerize [4], potentially providing a platform for dimerization of other MAPK components. We have incorporated these effects to produce more realistic models of the MAPK cascade as well as to explore their possible role in the pathway's regulation and dynamics.

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15:30–15:50

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A rule-based model for early events in B cell antigen receptor signaling

B cell antigen receptor (BCR) signaling regulates the activities and fates of B cells. Here, we present a rule-based model for early events in BCR signaling that encompasses membrane-proximal interactions of BCR, two membrane-tethered Src-family protein tyrosine kinases, Lyn and Fyn, the adaptor protein PAG, and two cytosolic protein tyrosine kinases, Csk and Syk. The signaling is triggered by aggregation of the BCR by foreign antigens, which increase the rate of BCR-Src kinases interactions. The interactions involve two feedback loops: a positive feedback loop acting on a short time scale and a negative feedback loop acting on a longer time scale. The positive feedback loop arises because of the way that the two

Src-family kinases, Lyn and Fyn, interact with the two signaling chains of the BCR complex, Igα (CD79A) and Igβ (CD79B). Lyn and Fyn constitutively associate with BCR via low-affinity interactions and trans-phosphorylate tyrosine residues in the immunoreceptor tyrosine-based activation motifs (ITAMs) of Igα and Igβ in neighboring receptors within antigen-induced clusters of BCR. These sites of phosphorylation then serve as high-affinity docking sites for the SH2 domains in Lyn and Fyn, which recruit more Lyn and Fyn to BCR clusters. Lyn and Fyn also undergo autophosphorylation within antigen-induced clusters of BCR, which upregulates their kinase activities. The negative feedback loop is mediated by PAG, which associates with Lyn and Fyn in a phosphorylation-dependent manner. PAG serves as a docking site for Csk, which mediates the phosphorylation of a C-terminal regulatory tyrosine residue found in both Lyn and Fyn. Phosphorylation of this residue enables an intramolecular interaction that downregulates Lyn/Fyn kinase activity. The model makes the distinction between the two Src kinases, Lyn and Fyn. Whereas Lyn is allowed to phosphorylate PAG at all tyrosine residues, Fyn may not phosphorylate its own binding sites on PAG due to allosteric constraints. This distinguishes Lyn as the only Src kinase capable to induce the negative feedback in the system. A dynamical stability analysis of the model reveals that the BCR circuit can display two interesting behaviors. Bistability can be expected in PAG -/-, Csk -/-, and Lyn -/- cells, whereas oscillatory pulse-like responses to BCR clustering can be expected in cells with the negative feedback loop intact (wild-type cells and Fyn -/- cells) under some conditions. The qualitative behaviors predicted by the model are consistent with the known behaviors of Lyn and Fyn deficient cells.

This study was supported by Foundation for Polish Science grant TEAM/2009-3/6 and National Institutes of Health grants GM076570 and GM085273.

15:50–16:10

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Type of noise defines the most stable attractor in bistable gene expression model

We consider simplified stochastic model of gene expression with the nonlinear positive feedback. It is assumed that the gene may be in one of the two states: active or inactive. Protein molecules are produced directly from the active gene. We focus on the case in which in the deterministic approximation the system has two stable steady state solutions. Two types of noise are considered; transcriptional (characteristic for bacteria) - due to the limited number of protein molecules, and gene

switching noise (important in Eukaryotes) - due to gene activation and inactivation transitions. We explore the correspondence between the stochastic system and its deterministic approximation in the limit of low noise. Analytical analysis of two approximations of the stochastic system, each with only one type of noise included, showed that when noise decreases to zero (I) the stationary probability density (SPD) converges to Dirac delta in one of two stable steady states, (II) in a broad range of parameters the SPD of the system with transcriptional noise converges to Dirac delta in a different steady state than the SPD of the system with gene switching noise. This suggest that the ratio of the transcriptional to the gene-switching noise dictates in which state the SPD concentrates. We verified this hypothesis by Monte Carlo simulations of the exact model. This finding has the following thermodynamic interpretation. The non interacting molecules diffusing in the uniform temperature field settle in the lowest potential well as temperature tends to zero. However when the temperature field is not uniform temperature profile dictates in which well molecules concentrate. Apparently, the two types of noise specific for gene expression are connected with two different temperature fields and thus favors the different attractors.

Our study demonstrates that in systems with the underlying bistability, like genetic switches, the noise characteristic controls in which of the epigenetic attractors cell population will settle.

16:10–16:30

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Stochastic switching in a spatially extended, bistable kinase autoactivation model

In this study we consider a spatially extended kinase autoactivation model with underlying bistability. We assume that kinases may diffuse on the cell membrane (or its restricted domain) and can be in one of three states: unphosphorylated, single or doubly phosphorylated. Catalitic activity of the kinase is regulated by its phosphorylation level; unphosphorylated kinases have the lowest activity, doubly phosphorylated – the highest. The emerging reactions are following:
$K_p \xrightarrow{d} K$, $K_{pp} \xrightarrow{d} K_p$ – dephosphorylation,
$K + K \xrightarrow{c_1} K + K_p$, $K + K_p \xrightarrow{c_1} K + K_{pp}$ – phosphorylation by K,

$K_p + K \xrightarrow{c_2} K_p + K_p$, $K_p + K_p \xrightarrow{c_2} K_p + K_{pp}$ – phosphorylation by K_p,
$K_{pp} + K \xrightarrow{c_3} K_{pp} + K_p$, $K_{pp} + K_p \xrightarrow{c_3} K_{pp} + K_{pp}$ – phosphorylation by K_{pp},
where d and $c_3 > c_2 > c_1$ are dephosphorylation and phosphorylations coefficients. Let us notice that for $c_1 = 0$ the state in which all kinases are unphosphorylated is absorbing.

We consider two limits:

(1) infinite diffusion for which the system can be considered as perfectly mixed and its dynamics is described by the two-dimensional Markov process, and simulated using the Gillespie algorithm,
(2) continuous limit in which evolution of concentrations is given by the system of partial differential equations.

We numerically investigated the activation process in the original model in SpatKin, a program designed to simulate reaction-diffusion processes on a triangular lattice. We observed that for biologically justified values of parameters the behavior of the system cannot be described in any of the two limits even qualitatively. In particular, we found that probability density distributions depend on the diffusion coefficient: bimodal distributions observed in the infinite diffusion limit become unimodal with decreasing diffusivity. We also found that in the bistable case the expected extinction time (i.e. the time in which the absorbing state is reached when $c_1 = 0$) grows with diffusivity and only in the infinite diffusion limit it becomes exponentially proportional to the number of molecules.

We conclude that the original Gillespie algorithm is not appropriate for simulations of spatially extended systems.

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936 and Foundation for Polish Science grant TEAM/2009-3/6.

MINI-SYMPOSIUM 51

Modeling of immune responses and calcium signaling III

Wednesday, June 29, 17:00, *Room*: **AM8**

Organizers: **Tomasz Lipniacki, Bogdan Kaźmierczak, Marek Kimmel**

17:00–17:40

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

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

17:40–18:00

Alexander Skupin
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How spatial cell properties shape Ca^{2+} signals

Ca^{2+} plays a major role in many physiological processes including muscle contraction and gene regulation. The versatility is achieved by a wide spectrum of Ca^{2+}

signals ranging from fast local events to cell wide repetitive spiking and plateau responses. It is still a challenge to understand how cells generate reliable cellular signals with microscopic noisy Ca^{2+} release channels like IP_3Rs. We have recently shown in experiments that the microscopic fluctuations are carried on the level of the cell by the hierarchical organization of the Ca^{2+} pathway. Here we use our detailed modelling approach to analyze how Ca^{2+} signals depend on physiological parameters. The model describes individual release channels by Markov chains the states of which act as stochastic source terms in a reaction diffusion system representing the cell. This allows for following the Ca^{2+} signal from its local triggering event to the cell wide response. In extensive simulations we analyzed how the spatial properties shape Ca^{2+} signals. The simulations can quantitatively describe experiments in which Ca^{2+} diffusion is reduced by additional buffer. In further simulations, the temperature dependence of Ca^{2+} signals could be mapped to a change in the SERCA pump strength that determines the spatial coupling between release sites. All these modelled and experimental data are in addition analyzed and compared by a moment based approach that points to a functional robustness of the Ca^{2+} pathway.

18:00–18:20

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Traveling Waves in the Buffered FitzHugh-Nagumo Model

In many physiologically important excitable systems, such as intracellular calcium dynamics, the diffusing variable is highly buffered. In addition, all physiological buffered excitable systems contain multiple buffers, with different affinities. We will discuss the properties of wave solutions in excitable systems with multiple buffers, and how multiple buffers interact.

18:20–18:40

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B cell activation triggered by the formation of the small receptor cluster: a computational study

B cells are activated in response to the binding of polyvalent ligands, which induces the aggregation of B cell receptors. The formation of even small clusters containing less than 1% of all the receptors is sufficient for activation. This observation led us to the model in which the receptor cluster serves only as a switch that turns on the activation process, involving also the remaining receptors. We have proposed that the system is bistable, and thus its local activation may start the propagation of a traveling wave, which spreads activation over the entire mebrane. We found that the minimal size of the activatory cluster decreases with the thickness of the cytoplasm and kinase diffusion coefficient. It is particularly small when kinases are restricted to the membrane. These findings are consistent with the properties of B cells, which have extremely thin cytoplasmic layer and in which the receptor interacting Src family kinases are tethered to the membrane.

18:40–19:00

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Bifurcation phenomena in spatially extended kinase-receptor interaction model

We consider a reaction-diffusion model of mutual interaction of membrane receptors with kinases proposed in [1]. It is assumed that membrane receptors and cytosolic kinases activate each other, which establishes the positive feedback. The kinases and the receptors are dephosphorylated by uniformly distributed phosphatases. The existence of positive feedback leads to bifurcation at which the positive stable solution appears.

In this study we consider, unlike the authors in [1], the case of nonuniformly distributed membrane receptors. We apply the Steklov eigenproblem theory [2] to analyze the linearized model and find the analytic form of solutions. This approach allows us to determine the critical value of phospahatase activity at which cell activation is possible as a function of kinase diffusion coeffcient and anisotropy of receptor distribution using only algebraic methods.

We showed that cell sensitivity grows with decreasing kinase diffusion and increasing polarity of receptor distribution. Moreover, these two effects are cooperating. The solutions to the original nonlinear system close to the bifurcation point can be approximated by the solution to the linearized one. Moreover this approximation can be improved by using the method of successive approximations.

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MINI-SYMPOSIUM 52

Modeling of immune responses and calcium signaling IV

Saturday, July 2, 08:30, *Room*: **SP1**

Organizers: **Tomasz Lipniacki, Bogdan Kaźmierczak, Marek Kimmel**

08:30–08:50

Jacek Miekisz
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Simple stochastic models of gene regulation

We will discuss simple models of gene regulation. We assume that the number of mRNA and protein molecules is small and therefore to describe biochemical processes of transcription, translation, and degradation, we use birth and death processes. We linearize Hill functions which describe regulation, use the generating function approach to the Masters equations, and show that translational repression contributes greater noise to gene expression than transcriptional repression [1].

Our main goal now is to derive analytical expressions for the variance (noise) of the number of protein molecules in models where changes of the DNA state between an active and inactive one are governed by birth and death processes whose intensities depend on the number of protein molecules [2]. We will discuss different approaches to the problem of closure of an infinite chain of equations for moments of the protein probability distribution and apply it to systems with two gene copies [3].

References.

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08:50–09:10

Paulina Szymanska

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Modeling of self-regulating gene

We study the variance of the number of proteins produced in a self-regulating gene in a steady state with both one and two copies of gene. Master equations and differential equations for the first and second moments of the variable describing the number of proteins are formulated in both models. Various approximation schemes are used in order to close the set of equations for the moments. Specifically, we examine the dependence of the variance on the adiabaticity parameter measuring the relative rate of DNA-protein unbinding and protein degradation. We compare the variance obtained in models with one and two gene copies.

09:10–09:30

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Positive feedback in NF-κB signaling

NF-κB is a key transcription factor controlling immune responses, such as inflammation, proliferation and apoptosis. Its regulatory system is tightly controlled by several feedback loops. The two negative loops mediated by NF-κB inducible inhibitors, IκBα and A20, provide the oscillatory responses to the tonic TNFα stimulation, in which NF-κB translocates in and out of the nucleus with period of about 100 min. These oscillations maintain NF-κB phosphorylation, and are indispensable for NF-κB dependent signalling. Here, we explore the role of the feedback loop mediated by the NF-κB inducible cytokine TNFα, which is secreted by the activated cells and can bind TNFα membrane receptors of the neighboring cells, or of the same cell that give rise to the positive feedback regulation. This positive feedback is negligible in most of cell lines, but may become, as suggested by our study, dominant in immune cells like monocytes or macrophages that have a high level of TNFα expression.

The proposed stochastic model pursues our earlier studies [1-2], by including the positive feedback loop regulation. The bifurcation analysis performed for the deterministic approximation of the stochastic model, revealed that for a broad range of the bifurcation parameter (rate of TNFα synthesis) the limit cycle and stable steady state coexist. As a result single cells stochastic trajectories may jump between these two attractors. Such jumps correspond to the spontaneous activatory – inactivatory transitions. In the stochastic model the bifurcation parameter controls the *on* and *off* rates and the probability that cell is in the oscillatory state. Interestingly, even in the parameter range in which the limit cycle oscillations of the deterministic approximation are not present, the spontaneous activation probability is not zero. The model satisfactorily reproduces single cell kinetic of SK-N-AS cell [3], which exhibit spontaneous activation in the absence of TNF stimulation.

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936 and Foundation for Polish Science grant TEAM/2009-3/6.

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09:30–09:50

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Quantification of noise in signalling systems - importance of controlled signal degradation

The phenomena of stochasticity in biochemical processes has been intriguing life scientists for the last few decades. Studies revealed that living cells take advantage of stochasticity in some cases and counterbalance stochastic effects in others. The intrinsic source of stochasticity in biomolecular systems has been identified with random timings of individual reactions, which in a cumulative effect lead to the variability in outputs of such systems. In the presentation I will demonstrate how stochasticity of individual reactions contributes to the variability of system's output; and that some reactions have dramatically different effect on noise that others.

Surprisingly, in the class of open conversion systems, that serve as an approximation model of signal transduction, degradation of an output contributes half of the total noise. We also demonstrate the importance of degradation in other relevant systems and propose a degradation feedback control mechanism that have capability of effective noise suppression. Our methodology constitutes novel, intuitive and simple framework to investigate stochastic effects in biochemical networks allowing for unprecedented insight into the origins of stochasticity.

09:50–10:30

Martin Falcke
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How does single channel behavior cause cellular Ca2+ spiking?

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

MINI-SYMPOSIUM 53

Modeling of immune responses and calcium signaling V

Saturday, July 2, 11:00, *Room*: **SP1**

Organizers: **Tomasz Lipniacki, Bogdan Kaźmierczak, Marek Kimmel**

11:00–11:30

Ruediger Thul
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Calcium alternans in a piecewise linear model of cardiac myocytes

Cardiac alternans is a beat-to-beat alternation in action potential duration and intracellular calcium cycling seen in cardiac myocytes under rapid pacing that is believed to be a precursor to fibrillation. The cellular mechanisms of these rhythms and the coupling between cellular calcium and voltage dynamics have been extensively studied leading to the development of a class of physiologically detailed models, which are often expressed as coupled nonlinear differential equations. Here we establish that the key dynamical behaviours of the model developed by Shiferaw and Karma are arranged around a set of switches. Exploiting this observation we show that a piecewise linear caricature of the Shiferaw-Karma model can be constructed that preserves the physiological interpretation of the original model whilst being amenable to a systematic mathematical analysis. We compute the properties of periodic orbits without approximation and show that alternans emerge via a period-doubling instability. We also demonstrate that when coupled to a spatially extended description for calcium transport the model supports spatially varying patterns of alternans. We analyse the onset of this instability with a generalisation of the master stability approach to accommodate the non-smooth nature of our system.

11:30–11:50

Kevin Thurley

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Martin Falcke
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Hierachic stochastic modelling of intracellular Ca(2+) signals - a new concept based on emergent behaviour of biomolecules

Biological systems often exhibit complex spatio-temporal dynamics and are stochastic at the same time. That is a challenge for mathematical modelling, since standard techniques then either apply rude assumptions like mean-field theories, or they lead to astronomic numbers of system states. As a new concept, we formulate a theory in terms of interevent interval distributions describing mesoscopic cluster states.

Here we consider intracellular Ca(2+) dynamics, where channel clusters are known to evoke local Ca(2+) release events that eventually induce cellular concentration spikes by diffusive coupling. However, the new modeling framework can potentially also be applied to other systems consisting of coupled clusters of biomolecules, like T cell receptor clusters or chemotaxis. Describing system dynamics in terms of probability distributions instead of rate-laws implies that the model becomes non-Markovian, but it has the advantage that the shape of the distributions reflects the microscopic dynamics without considering them in detail. Moreover, probability distributions of cluster state-changes can often be measured in vivo or calculated from known constraints, in contrast to kinetic parameters of state-changes of individual proteins.

Despite of the rather complicated integral equations appearing in the complete description of the dynamics, we arrive at simple expressions for stationary statistics at regular cluster arrangements, and stochastic simulations run quite efficiently. For Ca(2+) dynamics, we verify data input and output by fluorescence microscopy in HEK cells and thus provide strong support for the proposed stochastic model. Furthermore, we find valuable robustness properties of the stochastic mechanism, which might be one of the reasons for ubiquity of the Ca(2+) signalling toolkit in cell signalling.

Publications: Thurley and Falcke, PNAS 108:427-32 (2011); Thul, Thurley and Falcke, Chaos 19:037108 (2009).

11:50–12:10

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Three pool model of self sustained calcium oscilations

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

References.

[1] M. Marhl, T. Haberichter, M. Brumen, R. Heinrich *Complex calcium oscillations and the role of mitochondria and cytosolic proteins* BioSystems **57** 75–86.

12:10–12:40

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On mechanical effects accompanying and influencing the diffusion of calcium.

We discuss the coupling between chemical and mechanical processes which are accompanying and influencing the diffusion of calcium in biological tissues. The tissue as a whole, similarly as a single cell, is treated as a visco-elastic medium. The diffusion of calcium is enhanced by the autocatalytic release of calcium, and modified by reaction with diffusing buffers. In addition, the mechanical strain

can also influence the release of the cytosolic calcium. As a result, the waves of calcium concentration can be excited by the mechanical as well as by the chemical means. Developing certain asymptotic procedures with respect to the viscosity of the medium as well as with respect to its size (a thin cylinder as a model of a cell and a thin layer of tissue), and finally assuming the fast reaction terms in equations for buffers, we reduce the full system of equations to a single nonlinear reaction diffusion equation. The dimensionality of this equation corresponds to the dimensionality of the problem (a single space variable for the cell, two space variables for a thin layer of tissue, and three space variables in case of a bulk medium).

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936.

References.

[1] B. Kazmierczak. Z. Peradzynski, Calcium waves with fast buffers and mechanical effects, J. Math. Biol. 62 (2011), 1-38.

[2] Z. Peradzynski, Diffusion of calcium in biological tissues and accompanying mechano-chemical effects, Arch. Mech., 62 (2010), Issue 6, 423-440.

12:40–13:00

Bogdan Kazmierczak
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Buffered calcium waves with mechano-chemical effects

We analyze the following system of equations:

$$\begin{aligned} \frac{\partial c}{\partial t} &= D\frac{\partial^2}{\partial x^2}c + g(c) + \sum_{i=1}^{n} G_i(c, v_i) \ + R(c, \theta, J_1, J_2) \\ \frac{\partial v_i}{\partial t} &= D_i\frac{\partial^2}{\partial x^2}v_i - G_i(c, v_i), \quad i = 1, \ldots, n, \end{aligned} \tag{1}$$

$$0 = \nabla \cdot \left\{ \frac{E}{1+\nu}\left[\varepsilon + \frac{\nu}{1-2\nu}\theta\mathbf{I}\right] + \mu_1\frac{\partial \varepsilon}{\partial t} + \mu_2\frac{\partial \theta}{\partial t}\mathbf{I} + \tau(c)\mathbf{I}\right\} - \vartheta\mathbf{u}. \tag{2}$$

where c denotes the concentration of free cytosolic calcium ions, v_i the concentration of the i-th buffer, ε the strain tensor, $\mathbf{u}$ displacement field, τ active concentration stress resulting from the actomyosin traction $\tau(c)$. We assume that the ratio $(\mu_1 + \mu_2)/E$ is sufficiently small. We prove the existence of travelling waves to the above system, analyze the influence of viscosity on the speed of the wave and give the explicit formulae for some specific solutions. We confine ourselves to three geometrical cases: bulk medium (large in every direction), infinite plane layer of sufficiently small width and long cylinder of sufficiently small radius.

This study was supported by the Polish Ministry of Science and Higher Education grant N N 201548738 and Foundation for Polish Science grant TEAM/2009-3/6.

MINI-SYMPOSIUM 54

B and T cell immune responses

Wednesday, June 29, 11:00, *Room*: **SP1**

Organizer: **Yoram Louzoun**

11:00–11:40

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Alexandra Agaranovich
Lea Tsaban

Viruses selectively mutate their CD8+ T cell epitopes an optimization framework, a novel machine learning methodology and a large scale genetic analysis.

The relation between organisms and proteins complexity and between the rate of evolution has been discussed in the context of multiple generic models. The main robust claim from most such models is the negative relation between the organism complexity and the rate of mutation accumulation.

We here validate this conclusion, through the relation between viral gene length and their CD8 T cell epitope density. Viruses mutate their epitopes to avoid detection by CD8 T cells and the following destruction of their host cell. We propose a theoretical model to show that in viruses the epitope density is negatively correlated with the length of each protein and the number of proteins.

In order to validate this conclusion, we developed a novel machine learning methodology to combine multiple modalities of peptide-protein docking measurement. We use this methodology and large amount of genomic data to compute the epitope repertoire presented by over 1,300 viruses in many HLA alleles. We show that such a negative correlation is indeed observed.This negative correlation is specific to human viruses.

The optimization framework also predicts a difference between human and non-human viruses, and an effect of the viral life cycle on the epitope density. Proteins expressed early in the viral life cycle are expected to have a lower epitope density than late proteins.

We define the "Size of Immune Repertoire (SIR) score," which represents the ratio between the epitope density within a protein and the expected density. This

score is applied to all sequenced viruses to validate the prediction of the optimization model.

The removal of early epitopes and the targeting of the cellular immune response to late viral proteins, allow the virus a time interval to propagate before its host cells are destroyed by T cells. Interestingly, such a selection is also observed in some bacterial proteins. We specifically discuss the cases of Herpesviruses, HIV and HBV showing interesting selection biases.

11:40–12:05

Emmanuelle Terry
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Modelling CD8 T-Cell Immune Response

This work has been made in collaboration with Christophe Arpin (INSERM U851, Lyon), Fabien Crauste (Univ. Lyon 1), Clarisse Dubois (INSERM U851, Lyon), Olivier Gandrillon (Univ. Lyon 1), Stéphane Genieys (Univ. Lyon 1), Isabelle Lemercier (INSERM U851, Lyon), Jacqueline Marvel (INSERM U851, Lyon)

The primary CD8 T-cell response, due to a first encounter with a pathogen, happens in two phases: an expansion phase, with a fast increase of T-cell count, followed by a contraction phase. This contraction phase is followed by the generation of memory cells. These latter are specific of the antigen and will allow a faster and stronger response when encountering the antigen for the second time. Several works recently proposed models of the CD8 immune response [1, 2, 3, 4]. Some of these works do not consider any regulation of the immune response [1, 2, 4], whereas others propose very detailed and complex models [3].

We will present two models of the primary response, in which nonlinearities account for molecular regulation of cell dynamics. The first one, inspired by [2], is based on ordinary differential equations. The second one, inspired by [1], is based on partial delay differential equations, and the delay takes into account the time cells take to differentiate from one state to the other one. We will discuss in particular the roles and relevance of feedback controls that could regulate the response. Then, we will show some simulations we can get from the models and confront them to experimental data. Finally, we will consider the problem at the molecular scale, with a model describing the network of molecular regulations in a T-cell during the immune response.

References.

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[3] P.S. Kim, P.P. Lee and D. Levy, *Modeling regulation mechanisms in the immune system* J. Theor. Biol. **246** 33–69.
[4] I.M. Rouzine, K. Murali-Krishna and R. Ahmed, *Generals die in friendly fire, or modeling immune response to HIV* J. Computational and Appl. Math. **184** 258–274.

12:05–12:30

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A spatially extended model of B cell receptor cluster signaling

The process of B cell activation is initiated by the clustering of B cell receptors (BCR) upon specific engagement and cross-linking with antigens (Ag). A BCR-Ag microcluster must comprise a minimum number of receptors ($\sim$ 10-20) in order to create an immunon – the smallest signaling unit capable of triggering intracellular signaling leading to the development of immunogenic response.

We have approached the kinetic simulation of early signaling events within a two-dimensional cellular automaton in which the plane representing a region of the B cell membrane is discretized using the hexagonal tiling. Transmembrane molecules of BCR and membrane-tethered Src-family kinases (represented in our study by single kinase Lyn) diffuse over the tiles while Ag ligands are placed in trigonal cells of a dual lattice. We assume that the Y-shaped extracellular part of the BCR (mIg) can bind up to two Ag, that may have higher valency. Movements of Ag-bound BCR are limited: singly linked BCR can move only to the cells that are adjacent to Ag, and BCR is immobilized when bound twice. Lyn may bind to the cytoplasmic part of BCR either by its unique domain (week binding) or by SH2 domain (strong binding to phosphorylated BCR), resulting in the creation of complexes that by convention occupy a single hexagonal cell of the plane. Associated Lyn can phosphorylate the neighboring BCR or Lyn. Every binding reaction is reversible and molecules undergo spontaneous dephosphorylation. The process is coded in software in the way that ensures the exact state-to-state dynamics: reaction and diffusion events are selected from the catalog of possible events and are fired at random with their propensities proportional to corresponding rate constants.

We found that when the receptors are freely moving over the surface (in the absence of ligands) the system exhibits only small basal activity – characteristic for unstimulated cells. In the presence of ligands BCR form clusters which enhance the effective interaction rate and triggers kinase activity. Trivalent ligands are much more effective than bivalent ones in building dense, signaling-efficient, BCR clusters. Due to the positive feedback in mutual receptor and kinase activation (phosphorylation of receptor stabilizes kinase binding and autophosphorylation) clusters exhibit switch-like activation. The cluster inactivation propensity decreases with the the size of the cluster, and clusters of ten or more receptors activate virtually persistently.

This study was supported by the Polish Ministry of Science and Higher Education grant N N501 132936 and Foundation for Polish Science grant TEAM/2009-3/6.

12:30–12:55

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Modeling the T-cells dynamics in lymphopenic conditions

We investigated division dynamics of two types of CD8 T-cells (OT1 and F5) in lymphopenic conditions. We used two markers: 1) CFSE (Carboxyfluorescein succinimidyl ester) – to calculate the number of divisions that the cells have made at a given time, 2) 7AAD (7-Aminoactinomycin D) – to determine in what period of cell cycle cells were at a given time.

A modified Smith-Martin model was used [1, 2] for the observed data. This model assume a cell cycle consisting of two parts: A-phase with stochastic duration and following after it B-phase with deterministic duration. There were four main parameters: transfer rate from A to B-phase λ, duration of B-phase Δ, time of triggering to division T_0 and death rate δ. To estimate them we used a minimization of the sum of weighted squared residuals with comparison of: 1) predicted and observed frequencies of cells with given number of divisions that was made to a given time, 2) predictions of fraction of cells in B-phase with observed fraction of

7AAD+ cells. Comparisons between models were performed using a cross-validation criterion.

It was found that OT1 cells divides faster (higher transfer rate λ and earlier triggering to division) than F5 cells. Duration of B-phase Δ was slightly higher for OT1 cells. Using the information from 7AAD marker together with CFSE data improved parameters identifiability.

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MINI-SYMPOSIUM 55

Modeling of collective phenomena in biological systems

Saturday, July 2, 08:30, *Room*: **AM9**

Organizer: **Danuta Makowiec**

08:30–09:10

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Emergence of sparsity and motifs in gene regulatory networks

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

09:10–09:30

Andreas Deutsch
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Analyzing emergent behaviour in interacting cell systems

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

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

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

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

09:30–09:50

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University of Camerino
Emanuela Merelli
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A combined process algebraic and a stochastic approaches to bone remodeling

In adult life the bone is being continuously resorbed and replaced by new bone. Here we present a stochastic model of the homeostatic nature of bone remodeling, where osteoclasts perform bone resorption which is equally balanced by bone formation performed by osteoblasts. The stochastic model is embedded in an algebraic process based on Shape calculus, which provides an effective multiscale description of

the process. Our model considers increasing dimensionality from Rankl molecular signalling to osteoclast/osteoblast stochastic dynamics within a basic multicellular units (BMU) to a bone mass formation. We show that after a microfracture the simulated bone remodeling dynamics has timescale consistent with the biological process. Our combined methodology provides a first effective stochastic model of bone remodeling framework which could be used to test healthy and pathological conditions.

09:50–10:10

Danuta Makowiec
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Discrete modeling of the sinoatrial node automaticity

Each heart cell — myocyte, communicates with the outside world by rapid changes displayed by ion channels. The membrane activity is tranduced directly to the neighboring cells establishing cell-to-cell communication. Because of these cell-to-cell connections the heart tissue is perfectly suited for modeling as a network of interacting units. Differences in intercellular connections are known to be crucial in forming physiologically different parts of the heart tissue.

The rhythmic contractions of the heart begin in the area of the cardiac tissue located on the right atrium called the sinoatrial node (SAN), see [1] for description of SAN physiology. Understanding of the SAN means to known how pacemaker cells maintain the final function, namely, successful pacemaking of the whole heart. Much difficulty in understanding is related to the arrangement of cells — how rather poorly connected cells can produce a signal self-consistent enough to drive the heart contraction. There are two basic approaches to the organization of the SAN cells: the mosaic and gradient models. The first one considers coexistence of two types of cells: nodal and atrial. The second approach assumes the gradual change of properties of individuals cells when moving from the central part of the SAN to its border. The main objective of our presentation is to find whether the SAN automaticity can result from heterogeneity of intercellular links.

The complex cellular processes involved in the SAN functioning are modeled by modified Greenberg-Hastings cellular automaton [2]. Since, there is a consensus that SAN cells are remains of the heart tissue from its very early stage of development, namely from the embryo, then the construction of intercellular connections rooted on stochastical square lattice is physiologically justified. Synchronic activation of the large parts of such network denotes adjusting of cellular excitations into a robust spiral wave [3].

Effects of perturbations in the topology of intercellular connections on periodicity of the system are considered. The focus is how thorough wrinkling of initially flat structure influences the regular beating. Since automaticity of the sinoatrial node relies on a single cell activity, cyclical properties of individual cells are studied. It

appears that robust diversity of oscillations of a cell depends on both: properties of intrinsic cellular dynamics and the underlying topology of intercellular connections. Moderate nonuniformity of intercellular connections are found vital for the proper function of the sinoatrial node, namely, to respond effectively to the autonomic system control [4].

References.

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10:10–10:30

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Measures of heart rate complexity

For nearly three decades, human heart rate variability (HRV) has been consistently shown to display intriguing and puzzling characteristics, to a large degree defying satisfactory explanation and posing challenges for both modelling and clinical treatment. Recent findings confirm that the HRV regulatory system represents a prominent example of a biological complex system and remains a benchmark of biocomplexity.

Continued theoretical and experimental effort is required to achieve a thorough understanding of this systems complexity. From the point of view of control engineering, such an understanding should be capable of explaining regulatory mechanisms. Within a physics approach, it should reveal striking properties of universality. From a clinical perspective, it should demonstrate the utility of prognostic and predictive algorithms.

In my talk, I will provide a review of the measures of complexity utilised in various aspects of HRV signal processing, focusing on those providing a unifying thread for the challenges above. Particular stress will be laid on the most up-to-date multi-time and multiscale evaluation of non-Gaussian properties of HRV.

MINI-SYMPOSIUM 56

Mathematical Models in Eco-epidemiology I

Wednesday, June 29, 08:30, *Room*: **AM8**

Organizers: **Horst Malchow, Sergei V. Petrovskii, Ezio Venturino**

08:30–09:10

J.-C. Poggiale
Aix-Marseille University

A spatially extended trophic chain model with recycling : how spatial structure determines the matter cycle?

In this work, we study spatially extended trophic chain models. We focus on the role of nutrient recycling on the food chain dynamics. Top predators recycling is known to have some positive effects on the primary producers and that the importance of these effects can be compared to the role that top predators have on primary producers by regulation of herbivores. The role of recycling is here investigated by means of two models with different levels of details. Then these models are spatially extended to understand how the spatial structure affects the trophic chain dynamics. The spatial scales are assumed to be small enough to allow individuals to move fast with respect to local population dynamics. We aim to provide a mathematical formulation of the functional responses at the global scale, which can be suggested as the functional responses to use at larger scales. The global functional responses integrate the spatial effect and the recycling effects.

09:10–09:30

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

Eco-epidemiological models of prey-predator interaction in presence of disease affecting either or both the species have received significant attention from various

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

09:30–09:50

Michael Sieber
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Intraguild predation or not? Taking a different perspective on some eco-epidemiological models

The field of eco-epidemiology has integrated epidemiology with community ecology and similarities between host-parasitoid and host-pathogen interactions with classical intraguild predation (IGP) have been noticed. In this talk I want to show that certain eco-epidemiological scenarios not only fit into the IGP framework, but that they may suggest a different perspective on the underlying community structure. After an appropriate transformation of variables particular cases of IGP are found to be structurally similar to "simpler" community modules and this structural similarity also translates into remarkably similar community dynamics.

References.

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09:50–10:10

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Cellular automata modeling applied in eco-epidemiology - Simulation of the spatial spread of epidemics with individual contact

The spread of epidemics should be complex phenomena. As the exchange of economics and culture among different countries and areas become much closer in recent years, it has been an ecological issue that influences public health for invading of epidemics to new areas. Generally, there are two types of mathematical models to describe the spread of epidemics, determinate models and network dynamics models. Most of the existing mathematical models of simulating epidemics are built on the basis of ordinary and partial differential equations traditionally. These determinate models have an obviously weakness that the local characteristics of transmission were neglected. In particularly ,they could not simulate the problems properly as following: the process of individual contactthe effects of the individual behaviorthe spatial problems of epidemical transmissionthe effects of mixed pattern of individual.

As a typical representative of network dynamics models, cellular automata model has provided a useful and powerful tool for the research of complex systems. According to the definite of cellular automata model, it can be represented as an array of four elements, A=(Ld,S,N,f),where A is the cellular automata system; Ld is the cellular space; S is set of states; N is the set of neighbors of cell, N=(S1,S2,S3,,Sn),n is the number of neighbors of cell; f is the map of state transfer from Sn to S. Based on cellular automata, a simple theoretical model was presented in this work to simulate the spatial spread of epidemics with individual contact. Population is divided into three classes: infected, immunized and susceptible. Each state of the cell stands for one class of the populations. The epidemic model with the characteristic of vertical transmission and contact was considered particularly. The model, moreover, is extended to include the effect of population vaccination. This kind of effect can reduce the epidemic propagation. The proposed model can serve as a basis for the development of algorithms to simulate the spatial spread of epidemics using real data.

Keywords: Cellular Automata; Epidemics; Spatial Spread; Computer Simulation

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10:10–10:30

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A two-strain ecoepidemic model

In this talk we present a model in which two strains are considered. In a predator-prey demographic model, two contagious diseases are assumed to spread among the predators. Under the relatively strong assumption that one individual cannot be affected by both, we analyze the system to determine its long term behavior. While in some other already published models both populations have been considered subject to a disease, or the same disease is able to cross the species barrier, to our knowledge this is the first ecoepidemic model accounting for two diseases affecting the same population.

MINI-SYMPOSIUM 57

Mathematical Models in Eco-epidemiology II

Wednesday, June 29, 11:00, *Room*: **AM8**

Organizers: **Horst Malchow, Sergei V. Petrovskii, Ezio Venturino**

11:00–11:40

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Prey abundance, fragmented spatial structures and predator persistence in a predator-prey mathematical model

In this talk we develop a complex fragmented spatial model in which both dispersing well-fed and starving domestic cat populations are sharing a common multi-patch range occupied by non dispersing prey. The overall dynamic is rather intricate to decipher for Lotka-Volterra functional responses to predation. It becomes even quite complex when Holling type II functional responses to predation are considered. Assuming dispersal occurs at a fast time scale while reproduction and predation are much slower processes it is possible to transform our complex model into a simpler one for which some (local) stability analysis is feasible. A toy model consists of a spatial range made of three patches with two resident predators in the first two patches, that can be either a well-fed or a starving resident predator, and no predator at all in the third one, predators traveling all over the spatial range. For the three resulting toy models more (local) stability analysis results are available and illustrated by numerical simulations.

11:40–12:00

Narcisa Apreutesei
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Travelling wave solutions for integro-differential equations from population dynamics

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

12:00–12:20

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

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

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

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

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

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

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

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

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

and with some initial data.

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

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

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12:20–12:40

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Infection and biocontrol of an invading competitor

Biological invasions including the spread of infectious diseases have strong ecological and economical impacts. The perception of their often harmful effects has been continuously growing both in sciences and in the public. Mathematical modelling is a suitable method to investigate the dynamics of invasions, both supplementary to and initiating field studies as well as control measures.

Holling-type II and III predation as well as Lotka-Volterra competition models with possible infection of the prey or one of the competitors are introduced. The interplay of local predation, intra- and interspecific competition as well as infection and diffusive spread of the populations can cause spatial and spatiotemporal pattern formation. The environmental noise may have constructive as well as destructive effects.

A plant competition-flow model is considered for conditions of invasibility of a certain model area occupied by a native species. Short-distance invasion is assumed as diffusion whereas long-distance seed dispersal can be stratified diffusive or advective. The variability of the environment due to contingent landslides and artificial causes such as deforestation or weed control leads to the temporary extinction of one or both species at a randomly chosen time and spatial range. The spatiotemporal dimension of these extreme fragmentation events as well as a possible selected harvesting or infection of the invading weed turn out to be the crucial driving forces of the system dynamics.

12:40–13:00

Andrew Bate
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Complex dynamics in an eco-epidemiological model

In this talk, we incorporate a disease on a predator in a Holling type II predator-prey model. We establish that the disease can have a stabilising effect on the system, bringing predator-prey oscillations to coexistent equilibrium. However, results become complex when disease dynamics are much faster than the predator-prey

dynamics, i.e. for high transmission and disease-induced death rates. Numerical solutions indicate the existence of saddle-node and subcritical Hopf bifurcations, as well as turning points and branching in periodic solutions. This means that there are regions of bistability, in which the disease can have both a stabilising and destabilising effect. This holds for both density-dependent and frequency-dependent transmission.

MINI-SYMPOSIUM 58

Information, human behaviour and infection control

Saturday, July 2, 08:30, *Room*: **AM3**

Organizers: **Piero Manfredi, Alberto d'Onofrio**

08:30–09:10

Timothy Reluga
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Mathematical Epidemiology and the Economics of Social Planning

Over the last 50 years, mathematical biologists have developed a deep theory of infectious disease dynamics. Today, management problems are as much economic and social as biological. We face a variety of social, behavioral, and political challenges today in the public-health management of infectious diseases. In the last few years, a variety of new modelling approaches including social networks, game theory, information propagation and explicit-behavioral models have been proposed as descriptions of how these economic influences interact with the biology of disease transmission. In this talk, I will review some of recent work I've been involved with in game-theoretic economics models of infectious disease management, and mentioning some open problems in the field.

09:10–09:30

Piero Manfredi
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The impact of vaccinating behaviour on the natural history of immunization programmes.

Recent theoretical studies have provided increasing evidence that human behaviour can play a critical role in the achievement of public health targets, such as the mitigation of a pandemic influenza outbreak or the success of a vaccination programme for a childhood infection. As for the area of vaccine preventable infections, much of the recent research has focused on the impact of immunization choices - modelled as an evolutionary game with imitation dynamics - on voluntary vaccination regimes, particularly the issue of vaccination free-riding. In this paper we first use a simple transmission model with vaccination payoff modelled as an increasing function of the incidence of vaccine side effects, to interpret historical trends in serious morbidity and mortality from various childhood infections. This allows us to clearly show which are the major killers of vaccination programmes in industrialised countries. These seem mainly to be the technological progress and the ensuing epidemiological transition, which during the last century have brought down to negligible levels the perceived risks of serious disease given infection, and the sustained vaccination programmes conducted in the past, which have brought down to negligible levels the perceived risks of infection. This yields rather pessimistic predictions about the future lifetime of vaccination programmes. Subsequently, motivated by the fact no current vaccination regimes are fully voluntary, we propose a new framework aimed to predict the dynamic effects of the interplay between inter-human and public information on vaccine uptake, based on a modified evolutionary game equation for the vaccinated proportion, including the effort of the public health system as well. The underlying idea is that the hazard of becoming a vaccinator is the sum of two components, one due to information spread through inter-human contacts (e.g. imitation), and one due to information spread by the public health system. Unlike the former, the latter aims to suggest a very small, possibly zero, perceived risk of vaccine side effects, and a larger, possibly prevalence independent, risk of disease. Our main results show that public intervention can play a stabilising role capable to reduce the violence of 'imitation' induced oscillations, to allow for disease elimination, and to even make the so called Disease Free Pure Vaccinators Equilibrium Globally attractive. This suggests that keeping a degree of public intervention in otherwise voluntary vaccination regimes might be the only way to mitigate the pessimistic conclusions reported above.

09:30–09:50

Sebastian Funk
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Marcel Salathé
Pennsylvania State University

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

People can protect themselves against being infected by a disease by changing their behaviour in response to an outbreak, for example, through wearing face masks or

reducing their number of infectious contacts. This type of behavioural change can affect the epidemiology of the disease itself. Here, I will discuss different ways to model the influence of human behaviour on the spread of infectious diseases, as well as challenges therein. As an example, I will present a model in which individuals are influenced by their peers as awareness of the presence of a disease as well as the disease itself spread in the social networks of influence and disease.

09:50–10:10

Bruno Buonomo
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Nonlinear stability of epidemic models including information-related human behaviour

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

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MINI-SYMPOSIUM 59

Information, human behaviour and disease

Saturday, July 2, 11:00, *Room*: **AM3**

Organizers: **Piero Manfredi, Alberto d'Onofrio**

11:00–11:40

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Effects of Behavioral Changes in Smallpox and Influenza Models

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

impact of behavioral changes. This is especially true if the model predictions are being used to guide public health policy.

11:40–12:00

Raffaele Vardavas
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Modeling Adaptive Behavior in Influenza Vaccination Decisions

Classic game-theoretic approaches, whereby individuals are assumed to evaluate their options deductively based upon available information and perceptions, have previously been used to model vaccination-related decision making. However, for the case of influenza, individuals may rely on their memories and past experiences of having vaccinated. They thus use adaptation by evaluating their vaccination options inductively. We explore this concept by constructing an individual-level model of adaptive-decision making. Here, individuals are characterized by two biological attributes (memory and adaptability) that they use when making vaccination decisions. We couple this model with a population-level model of influenza that includes vaccination dynamics. The coupled models allow individual-level decisions to influence influenza epidemiology and, conversely, influenza epidemiology to influence individual-level decisions. By including the effects of adaptive-decision making within an epidemic model we show that severe influenza epidemics could occur due to the behavioral dynamics in vaccination uptake without the presence of a pandemic strain. These severe epidemics can be prevented if vaccination programs offer incentives. We find that when a family-based incentive is offered, the frequency of severe epidemics is increased. Instead, this frequency could be reduced if programs provide several years of free vaccines to individuals who pay for one year of vaccination. We conclude that individuals memories and flexibility in adaptive decision-making can be extremely important factors in influenza and voluntary vaccination determining the success of influenza vaccination programs. Finally, we discuss the implication of our results in success of a universal flu vaccine and for the case of a pandemic, and discuss some extensions of the model.

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12:00–12:20

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

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

References.

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12:20–12:40

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Multiple sources and routes of information transmission: implications for epidemic dynamics

In a recent paper [1], we proposed and analyzed a compartmental ODE-based model describing the dynamics of an infectious disease where the presence of the pathogen also triggers the diffusion of information about the disease. In this paper, we extend this previous work by presenting results based on pairwise and simulation models that are better suited for capturing the population contact structure at a local level. We use the pairwise model to examine the potential of different information generating mechanisms and routes of information transmission to stop disease spread or to minimize the impact of an epidemic. The individual-based simulation is used to better differentiate between the networks of disease and information transmission and to investigate the impact of different basic network topologies and network overlap on epidemic dynamics. The paper concludes with an individual-based semi-analytic calculation of R_0 at the non-trivial disease free equilibrium.

References.

[1] I.Z. Kiss, J. Cassell, M. Recker, and P.L. Simon. (2010) The effect of information transmission on epidemic outbreaks. Math. Biosci. 225, 1-10.

12:40–13:00

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Risk perception and 2009 H1N1 pandemic influenza spread in Italy

In Italy, the 2009 H1N1 pandemic influenza spread in a peculiar way: after an initial period characterized by a slow exponential increase in the weekly H1N1 incidence, a sudden and sharp increase of the growth rate was observed. Were behavioral changes spontaneously performed by the population responsible for such a notable pattern? In order to answer this question, a mathematical model of influenza transmission is proposed and validated. The performed investigation, based on

model fit to epidemiological data and on the analysis of antiviral drugs purchase, reveals that an initial overestimation of the risk of infection during the early stage of the epidemic, possibly induced by the high concern for the emergence of a new influenza pandemic, results in a pattern of spread compliant with the observed one. This study suggests that individual choices may have driven the H1N1 dynamics in Italy during its initial phases and that they can drastically affect the spread of future epidemics, by altering timing, dynamics and overall number of cases. In conclusion, to correctly inform public health decisions, spontaneous behavioral changes cannot be neglected in epidemic modeling.

MINI-SYMPOSIUM 60

Stem cells and cancer

Wednesday, June 29, 14:30, *Room*: AM9

Organizers: **Anna Marciniak-Czochra, Heiko Enderling**

14:30–14:50

John Lowengrub
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Feedback, lineages and cancer

We have developed a multispecies continuum model to simulate the dynamics of cell lineages in solid tumors. The model accounts for spatiotemporally varying cell proliferation and death mediated by the heterogeneous distribution of oxygen and soluble proteins. Together, these regulate the rates of self-renewal and differentiation of the cells within the lineages. Terminally differentiated cells release feedback factors that promote differentiation (e.g., from the TGF superfamily of proteins) and decrease rates of proliferation (and self-renewal) of less differentiated cells. Stem cells release a short-range feedback factor that promotes self-renewal (e.g., representative of Wnt signaling factors), as well as a long-range inhibitor (e.g., representative of Wnt inhibitors such as Dkk) of this factor. We find that the progression of the tumors and their response to treatment is controlled by the spatiotemporal dynamics of the signaling processes. The model predicts the development of spatiotemporal heterogeneous distributions of the feedback factors (Wnt, Dkk and TGF) and tumor cell populations with clusters of stem cells appearing at the tumor margin, cyesonsistent with recent experiments. The nonlinear coupling between the heterogeneous expression of growth factors, the heterogeneous distribution of cell populations at different lineage stages and the tumor shape may sufficiently depress feedback control in parts of tumors to favor eventual escape from control. This is shown to lead to invasive fingering, and enhanced aggressiveness after standard therapeutic interventions. We find that using a combination therapy involving differentiation promoters and radiotherapy is very effective in eradicating the tumor.

14:55–15:15

Cristian Tomasetti
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The role of symmetric and asymmetric division of cancer stem cells in developing drug resistance for various types of tumor growth

Often, resistance to drugs is an obstacle to a successful treatment of cancer. Many attempts to study drug resistance have been made in the mathematical modeling literature. Clearly, in order to understand drug resistance, it is imperative to have a good model of the underlying dynamics of cancer cells. One of the main ingredients that has been recently introduced into the rapidly growing pool of mathematical cancer models is stem cells. Surprisingly, this all-so-important subset of cells has not been fully integrated into existing mathematical models of drug resistance. In this work we incorporate the various possible ways in which a stem cell may divide into the study of drug resistance. We derive a new estimate of the probability of developing drug resistance by the time a tumor is detected, and calculate the expected number of resistant cancer stem cells at the time of tumor detection. We are also able to obtain analytical results for cases where the average exponential growth of cancer has been replaced by other, arguably more realistic types of tumor growth. Finally, to demonstrate the significance of this approach, we combine our new mathematical estimates with clinical data to show that leukemic stem cells must tend to renew symmetrically as opposed to their healthy counterparts that predominantly appear to divide asymmetrically. (Part of this work is joint with D. Levy, University of Maryland)

References.

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15:20–15:40

Thomas Stiehl
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Models of stem cell differentiation in hematopoiesis and leukemia

Cancers and hematologic malignancies differ with respect to interindividual symptomatology, course of disease, treatment susceptibility and prognosis. Over the last

decades oncological treatment strategies have been elaborated and optimized, nevertheless important aspects remain unknown. A systematic mathematical approach may help to better understand treatment failures and clinical heterogeneity of different cancers. Based on a model of cell differentiation and signal feedback possible scenarios of cancer development and their impact on consequences for treatment concepts will be compared. A calibration of the model to the hematopoietic system will serve to transfer theoretical results to the understanding of leukemias and myelodysplastic syndromes.

15:45–16:05

Hiroshi Haeno
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Ross L. Levine
Memorial Sloan-Kettering Cancer Center
D. Gary Gilliland
Merck Research Laboratories
Franziska Michor
Dana-Farber Cancer Institute/ Harvard School of Public Health

A progenitor cell origin of myeloid malignancies

All cancers rely on cells that have properties of long-term self-renewal or stemness to maintain and propagate the tumor, but the cell of origin of most cancers is still unknown. Here, we design a stochastic mathematical model of hematopoietic stem and progenitor cells to study the evolutionary dynamics of cancer initiation. We consider different evolutionary pathways leading to cancer-initiating cells in JAK2V617F-positive myeloproliferative neoplasms (MPN): (i) the JAK2V617F mutation may arise in a stem cell; (ii) a progenitor cell may first acquire a mutation conferring self-renewal, followed by acquisition of the JAK2V617F mutation; (iii) the JAK2V617F mutation may first emerge in a progenitor cell, followed by a mutation conferring self-renewal; and (iv) a mutation conferring self-renewal to progenitors may arise in the stem cell population without causing a change in the stem cell's phenotype, followed by the JAK2V617F mutation emerging in a progenitor cell. We find mathematical evidence that a progenitor is the most likely cell of origin of JAK2V617F-mutant MPN. These results may also have relevance to other tumor types arising in tissues that are organized as a differentiation hierarchy.

16:10–16:30

Charles Morton
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Tumor Growth Kinetics Modulated by Generational Lifespan of Non-Stem Cancer Cells

Numerous solid tumors are heterogeneous in composition. While growth is driven by cancer stem cells (CSCs), the reported relative frequencies of CSC versus non-stem cancer cells span wide ranges within tumors arising from a given tissue type. We have previously shown that tumor growth kinetics and composition can be studied through an agent-based cellular automaton model using minimal sets of biological assumptions and parameters. Herein we describe the pivotal role of the generational lifespan of non-stem cancer cells in modulating solid tumor progression. Although CSCs are necessary for expansion, tumor growth kinetics are surprisingly modulated by the dynamics of the non-stem cancer cells. Our findings suggest that variance in tumor growth curves and CSC content of solid tumors may be attributable to the proliferative capacity of the non-stem cancer cell population that arises during asymmetric division of CSCs. Remarkably, slight variations in proliferative capacity result in tumors with CSC fractions differing by multiple orders of magnitude. Larger proliferative capacities yield migration-limited tumors, as the emerging population of non-stem cancer cells spatially impedes expansion of the CSC compartment. Conversely, lower proliferative capacities yield persistence-limited tumors, with symmetric division frequency of CSCs determining tumor growth rate. Intermediate proliferative capacities give rise to fastest-growing tumors, indicating a between self-metastatic growth through symmetric CSC division and the availability of space facilitated by removal of senescent non-stem cancer cells. Our results offer novel explanations for the large variations in CSC ratio reported in the literature, and highlight the importance of non-stem cancer cell dynamics in the CSC hypothesis.

MINI-SYMPOSIUM 61

Structure and Dynamics of Biochemical Reaction Networks I

Tuesday, June 28, 14:30, *Room*: **SP1**

Organizers: **Maya Mincheva, Casian Pantea**

14:30–14:50

David Swigon
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Decomposition of chemical reaction networks

I will outline the ideas behind a novel theory for analyzing the long term dynamics of chemical reaction networks with mass action kinetics based on the combination of Deficiency Theory of Horn, Johnson, and Feinberg, and the decomposition of networks into extreme subnetworks, pioneered by Clarke. This is a work in progress, but among the results that have been obtained are the formulation of new sufficient conditions for the existence of a unique asymptotically stable positive equilibrium that generalize the Deficiency Zero Theorem.

14:55–15:15

Gábor Szederkényi
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Dynamically equivalent reaction networks: a computational point of view

It has been known from the 'fundamental dogma of chemical kinetics' that different mass action type reaction networks can give rise to the same ordinary differential equations describing the time evolution of specie concentrations. Finding dynamically equivalent network structures with preferred properties can significantly enhance the application range of the known and continuously developing strong results on the relation between network structure and qualitative dynamical

properties (deficiency theorems, structural conditions on the possibility of multiple steady states, Global Attractor and Persistency Conjectures etc.). It is also known primarily from systems and control theory that the numerical feasibility of many existence and design problems can often be checked via appropriately formulated optimization tasks even if the original problem is algebraically complex to treat. In this talk, an overview of linear programming (LP) and mixed integer linear programming (MILP) techniques will be given for the computation of reaction networks with prescribed properties. This includes the computation of structures with the minimal/maximal number of reactions/complexes, detailed/complex balanced, and fully/weakly reversible realizations.

15:20–15:40

Carsten Conradi
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Dietrich Flockerzi
MPI Magdeburg

Multistationarity in mass action networks by linear inequality systems

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

15:45–16:05

Gheorghe Craciun
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Persistence and the Global Attractor Conjecture: The Big Picture

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

16:10–16:30

Casian Pantea
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Persistence and the Global Attractor Conjecture: Recent Approaches

We describe recent approaches to proving the Persistence Conjecture (which describes a class of mass-action systems for which variables do not approach zero) and the Global Attractor Conjecture (which describes a class of mass-action systems for which trajectories converge to a single positive equilibrium). We introduce the class of "endotactic" networks (which contains the class of weakly reversible networks), and formulate the Extended Persistence Conjecture, which says that endotactic mass-action systems are persistent, even if the reaction rate parameters are allowed to vary in time (to incorporate the effects of external signals). We describe a proof of the Extended Persistence Conjecture for systems that have two-dimensional stoichiometric subspace. In particular, we show that in weakly reversible mass-action systems with two-dimensional stoichiometric subspace all bounded trajectories are persistent. These ideas also apply to power-law systems and other nonlinear dynamical systems. Moreover, we use these results to prove the Global Attractor Conjecture for systems with three-dimensional stoichiometric subspace. This is joint work with Gheorghe Craciun and Fedor Nazarov.

MINI-SYMPOSIUM 62

Structure and Dynamics of Biochemical Reaction Networks II

Tuesday, June 28, 17:00, *Room*: **SP1**

Organizers: **Maya Mincheva, Casian Pantea**

17:00–17:20

Santiago Schnell
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A model of threshold behavior reveals rescue mechanisms of bystander proteins in conformational diseases

Conformational diseases result from the failure of a speci

c protein to fold into its correct functional state. The misfolded proteins can lead to the toxic aggregation of proteins. Protein misfolding in conformational diseases often displays a threshold behavior characterized by a sudden shift between nontoxic to toxic levels of protein misfolds. In some conformational diseases, evidence suggest that misfolded proteins interact with bystander proteins (unfolded and native folded proteins), eliciting a misfolded phenotype. These bystander isomers would follow their normal physiological pathways in absence of misfolded proteins. In this paper we present a general mechanism of bystander and misfolded protein interaction which we have used to investigate how the threshold behavior in protein misfolding is triggered in conformational diseases. Using a continuous flow reactor model of the endoplasmic reticulum, we found that slight changes in the bystander protein residence time in the endoplasmic reticulum or the ratio of basal misfolded to bystander protein in ow rates can trigger the threshold behavior in protein misfolding. Our analysis reveals three mechanisms to rescue bystander proteins in conformational diseases. The results of our model can now help direct experiments to understand the threshold behavior and develop therapeutic strategies targeting the modulation of conformational diseases.

17:25–17:45

Murad Banaji
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Monotone dynamics in chemical reaction networks

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

17:50–18:10

Grzegorz A. Rempala
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Jaejik Kim
Georgia Health Sciences University

Statistical inference for reaction constants in stochastic biochemical networks

The problem of estimating values of reaction constants in biochemical networks if fundamental for any network reconstruction from the trajectory data. The talk will outline some recent developments in statistical inferential procedures for reaction constants in stochastic biochemical network models. We will especially focus on some newly proposed dynamical programming methods, which are similar to the Viterbi-type imputation algorithms for hidden Markov chain and are especially suitable when observed trajectories contain missing data for some species. It will be shown how the use of dynamic programming principles allows for efficient inference via either the Gibbs sampler or the EM algorithm and g the so-called uniformization representation of a Markov jump process. The applicability of the inferential procedures will be illustrated with data from the longitudinal mamalian genetic studies as well as the US CDC data from the onset of the 2009 H1N1 flu pandemic in the US

18:15–18:35

Hiroko Kamei

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Classification of networks for their synchronous dynamics

Small subnetworks, such as network motifs, and their modularity have been considered to play an important role in large complex networks. In this context, a major topic is the interplay between network structures and their corresponding dynamics. We consider one form dynamics, synchrony-breaking in a network. This can be interpreted as speciation, differentiation of cells, or clustering of gene expression patterns. For any network we construct a mathematical structure, a lattice, which results from the eigenvalues and eigenvectors of the network's adjacency matrix. Many networks have the same lattice, allowing a large number of networks to be classified into a smaller number of lattice structures. Furthermore, by looking at the lattice structure we can identify networks with similar synchronous dynamics.

References.

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18:40–19:00

Maya Mincheva
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Oscillations in Biochemical Reaction Networks

Understanding the dynamics of interactions in complex biochemical networks is an important problem in modern biology. Biochemical reaction networks are modeled by large nonlinear dynamical systems with many unknown kinetic parameters, which complicates their numerical analysis. Important properties, such as the potential of a biochemical reaction network to oscillate can be determined by the network's structure. We will discuss a new graph-theoretic condition which includes the negative cycle condition for oscillations as a special case.

MINI-SYMPOSIUM 63

Mathematical Modelling of Macromolecules and Molecular Aggregates

Saturday, July 2, 14:30, *Room*: **AM6**

Organizer: **Rubem Mondaini**

14:30–15:10

Rubem P. Mondaini
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Global optimization analysis of viral capsids and amide planes

A scheme of Combinatorial Optimization (CO) is introduced in order to describe the geometrical pattern of the macromolecular structures like A-DNA and molecular aggregates like Tobacco Mosaic Virus (TMV). Backbone sequences of internal atom sites are seen to be associated to sequences of Steiner points of an Euclidean Steiner Tree Problem. The agreement with experimental data is 94.6% and 98.2% for A-DNA and TMV, respectively.
Another CO scheme in which the Steiner points have a fundamental role, is the introduction of an objective function which minimum will lead to the confirmation of the existence of Amide planes in protein structure. This is a Mathematical Programming approach such that the variables are small perturbations of bond and dihedral angles. Objective function and constraints are derived only from knowledge of the 3-dimensional molecular structure.
These results provide excellent examples of robust methods of optimization as applied to the study of geometrical modeling of biopolymers and molecular aggregates.

References.

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15:10–15:30

Richard Kerner
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Discrete groups and internal symmetries of icosahedral capsids.

The Caspar-Klug classification of icosahedral capsids [**1**] takes into account only their size, given by the triangular number T = p + pq + q. It can also note the difference between chiral and non-chiral capsids. But it does not take into account more subtle differences resulting from the differentiation of coat proteins serving as elementary blocks from which capsids are assembled by agglomeration. [**2**], [**3**]. We develop further the classification of icosahedral capsids introduced a few years ago [**4**], [**5**], using the symmetry group action on the elementary triangles

We analyze the differentiation of coat proteins forming an icosahedral viral capsid with a given triangular number T. A typical icosahedral capsid can be subdivided into twelve pentagons and 10(T-1) hexagons, which can be realized either as genuine hexamers, or as a combination of dimers or trimers.We assume that the pentamers, which are found in twelve vertices of the capsid, display five identical sides. This is usually the case, except for the Papovaviridae family in which all pentamers are maximally differentiated, displaying five different sides (abcde) instead of five identical ones (aaaaa).

Hexamers can display various degrees of differentiation. The symmetry imposes that their sides can be either of two types, or three types, or six different types: (ababab), (abcabc) or (abcdef), respectively, because 6 is divisible by 2, 3 and 6. These cases have been discussed in our previous work, and enabled us to introduce four internal symmetry classes in capsid viruses, according to the presence or absence of the aforementioned hexamer types. The full information about a given icosahedral capsid structure can be read from one of the twenty identical triangular faces. The first hexamer type, (ababab) is fouund only in triangles's centers, because of its three-fold symmetry; the type (abcabc) can be found at the edges of the triangular face, and maximally differentiated hexamers (abcdef) can be found in any position.

However, a more subtle analysis can be made if other hexamer types are taken into account. The partition into 2, 3 or 6 different sides must be maintained, but the two (ab) and three (abc) proteins can be placed differently in a hexamer, e.g. like (aaabbb) instead of (ababab), or (aabbab); the three different proteins (abc) can be displayed as (abccba) instead of (abcabc), generating even instead

of chiral symmetry around the edge. With these new configurations included, the classification of icosahedral capsids becomes more complete.

We also show how the capsids agglomerate in a way that always minimizes the number of different proteins needed for the construction. This is being illustrated on the examples provided by the herpesvirus (T=16) and human adenovirus (T=25). Our classification gives some extra hints concerning genetic proximity of viruses displaying similar classes of capsid symmetries.

References.

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15:30–15:50

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Nick Grayson
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Tom Keef
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Jess Wardman
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Neil Ranson and Peter Stockley
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Genome Organisation and Assembly of RNA Viruses: Where Geometry Meets Function

Cryo-electron microscopy and X-ray crystallography have revealed ordered features in the genome organisation of a number of ssRNA viruses. These include a dodecahedral RNA cage in Pariacoto virus and a double-shell organisation in bacteriophage MS2. We show here that these ordered features are due to symmetry constraints on the overall organisation of these particles.

We moreover show that these mathematical results can be used to better understand the mechanisms underlying the formation (assembly) of viruses. In particular, we demonstrate that the geometric constraints on genome organisation result in a strong reduction of the combinatorially possible pathways of assembly and hence contribute to the remarkable assembly efficiency of these viruses. Since assembly efficiency is important for viruses in order to outcompete their hosts immune system, these results provide important insights into the strategies and mechanisms underlying the viral infection process.

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15:50–16:10

Giuliana Indelicato
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The dynamic behaviour of viral capsids under structural transitions important for infection

We present a general method for the investigation and prediction of likely transition mechanisms for capsids of icosahedral viruses. Concepts from the theory of three-dimensional (3D) quasicrystals, and from the theory of structural phase transformations in 3D crystalline solids, are combined to give a framework for the study of these structural transformations. Applications to a number of viruses will be discussed.

16:10–16:30

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Penrose-like tilings as geometric constraints on the structures of protein assemblies.

Non-crystallographic symmetry is common in protein assemblies, from icosahedral symmetry in viral capsids to five-fold and seven-fold axial symmetry in C-reactive proteins and chaperonin molecules, respectively. We have shown that the overall organisation of such structures can be predicted using affine extensions of non-crystallographic symmetry. In particular, important insights can be gained not only into the outer surfaces of these clusters, but also in how symmetry is correlated at different radial levels. For example, in applications to viruses, this has led to the discovery of a molecular scaling principle between different viral components. Here I will show that Penrose-like non-crystallographic tilings derived from higher dimensional lattices can be used to provide bounding boxes for proteins in non-crystallographic assemblies.

MINI-SYMPOSIUM 64

Crowd Dynamics: Modeling, Analysis and Simulation (Part 1)

Wednesday, June 29, 11:00, *Room*: **AM7**

Organizer: **Adrian Muntean**

11:00–11:40

Maury Bertrand
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Handling of congestion in crowd motion modeling

We propose a general framework to incorporate congestion in the modeling of crowd motion in evacuation situations. This approach can be seen as a first order (in time) counterpart of the evolution problem associated to the collective motion of rigid spheres (or discs) with a non elastic collision law. In its simpler, microscopic, form (see [**4**]), the approach we propose is based on the definition of a desired velocity (corresponding to the velocity one would have in the absence of others); the actual velocity is then defined as the projection of this desired velocity onto the set of feasible velocities (velocity which do not violate the non-overlapping constraints between individuals). This model fits into the general framework of sweeping processes by convex sets [**5**], and its generalization to non-convex sets [**1**]. Well-posedness results rely on a so called *catching up algorithm*, which follows a prediction-correction strategy, where the correction consists in projecting a configuration which violates the constraints onto the set of feasible configurations.

We proposed recently a macroscopic version of this approach ([**2**]): the crowd is described by a density which is subject to remain below a maximal value (congestion). We shall present how the general framework of optimal transportation endows the space of densities with a natural distance (Wasserstein distance) which makes it possible to generalize the catching up approach to this non-Hilbertian setting [**3**].

We shall address the links and deep differences between micro and macro approaches, from both mathematical and modeling standpoints.

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11:40–12:00

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A multiscale look at crowd dynamics by time-evolving measures

The dynamics of particle-like living systems, such as human crowds, are mainly ruled by mutual interactions among the individuals. This is because the latter have the ability to express different behavioral strategies depending on the presence of other individuals in the environment. For instance, pedestrians heading for a certain destination deviate from their preferred paths when encountering other pedestrians. Remarkably, interactions are usually non-cooperative, i.e., walkers do not pursue a goal collectively.

Due to the intrinsic granularity (discreteness) of the system (the number N of pedestrians is possibly large, yet the approximation $N \to \infty$ may not be acceptable), interactions are better described at an individual-based level. On the other hand, an ensemble representation of the crowd is often preferable over an agent-based one, in order to catch the average group behavior spontaneously emerging from interactions (self-organization) and also in view of further analysis, numerics, and optimization issues. Measure-theoretic stochastic approaches, such as those that will be discussed in this talk, offer useful conceptual tools to this purpose. Indeed, they make possible an Eulerian particle-free representation of the crowd, in which single pedestrians are blurred into the probability distribution of their spatial positions. At the same time, they allow the description of the interactions to stem from (stochastic) individual-based reasonings. Finally, they enable one to treat discrete and continuous models under a common framework, as well as to deduce models at intermediate scales with interesting implications on the predicted dynamics.

References.

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12:00–12:20

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Jan Vybiral
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Particle systems and kinetic equations modelling interacting agents in high dimension

We explore how concepts of high-dimensional data compression via random projections onto lower-dimensional spaces can be applied for tractable simulation of certain dynamical systems modeling complex interactions. In such systems, one has to deal with a large number of agents (typically millions) in spaces of parameters describing each agent of high-dimension (thousands or more). Even with todays powerful computers, numerical simulations of such systems are prohibitively expensive. We propose an approach for the simulation of dynamical systems governed by functions of adjacency matrices in high-dimension, by random projections via Johnson-Lindenstrauss embeddings, and recovery by compressed sensing techniques.

12:20–12:40

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Calibrating walker models: variations of parameters due to traffic regimes

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

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

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12:40–13:00

Joep Evers

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

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

MINI-SYMPOSIUM 65

Crowd Dynamics: Modeling, Analysis and Simulation (Part 2)

Wednesday, June 29, 14:30, *Room*: **AM7**

Organizer: **Adrian Muntean**

14:30–15:10

Andreas Schadschneider
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Modeling of pedestrian dynamics – Cellular automata models

In the talk we first give a classification of the different modelling approaches that have been used to describe pedestrian flows and crowd dynamics. The merits and problems of these approaches are discussed [**1, 2**].

Then we focus on cellular automata models. This model class has successfully been applied to a variety of complex systems [**2**]. One main advantage of this approach is its computional efficiency. Large crowds can be simulated faster than real-time. The floor field model [**3, 4, 5, 6**] is introduced which allows to reproduce the empirically observed collective phenomena like lane formation. The interactions between the pedestrians are implemented in the form of virtual chemotaxis [**6**]. Several extensions of the model are discussed which improve its realism in certain situations. We also present a calibration of the model using empirical data from laboratory experiments and an application to the evacuation of a football stadium.

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15:10–15:30

Bertram Düring
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Kinetic modelling of opinion leadership

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

15:30–15:50

Armin Seyfried
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Quantitative description of pedestrian dynamics: Experiments and Modeling

The first part of the lecture gives an introduction to empirical results in pedestrian dynamics. Basic quantities of pedestrian streams (density, flow and velocity) are introduced along the measurement methods. But density and flow are concepts of fluid mechanics where the size of the particles is much smaller than the size of the measurement area. Thus standard methods in pedestrian dynamics suffer from large scatter when local measurements are needed. A concept for measuring microscopic characteristics on the basis of trajectories is introduced. Assigning a personal space to every pedestrian via a Voronoi diagram reduces the scatter and allows analyzing the fine structure of the data.

The second part focuses on a model continuous in space. Basic ideas of a force model representing pedestrians as self driven particles interacting via a repulsive force are outlined. To get precise volume exclusion in two dimensions the model represents the velocity dependent shape of pedestrians by ellipses changing the size of their semiaxis with speed. In addition routing strategies are modeled to incorporate certain intelligence to the self driven particles. The particles perceive their environment and take their decision based on an observation of the current situation.

15:50–16:10

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Derivation of macroscopic equations for individual cell-based models.

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

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

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

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

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16:10–16:30

Nikolai Bode
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Social networks and models for collective motion

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

MINI-SYMPOSIUM 66

Multiscale modelling of biological systems: the Chaste framework

Tuesday, June 28, 11:00, *Room*: **AM7**

Organizer: **James Osborne**

11:00–11:40

Dr James Osborne
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A multiscale computational framework for modelling biological systems: Chaste

The Chaste framework (http://web.comlab.ox.ac.uk/chaste) in an Open Source numerical library which enables multicellular and multiscale simulations of biological processes. In this, the first talk of the mini-symposium, we introduce the multiscale framework on which Chaste is based on, discuss the development of the framework, and provide a demonstration of how to set up a simulation.

The mathematical framework is based upon the observation that the natural structural unit of biology is the cell, and it consists of three main scales: the tissue level (macro-scale); the cell level (meso-scale); and the sub-cellular level (micro-scale), with interactions occurring between all scales. The cell level is central to the framework and cells are modelled as discrete interacting entities using one of a number of possible modelling paradigms, including lattice based models (cellular automata and cellular Potts) and off-lattice models (cell centre and vertex based representations). The sub-cellular level concerns numerous metabolic and biochemical processes represented by interaction networks rendered stochastically or into ODEs. The outputs from such systems influence the behaviour of the cell level affecting properties such as adhesion and also influencing cell mitosis and apoptosis. Tissue level behaviour is represented by field equations for nutrient or messenger concentration, with cells functioning as sinks and sources. This modular approach enables multiple models to be simulated and is easily extensible allowing more realistic behaviour to be considered at each scale.

Chaste is comprised of libraries of object orientated C++, developed using an agile development approach. All software is tested, robust, reliable and extensible. The library enables general simulations to be undertaken and includes tools to automatically curate and store simulation results expediting model development. One

key aspect of such a framework is the ability to model specific biological systems using multiple modelling paradigms, as a case study we present a simple model of the colorectal crypt using four different cell level models and illustrate the similarities and differences.

11:40–12:00

Dr Alexander Fletcher
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Modelling biological systems in Chaste: an overview

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

12:00–12:20

Sara-Jane Dunn
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Modelling the Effect of the Actin Basket and Basement Membrane in the Deformation of the Colonic Crypt

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

geometry is required, which takes into account the role of the surrounding tissue stroma in maintaining crypt homeostasis throughout these cell events.

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

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

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

12:20–12:40

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Prof. Philip Maini
University of Oxford
Prof. Helen Byrne
University of Oxford
Prof. Angela Shifflet
Wofford College
Prof. George Shifflet
Wofford College

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

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

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

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

12:40–13:00

Philip J. Murray, Philip K. Maini, Ruth E. Baker
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Using Chaste to simulate a multiscale problem in developmental biology

During somitogenesis the posterior PSM segments at regular time time intervals into blocks of epithelial cells called somites. A clock and wavefront mechanism is the widely accepted model for this process, with cellular clocks and a travelling molecular wavefront determining when and where the somites form, respectively. Recent experimental findings in zebrafish have highlighted the fundamental role of Notch-Delta signalling in the coupling of neighbouring cellular oscillators. Using the framework of phase coupled oscillators to model the Notch-Delta coupled molecular oscillators, we demonstrate how oscillator coupling alone is sufficient to yield a range of experimentally observed results. A notable feature of the considered phase-coupled framework is that the clock and wavefront are not separate entities, rather the wavefront that slows clock oscillations is a gradient in clock phase.

Cell movements in the chick PSM have recently been quantified: cells are most motile in the posterior PSM while cell densities are largest anteriorly. Using a cell-based model implemented in Chaste, we investigate the interaction between three tightly-coupled processes: embryo elongation, embryo convergence and cell proliferation. Results from the numerical simulations are compared with available experimental data and the model is used to suggest further experimental studies.

MINI-SYMPOSIUM 67

Mathematical modeling of biomechanical regulation in bone tissue (Session I)

Wednesday, June 29, 08:30, *Room*: **CP1**

Organizers: **Peter Pivonka, Stefan Scheiner, Pascal Buenzli**

08:30–09:10

Christian Hellmich
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Bone fibrillogenesis and mineralization: Quantitative analysis and implications for tissue elasticity

Data from bone drying, demineralization, and deorganification tests, collected over a time span of more than eighty years, evidence a myriad of different chemical compositions of different bone materials. However, careful analysis of the data, as to extract the chemical concentrations of hydroxyapatite, of water, and of organic material (mainly collagen) in the extracellular bone matrix, reveals an astonishing fact: it appears that there exists a unique bilinear relationship between organic concentration and mineral concentration, across different species, organs, and age groups, from early childhood to senility: During organ growth, the mineral concentration increases linearly with the organic concentration (which increases during fibrillogenesis), while from adulthood on, further increase of the mineral concentration is accompanied by a decrease in organic concentration. These relationships imply unique mass density-concentration laws for fibrillogenesis and mineralization, which - in combination with micromechanical models - deliver 'universal' mass density-elasticity relationships in extracellular bone matrix - valid across different species, organs, and ages. They turn out as quantitative reflections of the well-instrumented interplay of osteoblasts, osteoclasts, osteocytes, and their precursors, controlling, in a fine-tuned fashion, the chemical genesis and continuous transformation of the extracellular bone matrix. Considerations of the aforementioned rules may strongly affect the potential success of tissue engineering strategies, in particular when translating, via micromechanics, the aforementioned growth and mineralization characteristics into tissue-specific elastic properties.

09:10–09:30

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A coupled systems biology-micromechanical model for mechanostat-type regulation of bone remodeling

The capacity of bone tissue to alter its mass and structure in response to mechanical demands was recognized more than a century ago and Frost formulated the so-called mechanostat theory for capturing this phenomenon mathematically. This theory proposes that bone responds to changes from a loading relating to an equilibrated bone turnover by triggering either increased bone resorption or formation as response to decreased or increased loading. While this conceptual theory is useful for a qualitative understanding of bone tissue level responses to mechanical loading no quantitative estimates of bone volume/mass changes can be made. Also incorporation of the underlying cellular mechanisms is still outstanding. Over the last several years significant progress has been made to identify the cells and signaling molecules involved in the mechanical adaptation of bone. It is now well accepted that osteocytes act as mechanosensory cells in bone which express several signaling molecules able to trigger bone adaptation responses. Here we present an extended bone cell population model incorporating a simplified osteocyte-feedback to simulate bone remodeling events corresponding to the actual mechanical loading. The mechanical feedback to bone biology is achieved by employing continuum micromechanics-based homogenization of bone stiffness, allowing for estimation of the deformation osteocytes are subjected to. This methodology allows for monitoring effects of mechanical load changes on the composition, and thus on the load-carrying capacity of bone. To the authors knowledge, this is the first model which incorporates the mechanostat theory based on cellular feedback mechanisms.

09:30–09:50

Bert van Rietbergen
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A theory for load-adaptive bone remodeling at the cellular level

It is well known that bone tissue can adapt its shape and density to the mechanical demands it is subjected to. However, how, exactly, this process is regulated is not

well known. Over the last decade we have developed a theory for load adaptive bone remodeling that is based on the hypothesis that osteocyte cells in the bone tissue can sense local loading conditions and based on this information regulate the activity of bone forming cells (osteoblast) and bone resorbing cell (osteoclasts) [1]. We tested this hypothesis using computational models that included finite element models to represent trabecular bone architectures and to calculate loading conditions at the location of osteocytes, In the earlier of these studies [2], only the net result of bone formation and resorption was represented by changes in the model geometry. In these studies we demonstrated that this theory can explain many aspects of bone remodeling that could not be explained before. First, it was shown that this theory can explain the formation of typical trabecular architectures (osteogenesis). Second, it was shown that the theory can explain the adaptation and alignment of trabecular bone as the result of a local adaptation process. Third, it was shown that the theory could explain the development of osteoporosis as the result of changes in cell activity or loading magnitude. In later studies [3] we increased the resolution to also represent individual cells. In these studies we demonstrated that the theory can explain the coupling between osteoclast and osteoblast cells in basic multicellular units as the result of changes in local loading condition sensed by osteocytes. It could also explain the formation of osteons in cortical bone and why these are oriented in the loading direction. Finally, although the biochemical pathway by which the osteocytes regulate the other cells was never specified, we were ble to demonstrate that both a stimulatory pathway, in which inicreased loading leads to increased stimulation of osteoblast, and an inhibitory pathway, in which increased loading leads to decreased inhibition of osteoblast (typically for sclerostin) could work. Presently it is investigated if this theory can be transformed into a clinical tool to predict bone remodeling in patients as expected due to changes in cell metabolism or loading conditions.

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09:50–10:10

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A Computational Model of Bone Resorption Behavior

Bone resorption by osteoclasts plays a fundamental role in the bone remodeling cycle which serves the purpose of repairing micro-damage and/or achieving mineral homeostasis. This process is also essential in growth and remodeling of bone, where it is tightly coupled to bone formation by osteoblasts. In order to study the

static and dynamic behavior of bone resorption, a computational model of bone resorption has been developed using a cellular automaton method and its hybrid method with finite element calculation. In the model, essential features of bone resorption include the interaction of osteoclasts with the bone matrix and with other osteoclasts, and a recruiting signal for osteoclasts from osteocytes that can sense the change in mechanical properties of the bone matrix such as strain and strain-energy density. The computational model provides a theoretical tool to address various questions on bone resorption in terms of the shape and size of resorbed bone. From the simulations of the computational model of bone resorption, it is found that the process of bone resorption is strongly affected by the strength of interactions between osteoclasts with the bone matrix and with other osteoclasts, external mechanical loads, and velocity of a blood vessel.

10:10–10:30

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BMU remodelling simulation using reducer order method

Adam Moroz, Mikhail Goman, David I. Wimpenny BMU remodelling simulation using reducer order method The bone remodelling process, performed by the Bone Multicellular Unit (BMU) is a key multi-hierarchically regulated process, which provides and supports various functionality of bone tissue. It is also plays a critical role in bone disorders, as well as bone tissue healing following damage. Modelling of bone turnover processes could play a significant role in helping to understand the underlying cause of bone disorders and thus develop more effective treatment methods. The reducer order approach to modelling of bone turnover, based on the osteocyte loop of regulation, have been employed, thin wide range of rate parameters using the Monte Carlo method. The optimal control framework for regulation of remodelling has been discussed. The study illustrates the complexity of formalisation of the metabolic processes and the relations between hierarchical subsystems in hard tissue where a relatively small number of cells are active.

MINI-SYMPOSIUM 68

Mathematical modeling of biomechanical regulation in bone tissue (Session II)

Wednesday, June 29, 11:00, *Room*: **CP1**

Organizers: **Peter Pivonka, Stefan Scheiner, Pascal Buenzli**

11:00–11:40

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Tissue adaptation driven by chemo-mechanical coupling with application to bone

Based on the current knowledge of bone remodelling process, a biochemical model is proposed which describes the essential interactions that governs the whole bone remodelling process. Further, the influence of mechanical stimulation on bone tissue is well known. Considerations from non-equilibrium thermodynamics are used to quantify this effect and moreover to stress the importance of dynamic character of the loading. Particularly, the question of what constitutes a mechanical stimulation of biochemical reactions in general will be addressed and further to compare the importance of the two possible mechanical stimulations: shear rate and the rate of volume variation. Consequently, a modified form of the Law of Mass Action is derived which includes also the mechano-chemical coupling and not only the affinity of interaction based on the difference in chemical potentials. This rather different approach from the classical ones can predict bone density distribution as will be shown on some examples including the effect of stem insertion or osteoporosis.

Acknowledgement. This research has been supported by the Czech Science Foundation project no. 106/08/0557.

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11:40–12:00

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A multiscale bone remodelling framework using the Physiome Project markup languages

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

Project [3]; and (ii) demonstrate this framework by looking at an anabolic treatment, Lactoferrin, and how it modifies osteoblast/osteoclast numbers, influences the strain pattern at the micro bone level and changes whole bone strength.

The multiscale modelling framework developed as part of the IUPS Physiome Project [4] was used to link the spatial scales. At the cell level the bone remodelling process describing the RANK-RANKL-OPG pathway [5] was implemented in the CellML markup language [6]. This describes the amount of osteoblasts (bone forming) and osteoclasts (bone resorbing) cells in response to a healthy, diseased or treatment state. At the micro level a particulate method, 'Smooth Particle Hydrodynamics' (SPH) was used to model the micro strain of a bone cube (1mm x 1mm x 1mm) [7]. SPH has the ability to handle highly fragmenting solid structures, bone addition and removal. At the micro level a bone remodelling algorithm based on strain excitation adapted from the work of Prendergast [8] was used to add or remove bone in order to maintain bone density. At this level the osteon cortical pore structure was visible and the bone growth and resorption patterns based on the number of osteoclasts/osteoblasts lead to a changing architecture and overall bone strength. The macro model (whole bone) was a Femur geometry from the AnatML database, with material properties described using FieldML. A spatially varying density and Young's modulus was fitted from CT images using the CT number and a grey-scale mapping. The macro level models are physiologically loaded from muscle forces and ground reaction force data taken from gait experiments [9]. The whole bone model provides the boundary conditions for the micro models. The proposed computational framework has the potential to improve understanding of how cellular level changes influence whole bone strength.

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12:00–12:20

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Mathematical Modeling and Analysis of Force-induced Bone Adaptation

In biological systems, all living organisms are able to react to the biophysical signals arising in their environment. To do that, the constituent cells are provided with mechanisms that allow them to perceive biophysical signals and to react accordingly to accommodate to the demanding environment. Bone as a biological system is not exempted from this mechanoresponsive capacity. In the last decades significant progress has been made from the experimental site as well as the medical insights [1], to understand the effects produced by application of mechanical loading on bone tissue and on bone cells. Experimental studies have shown the key role played by mechanical usage on bone tissue adaptation, and the promotion of cellular behaviors, like proliferation, differentiation, or apoptosis. However, the precise biological mechanisms behind the organization and regulation of the site-specific bone adaptation process remain poorly understood.

The functional adaptation of bone is the process whereby bone adapts its mass and structure to withstand changes in biophysical demands. The process of bone remodeling is the suitable mechanism used by bone to renew, repair and maintain bone surfaces along life. In bone remodeling, two cellular activities are highly coordinated to achieve the renewal process at a particular site, mainly resorption and formation. Resorption is the process by which highly specialized cells, the osteoclasts, destroy bone tissue by creating resorption pits, and afterwards release the bone matrix constituents to the blood. Conversely, in the formation process osteoblast cells synthesize and secrete the osteoid, new unmineralized matrix, and afterwards organize as well the osteoid mineralization.

Following the mechanostat hypothesis [2], bone can adapt its shape and structure by the tissue level mechanisms of modeling and/or remodeling. In bone modeling, resorption and formation happen on different bone sites, a process that arises during growth and development. Conversely, in bone remodeling, both cellular activities occur sequentially at the same bone site, with resorption being followed by formation. In adult skeleton, bone remodeling runs in general as a self-maintenance mechanism used to repair microdamage or fractures, or to strengthen a bone surface supporting increasing mechanical stress. To organize and regulate the sequencing events in remodeling, the involved cells act as a multicellular team which evolves accordingly and is known as the basic multicellular unit or BMU.

To start bone remodeling a bone surface target is activated, maybe due to microdamage reparation or osteocytes apoptosis. Then, the BMU operation starts by recruiting osteoclast and osteoblast progenitors to the site to be resorbed. Osteoclast progenitors differentiate and get fused into multinucleated osteoclasts who are attracted to the site and start resorption. In osteonal remodeling [3], a fully developed BMU contains teams of osteoclasts actively resorbing at the cutting cone, followed by teams of osteoblasts producing and depositing layers of osteoid at the

closing cone. The coupling among resorption and formation may happen during the reversal stage coming after resorption, where the site may be prepared for the coming formation phase. During bone remodeling tight organization and regulation of the cellular interactions are required because sustained imbalances in the quantity or quality of the renewed bone can derive in bone disorders compromising the biomechanical integrity and performance of the skeleton.

The bone cells involved in the remodeling process are osteoclasts, osteoblasts, lining cells, and osteocytes. Osteoclasts are cells of hematopoietic origin responsible for bone resorption, whereas osteoblasts are cells of mesenchymal origin that produce and deposit the new matrix. Osteoclasts and osteoblasts are cells found, however, only temporary on bone surfaces. Osteoclasts are found actively resorbing a surface, while osteoblasts are found actively producing new matrix. Instead, osteocytes and lining cells are the osteoblastic lineage cells residing in the bone matrix. Lining cells derive from osteoblasts who have stopped synthesizing osteoid during bone formation and differentiate to a very flat cell covering the bone surfaces. Osteocytes are terminally differentiated osteoblasts, which are embedded into the matrix during the mineralization process. They live in lacunae that are small cavities inside the matrix, and extend their cytoplasmic extensions through the canaliculi. Due to these fingerlike extensions osteocytes keep in contact with other osteocytes within the matrix and other cells on the bone surface, thus forming a highly interconnected network that makes them the suitable cells for sensing and transducing the mechanochemical signals [4].

The understanding of the bone remodeling dynamics and the adaptation of bone to mechanical loading is of relevant scientific interest due to the potential use of physical exercise to counteract aging-induced bone loss and to avoid the decline of bone mass and strength in conditions of bone loss, such as osteoporosis or immobilization. Osteoporosis is a worldwide spread bone disorder where bone strength and mass are highly compromise thus increasing the risk of fractures. For instance, postmenopausal osteoporosis has been associated to a failure of the capacity of bone to maintain bone strength when estrogen levels are diminished [5]. In addition, the fact that astronauts lose bone mass during prolonged spaceflights, or patients in bed rest condition present osteopenia, show the key role play by earth gravity, locomotion and physical activity on the body, specially on the skeleton maintenance [1].

In this work, we employ a systems biology approach to get a better understanding of the process of force induced bone adaptation. To achieve this, firstly a mathematical model describing the adaption of bone due to mechanical and chemical stimuli was developed [6,7], and secondly, system theoretical methods are applied for the analysis of the complex interactions and the design of treatment therapies for bone disorders [8,9].

The mathematical description focuses on the remodeling process as an essential tissue level mechanism used by adult skeleton to maintaining bone strength throughout life. The main operational stages of the bone multicellular unit during bone remodeling covered are activation, resorption, and formation. In the model, osteocytes are introduced as the main mechanotransducers, sensing the mechanical loading changes and releasing local factors, e.g. nitric oxide and prostaglandins, that influence the interactions among osteoclast and osteoblast cell populations, mainly regulated through the RANKL/RANK/OPG signaling pathway.

For a better understanding of the bone adaptation process, and the identification/discrimination of possible therapeutic targets for remodeling-related bone disorders, a theoretical method for global sensitivity analysis is applied to the mathematical model to explore the effects of parameters/inputs variation on the stationary behavior of bone cells and tissue adaptation. In addition, the use of theoretical methods allows to explore for beneficial effects of combining mechanical and non-mechanical agents in the treatment of particular bone disorders, such as postmenopausal osteoporosis, or bed rest/immobilization.

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12:20–12:40

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Mathematical modeling of trabecular bone remodeling induced by osteocytic response to interstitial fluid flow

Bone is a load-bearing tissue that can adapt its internal structure and outer shape by remodeling to a changing mechanical environment. The morphological changes

in the trabecular microstructure are realized by the coupling of osteoclastic bone resorption and osteoblastic bone formation. It is widely believed that the metabolic activities of these executive cells are regulated by a mechanosensory system of osteocytes buried in the extracellular bone matrix, forming a three-dimensional intercellular network through cellular processes in lacuno-canalicular porosity [1]. The small space surrounding the osteocytes in the porosity is filled with interstitial fluid. When the bone is subjected to dynamic loading, bone matrix deformation induces an interstitial fluid flow [2]. The fluid flow in the lacuno-canalicular porosity seems to mechanically activate the osteocytes and serve as the prime mover for bone remodeling, as well as transport cell signaling molecules [3]. To understand the mechanism of bone functional adaptation, it will be useful to propose a theoretical framework of trabecular bone remodeling that interconnects the microscopic cellular activities to the macroscopic morphological changes through the mechanical hierarchy. In this study, first, we constructed a mathematical model for trabecular bone remodeling, taking cellular mechanosensing and intercellular communication into consideration [4]. This model assumes that osteocytes respond to fluid-induced shear stress and deliver their mechanical signals to the surface cells by intercellular communication. The mechanical behavior of a trabecula with lacuno-canalicular porosity is modeled as a poroelastic material to evaluate the interstitial fluid flow under mechanical loading. Second, on the basis of the proposed mathematical model, we simulated morphological changes in a single trabecula under cyclic uniaxial loading with various frequencies, which is thought to be a significant mechanical factor in bone remodeling. The results of the simulation show the trabecula reoriented to the loading direction with the progress of bone remodeling. As the imposed loading frequency increased, the diameter of the trabecula in the equilibrium state was enlarged by remodeling. Finally, we conducted a remodeling simulation for a cancellous bone cube under monotonously increasing compressive loading, where all the trabeculae are randomly-oriented in the initial geometry. As a result, the degree of trabecular connectivity was gradually decreased and the trabeculae in cancellous bone aligned along the loading direction. These results indicate that our remodeling simulation model can successfully express the macroscopic changes in trabecular morphology from the microscopic cellular activities.

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12:40–13:00

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Evolutionary simulation of the emergence of the mechano-regulated endochondral healing process

The ability of tissues to adapt to the mechanical environment is a remarkable feature of the skeleton. Several mechano-regulation theories have been proposed for describing how the mechanical environment modulates mesenchymal stem cell differentiation into bone, cartilage and fibrous tissue. Despite the biological complexity of the process, these theories have often been able to predict osseous healing through both membraneous and chondral healing, with reasonable success [1,2].

It is intriguing to wonder about the emergence of these healing processes, in particular the endochondral ossification process, in evolution and whether the ability of mechano-regulation has been involved in the emergence of new healing processes through natural selection. Early vertebrates, like cartilaginous fishes, could modulate their tissues to the mechanical environment and it is likely that evolution worked with adapting the skeletal tissues to the local conditions rather than involving major changes in cells or tissue types [3].

This study shows how the mechano-regulated endochondral ossification process could have emerged in evolution by being favoured in natural selection. The combination of a mechano-regulated tissue differentiation model [4] and a genetic algorithm for simulating evolutionary change [5], used in this investigation, was further able to capture inter-population variability in the mechano-regulated response and arrived at results that are in agreement with experimental studies of mechano-regulated differentiation and maintenance of bone [6,7].

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MINI-SYMPOSIUM 69

Computational toxicology and pharmacology - in silico drug activity and safety assessment

Saturday, July 2, 11:00, *Room*: **CP4**

Organizers: **Sebastian Polak, Aleksander Mendyk**

11:00–11:40

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Hematopoietic cell populations as therapeutic targets

Pharmacodynamics is a rapidly growing field with a focus on mathematical modeling of drug effects. A very important class of therapeutic/toxic effects is hematological cell populations, dynamics of which have been a well investigated subject of physiologically structured population models. However, only recently such models have incorporated drug effects on cell populations.

This talk will introduce the pharmacodynamic models of drug effects on hematopoietic cell populations. It will also make a link to physiologically structured population models through such structures as cell age and fluorescent label. The roles of physiological structures in describing therapeutic effects of various drugs will be emphasized.

11:40–12:00

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Systems Biology driven Pharmacokinetics and Pharmacodynamics

Pharmacokinetics is probably the most neglected field in the medically relevant biosimulations. It is a science about the drug fate in a living organism and embraces in broader sense four main domains: absorption, distribution, metabolism, and excretion, in short ADME. It is often combined and considered together with pharmacodynamics, a science branch dealing with the influence the drug has on its target and eventually on the whole body and disease progression. At the same time, the mechanism based but in most cases drugfree models and simulations are highly appreciated and developed in the Systems Biology community. There is no doubt that the full understanding of the underlying phenomena like physiological regulation and control, phenotypes, mutations and in general diseases is essential for the progress in medicine. However, much has been achieved in the last decades without sophisticated algorithms and supercomputers. Semimechanistic models or even simple phenomenological formulas and models are in use since beginning of the 20th century providing useful insights in e.g. physiology and pharmacokinetics related issues. We are convinced, that parallel application of these two seemingly unconnected approaches can eventually converge into more effective treatments methods now or in near future. We are making an attempt to introduce a new platform combining standard phenomenological models used in the PK/PD field with mechanistically based Systems Biology models and approaches. There are many examples of wellknown 1, 2 or more compartmental models providing valuable initial guesses and insights into the metabolism, and ADME processes in general, of a particular drug. However, their use is limited due to the non-mechanistic nature of such models. We consider Systems Biology driven models as complementary to their phenomenological counterparts. The ultimate goal of a wholebody full mechanistic model for the combined PKPDADME is doable on the scale of next few decades, but to support modern drug development now, we need the imperfect but useful phenomenological models in combination with mechanistic models under development.

12:00–12:20

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Artificial neural networks for carditoxicity prediction of drugs - practical considerations

Introduction Early toxicity prediction for potential drugs is considered as a necessary safety measure regarding recent withdrawals of many substances from the pharmaceutical market. The latter was substantially based on the identified cardiotoxicity related to the inhibition of the potassium channels encoded by hERG (the human ether-a-go-go related gene). Thus, the drugs affinity to hERG channels is considered now as one of the major screening factors for potentially dangerous substances. There are theories describing relationships between hERG channels blocking activity and chemical structure but they often lack of physiological/pathological factors and drug concentration influence. Thus, it is feasible to use empirical modeling to fill this gap. The aim of this work was to create predictive model for chemical substances affinity to hERG channels by means of artificial neural networks (ANNs).

Materials and methods Database used for the modeling purposes was recently published and is freely available from the CompTox project website (www.toxportal.net). Input data were derived from the published in vitro experiments. Inputs represented in vitro experiment settings, chemical descriptors of drugs and drug concentration. Output was simply percent of hERG channel inhibition (range 0 to 1). Final set contained 1969 records describing 200 drugs. Initial number of inputs was 109. Enhanced 10-fold cross validation (10-cv) was applied, where whole drugs information was excluded from test sets. For external validation a test set of 193 records (25 substances) for drugs both previously present (different in vitro settings) and absent in the native dataset was used. Drugs chemical structures were drawn in MarvinSketch or downloaded from PubChem Compound database. The molecules were structurally optimized with use of molconvert command-line program included in Marvin Beans package. Resulting *.sdf files were the subject to descriptor calculations by cxcalc program with selected 41 plugins. The default parameters were used in both cxcalc and molconvert programs. Multi-layer perceptrons (MLPs) and neuro-fuzzy ANNs (NFs) were trained with use of back-propagation (BP) algorithm with momentum, delta-bar-delta and jog-of-weights modifications. Various activation functions were tested: hyperbolic tangent, logarithmic, logistic and linear. MLPs architectures were varied from 1 to 6 hidden layers and up to 200 nodes in each layer. For NFs of Mamdani (multiple input single output) MISO type only one layer was applied. Adjacent layers were fully interconnected. Sensitivity analysis was performed in order to reduce initial number

of inputs to the crucial variables set by means of iterative algorithm with gradual inputs reduction and models predictive performance assessment. The latter was generalization error estimated by means of 10-cv with root mean squared error (RMSE) measure. Ensemble ANNs systems were applied and combined by simple average of their outputs in order to improve predictability of the model.

Results The input reduction procedure resulted in 39 parameters describing in vitro setting (8), drug physico-chemical properties (30), and concentration (1). The best ANNs architectures found were as follows: (1) ANN with 3 hidden layers with 15, 7 and 5 nodes in each one respectively and logistic activation function; 2) ANN with 2 hidden layers with 20 and 10 nodes. The resulting 10-cv RMSE was 0.22 with respect to the validation data set RMSE = 0.2. This result, although not satisfactory seems to be final with the available data representation. Future research will be devoted to the improvement of the model by enhancing input data by new factors/variables, if available.

12:20–12:40

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Systems Biology in drug development - cardiotoxicity prediction

Cardiac liability testing of the drugs candidates during development process has gained increased regulatory and public attention due to a growing awareness of the cardiac risks across a variety of marketed products. Nowadays, cardiac safety assessment in pre-approval clinical trials is obligatory and possible failure at this late stage of the R&D pipeline has tremendous impact on pay-off of the whole process. Thus it is desirable to screen compounds as early as possible, before large amounts of time and money have been spent. Traditional pre-clinical in vivo and ex vivo animal studies employed in risk assessment are criticised due to the ethical and meritorious reasons and in vitro cell lines based studies are currently effectively utilized. Results extrapolation from the in vitro tests to in vivo human risk became an issue and systems biology approach is proposed to derive appropriate conclusions from in vitro lab observations. Developed system is hybrid in nature and combines mathematical model of the human left ventricle cardiomyocyte with in vitro assessed drug induced ionic channels inhibition. The third main element is a virtual population generator. Based on the data derived from available scientific literature dynamic database of the population was developed. Randomly chosen virtual individuals are described by physiological and genetic parameters, namely cardiomyocyte volume, sarcoplasmic reticulum volume, cell electric capacitance, potassium channels genetic polymorphism, which are used as simulation parameters. Therefore the system allows for the inter-individual variability assessment

which is a fundamental advantage comparing with animal in vivo and other available muli-scale models. Combination of above-described approach with physiology based pharmacokinetic models (PBPK) used for plasma and tissues drug concentration changes prediction can be used for concentration dependent in vitro - in vivo extrapolation of the cardiotoxic effect for new chemical entities.

12:40–13:00

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Combining two model paradigms: How an agent-based hematopoietic stem cell model couples to an ordinary differential equations model of mature granulopoiesis and chemotherapy

To model the organization of hematopoietic stem cells Roeder *et al.* have introduced an agent-based model which succeeded well in explaining several experimental data of clonal competition and stem cell dynamics with clinically relevant applications in the field of chronic myeloid leukemia [**1**]. The model assumes two growth-environments and regulates stem cell activity by an intrinsic feedback that controls the transition between these environments.

In order to model the effects of chemotherapy and growth factor applications on the number of mature granulocytes, a compartment-based ordinary differential equations (ODE) model of granulopoiesis has been introduced by Scholz *et al.* [**2**]. Here the stem cell compartment is represented in a very simplified fashion.

To overcome this simplification and to take advantage of the established model of hematopoietic stem cells we replaced the ODE stem cell compartment with a difference equation formulation of the agent-based stem cell model [**3**]. Two feedback mechanisms for stem cell activation were introduced for replacing the regulation of self-renewal probability and proliferative fraction in the stem cell compartments of the ODE model. Stem cell activation was implemented firstly by increasing the probability of exiting quiescent states and secondly by a general acceleration in the stem cell compartment.

The resulting hybrid model was capable of reproducing the experimental data for the chemotherapy regime of Chop21. Interestingly, the comparison of feedback mechanisms for stem cell activation showed that the best agreement with the regeneration response in the clinical trials was achieved for the intrinsic regulation of the agent-based model without additional activation.

On the basis of the combined model, we aim to improve the modeling of chemotherapy effects on the hematopoietic system in the future. In particular we

expect further insights into the role of role of hematopoietic stem cells with respect to the development of a toxicity induced leukopoenia with subsequent regeneration

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MINI-SYMPOSIUM 70

Speciation

Wednesday, June 29, 08:30, *Room*: CP2

Organizer: **Tadeas Priklopil**

08:30–08:55

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Dobshansky-Muller incompatibilities in parapatry

The accumulation of Dobshansky-Muller incompatibilities is a widely accepted mechanism for speciation in allopatric populations. In this presentation, we analyze the scope and limits of this mechanism if the populations are not fully separated. We use classical migration-selection models to determine the limiting rates of gene-flow that allow i) for the origin and ii) for the maintenance of a single Dobshansky-Muller incompatibility in parapatry. We use our results to discuss the importance of ecological and genetic factors (such as recombination rate, strength of the incompatibility, level of local adaptation) for the speciation process in the presence of gene-flow.

08:55–09:20

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Darwinian speciation on a regulated landscape

Darwin envisioned speciation as a gradual transformation from within-species diversity to between species one, driven by the fitness-advantage of reduced competition via niche-segregation. We identify three issues why Darwins suggestion has been

considered problematic since the New Synthesis: I: The notions of niche and reduced competition have no meaning in the context of a rigid adaptive landscape. Instead, one has to consider the landscape (i.e. the fitness function) as a function of the phenotype-distribution in a functional analytic context. The functional derivative of this map is the competition function with the correct biological meaning. The adaptive dynamics phenomenology, including evolutionary branching, can be derived from this setup. II: The observed often-allopatric nature of speciation seems to exclude a role for competition. However, the theory of structured populations allows considering spatially distributed populations as a single population with an over-all fitness value. Therefore, we can define the adaptive landscape on the large spatial scale and apply the considerations above for allopatric and parapatric speciation modes analogously to the sympatric case. III: Biological species concept declared reproductive isolation as the defining issue of speciation. In our picture emergence of isolation is secondary to ecological segregation on the regulated/changing landscape. As selection for ecological divergence is caused by a fitness minimum, it is always accompanied by a selection pressure for isolation. Whether this pressure results in an evolutionary buildup of reproductive isolation depends on the availability and genetic organization of the possible isolating mechanisms. Considering these three issues together leads us to conclude that Darwins original idea is still the most parsimonious theory of speciation. Species diversity is necessarily based on competition-reducing niche segregation, i.e. segregation with respect to the way of being regulated. This structure translates to the concept of regulated adaptive landscape, providing selection pressure for competition-reducing branching evolution, which may, or may not be related to spatial segregation.

09:20–09:45

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Can dominance prevent the evolution of assortative mating and sympatric speciation?

Consider a quantitative trait that is under a mixture of frequency-independent stabilizing selection and density- and frequency-dependent selection caused by intraspecific competition for a continuum of resources. The trait is determined by a single (ecological) locus and expresses intermediate dominance, and the population mates assortatively with respect to this trait.

We study weather mutations at modifier loci can invade, which either increase the level of dominance or the level of assortment. From a naïve point of view, complete dominance and complete assortative mating seem to be two alternative mechanisms to eliminate unfit offspring with intermediate traits. However, we will see that the interaction of assortative mating and dominance is rather complex. The two evolutionary responses can promote each other or hinder each other. Overall, we find that dominance might be the more likely evolutionary outcome, and that

the evolution of assortative mating in small steps leading to sympatric speciation seems unlikely.

09:45–10:10

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Alexey Yanchukov
UC Santa Barbara

Evolutionary responses to migration load: A tall fence or a melting pot?

Gene flow between populations in different ecological conditions can reduce fitness in both populations. This can be due to immigration of alleles that are not adapted to local ecological condition or because hybrids between populations have lower fitness. But this reduction in fitness, or genetic load, is also a potential engine to drive evolution: The magnitude of the genetic load sets an upper bound to the strength of selection to compensate for the cost of migration. This load can be reduced through mating preferences for high quality mates, mating preferences for local genotypes, or by changes in the genetic architecture. Preferences for local mates would lead to reinforcement of low hybrid fitness and potentially speciation. Alternatively, preferences for high quality mates or changes to the genetic architecture might allow incipient species to continue to transfer genetic information without population collapse. I will discuss the relative strength of each pathway and the implications for local adaptation and speciation.

10:10–10:30

Tadeáš Přiklopil
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Magic traits, mate choice and speciation

Many theoretical models on sympatric speciation rely on assortative mating functions, in which the probability that two individuals mate decreases with increasing phenotypic difference. We give results on the effect of assortative mating functions in models, where the trait that controls mate choice also determines fitness in ecological selection (so called magic traits). In particular, we concentrate on the deficiencies of these mating functions and contrast the results with mate choice which is also based on indicators of adaptedness. Further, we introduce mate choice

that is based on a strategy of sequential search, where the decision to mate depends on the density distribution of the population and the fitness returns to the searcher.

References.

[1] E. Kisdi & T. Priklopil, *Evolutionary branching of a magic trait* J. Math. Biol. DOI 10.1007/s00285-010-0377-1

MINI-SYMPOSIUM 71

Mathematical models of evolutionary dynamics of infectious agents

Tuesday, June 28, 17:00, *Room*: **AM9**

Organizers: **Andrea Pugliese, Viggo Andreasen**

17:00–17:25

Adam Kucharski
University of Cambridge
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Julia Gog
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Strain dynamics and influenza drift

One of the most exciting current areas in infectious disease modelling is in bringing together the epidemic and evolutionary dynamics. Influenza drift is perhaps the most striking example of where the two processes must be considered together: epidemics give rise to new strains, which in turn permit new epidemics.

We will begin with a general introduction to models of multiple strains, and some of their challenges, both technical and in terms of capturing observed biological phenomena. In most population-based models of strain dynamics, the number of variables grows exponentially with the number of strains. We present two items of our recent work, each of which avoids this problem in one way or another:

1) The impact of evolutionary constraints on influenza drift: standard drift models assume influenza is free to mutate to escape host immunity. In practice, there may be some functional cost associated with these mutations, and this can be incorporated into a mathematical model. In contrast to unconstrained drift models, this system is bistable, exhibiting both drift-like patterns and single strain dynamics for the same parameter values. This raises some important questions for vaccination strategies.

2) Age-structure and immune history: although relatively simple assumptions about the acquisition of immunity capture well the general dynamics of influenza drift, recent outbreaks have highlighted the importance of considering the details of precisely how immunity is acquired by an individual over their lifetime. In particular, strains that infect us when we are young may be disproportionately important (e.g. through original antigenic sin), and the immune response may be weakened in the elderly.

17:25–17:50

Gabriela Gomes
Instituto Gulbenkian de Ciencia, Oeias, Portugal
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Andrea Parisi
Departamento de Fisica, Faculdade de Ciencias, Universidade de Lisboa
Ana Nunes
Departamento de Fisica, Faculdade de Ciencias, Universidade de Lisboa

Heterogeneity in antibody range is required for the antigenic drift of influenza A viruses

In this paper we explore the consequences for the evolution of a rapidly mutating virus of a heterogeneous immune response in the population. We show that several features of the incidence and phylogenetic patterns typical of influenza A may be understood in this framework. Limited diversity and rapid drift of the circulating viral strains result from the interplay of two interacting subpopulations with two different types of immune response, narrow or broad, upon infection. The subpopulation with the narrow immune response acts as a reservoir where consecutive neutral mutations escape immunity and can persist. Strains with a number of accumulated mutations escape immunity in the other subpopulation as well, causing larger epidemic peaks in the whole population, and reducing strain diversity. These recurrent larger epidemics have been identified in the data and associated in the modelling literature with "cluster jumps", or mutations whose antigenic effect is larger and generate strains for which the pool of susceptibles in the population is also larger. Our model reproduces the observed epidemic peak height variation and antigenic drift patterns without any assumption of punctuated antigenic evolution.

17:50–18:15

Yael Artzy-Randrup
Department of Ecology and Evolutionary Biology and Howard Hughes Medical Institute, University of Michigan
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Severe First and Mild Later: Temporal Strategies in Pathogen Evolution

Because pathogens replicate within hosts and transmit between them, selection takes place on multiple levels. There has been ongoing interest for more than two decades in trying to understand the conditions favoring the evolution of acute, highly transmissible infections, focusing on trade-offs such as the transmissibility-virulence trade-off and the invasion-persistence trade-off. Studies have shown that

these types of trade-offs lead to intermediate pathogen attack rates. These earlier studies typically consider the evolution of a single trait under a defined trade-off. However, for some pathogens, the course of infection within the host is likely to be more complex, determined by more than a single dimension, opening the door for more complicated strategies related to disease severity. The protozoa Plasmodium falciparum (Pf), which causes the most severe type of malaria in humans, is one example of such a pathogen. During the course of an infection, Pf has the ability to express up to 60 different variants of surface proteins (PfEMP1) encoded by a family of var genes, which are recognized by the host immune system and which also act as virulence factors.

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

18:15–18:40

Barbara Boldin
Faculty of Mathematics, Natural Sciences and
Information Technologies
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Within-host viral evolution in a heterogeneous environment: insights into the HIV co-receptor switch

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

the virus population to target cell heterogeneity. More generally, we argue that evolutionary ecology can help us better understand the course of some infections. The talk is based on joint work with Samuel Alizon [**1**].

References.

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

18:40–19:05

Viggo Andreasen
Roskilde University
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The final size of an epidemic with two competing strains

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

MINI-SYMPOSIUM 72

Undergraduate Biomathematics Education Beyond BIO 2010 (Part I)

Wednesday, June 29, 14:30, *Room*: **UA3**

Organizers: **Raina Robeva, Timothy Comar, Meghan Burke**

14:30–14:50

Holly Gaff
Old Dominion University
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Agent-based models of interacting populations

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

14:50–15:10

Claudia Neuhauser
University of Minnesota Rochester
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Mathematics, Statistics, and Biology: An Integrative Approach

Over the past five years, with funding from the Howard Hughes Medical Institute, we have developed courses and shorter teaching units to enhance the quantitative education of life science majors. We will present examples that illustrate how biological applications can enhance mathematics and statistics courses at the lower

division and how mathematics and statistics can be integrated into biology courses, in particular into labs. We will report on the implementation of the curricula at the University of Minnesota Rochester and the dissemination strategy through the Numbers Count website and workshops held in collaboration with BioQUEST.

15:10–15:30

Raina Robeva
Sweet Briar College
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Modeling of the Growth Hormone Network

Hormone secretion patterns are determined by the frequency of secretion events, the amount secreted, and the length of time the secretion event lasts. They encode messages for the target cells that control vital physiological processes, and an alteration of a secretion pattern may impede one or more of these processes. Understanding hormone secretion and developing the capability to recognize both normal and pathological patterns of hormone production is of utmost importance for establishing medical diagnoses, initiating treatment, and assessing the effects of treatment. It is generally impossible to collect data directly from the endocrine glands, where the hormones are secreted. Secretion patterns have to be inferred from hormone concentration in the blood where distortions, due to binding, excretion and/or biotransformation, begin immediately after the hormones enter the bloodstream. Thus, mathematical models of the hormone network interactions and control mechanisms play a critical role in the understanding of endocrine osciallations. The talk will outline a model of the growth hormone network and a related undergraduate project appropriate for use in calculus-based courses.

15:30–15:50

Winfried Just
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Discrete *vs.* indiscrete models of network dynamics

A key step in modeling biological network dynamics is the decision whether to use a stochastic process, a system of differential equations, or a discrete dynamical system. This step in the modeling process poses both special challenges and special opportunities for undergraduate teaching. The challenge is that performing this step requires familiarity with a number of different areas of mathematics, which cannot be taken for granted in undergraduate teaching. Moreover, undergraduates

tend to view mathematics as neatly compartmentalized into subdisciplines, each with their own set of standard word problems. The opportunity is for leading students beyond this view and giving them a taste of *bona fide* mathematical modeling where the tools need to be chosen depending on the system and available computational resources. Moreover, one can introduce quite sophisticated mathematical concepts from a variety of areas of mathematics along the way.

This presentation will illustrate the potential of this approach based on ODE and discrete models with finite state spaces for certain networks. We will investigate conditions under which the coarse-graining via discrete models is a valid modeling approach and give examples of open problems that can be explored as undergraduate research projects.

MINI-SYMPOSIUM 73

Undergraduate Biomathematics Education Beyond BIO 2010 (Part II)

Saturday, July 2, 08:30, *Room*: **AM5**

Organizers: **Raina Robeva, Timothy Comar, Meghan Burke**

08:30–08:50

Semen Koksal
Florida Institute of Technology
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David Carroll
Florida Institute of Technology
Robert van Woesik
Florida Institute of Technology
Richard Sinden
Florida Institute of Technology
Eugene Dshalalow
Flroida Institute of Technology

Establishing an Undergraduate Program and Major in BioMathematics

To provide increased opportunity for students interested in the intersection of Biology, Mathematics and Computer Science, an interdisciplinary degree-granting program in BioMathematics was established at the Florida Institute of Technology (FIT). This new major encompasses a program that includes a significant undergraduate research component. The research students are supported by an NSF grant, UBM. Our emerging UBM program has already had a strong impact on the FIT campus, helping to create an atmosphere of excitement in undergraduates interested in exploring a new field and gaining novel research experience.

In this talk, the positive aspects as well as the difficulties in establishing this program at the departmental and institutional level will be discussed. Sample of projects and the newly established three biomath courses will be presented.

08:50–09:10

Paola Vera-Licona

Institut Curie
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Ana Martins
Virginia Bioinformatics Institute
Reinhard Laubenbacher
Virginia Bioinformatics Institute

Computational Systems Biology: Discrete Models of Gene Regulatory Networks

In this talk we will describe a hands-on project in computational systems biology for students and that can be used in a variety of settings, from high school to college, with a particular focus on the use of discrete mathematics. The biological focus is the Escherichia coli lactose operon, one of the first known intracellular regulatory networks. The modeling approach uses the framework of Boolean networks and tools from discrete mathematics for model simulation and analysis.

The talk is based on materials from a workshop for high school teachers described in Martins et al. [1] and conducted as a collaboration between the Virginia Bioinformatics Institute (VBI) at Virginia Tech and the Institute for Advanced Learning & Research (IALR) in Danville, VA. The workshop structure simulated the team science approach common in today practice in computational molecular biology and thus represents a social case study in collaborative research.

During the workshop the participants were provided with all the necessary background in molecular biology and discrete mathematics required to complete the project, and developed activities intended to show students the value of mathematical modeling in understanding biochemical network mechanisms and dynamics.

References.

[1] A. Martins, P. Vera Licona, R. Laubenbacher. Computational systems biology: Discrete models of gene regulation networks. To appear in MAA Notes volume: Undergraduate Mathematics for the Life Sciences: Processes, Models, Assessment, and Directions. 2011.

09:10–09:30

Hannah Callender
University of Portland

What My Biology Students Taught Me About Mathematics

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

about mathematics pre- and post-biocalculus as well as similarities and differences in their styles of learning mathematics.

MINI-SYMPOSIUM 74

Stochastic models in computational neuroscience I

Wednesday, June 29, 14:30, *Room*: **UA2**

Organizer: **Laura Sacerdote**

14:30–15:10

Wulfram Gerstner
Richard Naud
Skander Mensi
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Predicting action potentials and membrane potential of neurons

If neurons receive a current that is generated by a filtered point process, they fire spikes at specific moments in time, with little variation from one trial to the next.

In this talks I will discuss

(i) how to compare spike trains and measure reliability

(ii) how to extract adaptative currents from the data

(iii) how to systematicaly construct neuron models from simple models to more complex ones.

15:10–15:30

Roberta Sirovich
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About a modification of the firing time definition in stochastic leaky integrate–and–fire neuron models

The integrate-and-fire neuron model is one of the most widely used models for studies of neural coding [1,2]. It describes the membrane potential of a neuron

in terms of the synaptic inputs and the injected current that it receives. An action potential (spike) is generated whenever the membrane potential crosses some threshold level from below. In integrate-and-fire models the form of an action potential is not described explicitly. Spikes are formal events fully characterized by a 'firing time' after which the membrane potential is reset and the process starts from scratch.

The observation of experimental intracellular recordings seems to suggest that the membrane potential may cross the threshold level several times before an action potential is detected [3]. We study a modified version of the leaky integrate-and-fire neuron model where a spike is generated whenever the membrane potential remains above the threshold level for a 'sufficiently' long time. Hence the firing time is not defined by an instantaneous crossing of the level, but depends on a longer history of fluctuations of the membrane potential. Comparisons with the dynamics exhibited in the classical models are presented.

References.

[1] A. N. Burkitt, *A review of the integrate–and–fire neuron model: I. Homogeneous synaptic input* Biol Cybern (2006) **95** 1–19.

[2] A. N. Burkitt, *A review of the integrate–and–fire neuron model: II. Inhomogeneous synaptic input and network properties* Biol Cybern (2006) **95** 97–112.

[3] P. Lansky, P. Sanda and J. He *The parameters of the stochastic leaky integrate–and–fire neuronal model* J Comput Neurosci **21** 211.

15:30–15:50

Michele Thieullen
Universite Pierre et Marie Curie
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Piecewise Deterministic Markov Processes and detailed neuron models.

In this talk I will introduce the family of Piecewise Deterministic Markov Processes. Systems described by these processes undergo deterministic evolution on random intervals. I will present some results about these processes including limit theorems and diffusion approximation. Models of neurons taking into account the stochasticity of ion channels make a natural example.

15:50–16:10

Priscilla Greenwood
University of British Columbia
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Priscilla Greenwood
University of British Columbia, Vancouver

Peter Rowat
University of California, San Diego

Continuity across bifurcations of stochastic Morris Lecar output distributions

Using the stochastic Morris Lecar model neuron, type II, with ion channel noise,we investigate the inter-spike interval distribution as increasing levels of applied current drive the model through a sub-critical Hopf bifurcation. We show that the parameter of the exponential tail of the ISI distribution is continuous over the entire range of plausible applied current, regardless of discontinuities in the phase-portrait of the model. Further, we show that the seldom-considered distribution of number of consecutive spikes is geometric with associated parameter similarly continuous as a function of applied current over the entire input range.

16:10–16:30

Shigeru Shinomoto
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A state space method for decoding neuronal spiking signals

Cortical neurons *in vivo* have often been approximated as Poisson spike generators that convey no information other than the rate of random firing. Recently, it has been revealed by using a metric for analyzing local variation of interspike intervals that individual neurons express specific patterns in generating spikes, which may symbolically be termed regular, random or bursty [1,2]. Two hypotheses have been proposed for potential advantage of using non-Poisson spike trains in transmitting information; neurons may signal the firing irregularity by changing it in addition to the rate of firing [3], or alternatively, the receiver may estimate the firing rate accurately by making the most of non-Poisson inter-spike dependency in the received signals [4-6]. In order to determine which hypothesis is more plausible for a given spike train, we have implemented a state space method for simultaneously estimating firing irregularity and the firing rate moment by moment [7,8]. I review the recent development of the state space analysis and demonstrate new results obtained for a variety of electrophysiological data.

References.

[1] S. Shinomoto, K. Shima, & J. Tanji (2003), *Differences in spiking patterns among cortical neurons.* Neural Computation **15** 2823–2842.

[2] S. Shinomoto et al. (2009), *Relating neuronal firing patterns to functional differentiation of cerebral cortex.* PLoS Computational Biology **5** e1000433.

[3] R.M. Davies, G.L. Gerstein, & S.N. Baker (2006) *Measurement of time-dependent changes in the irregularity of neural spiking.* Journal of Neurophysiology **96** 906–918.

[4] R. Barbieri et al., *Construction and analysis on non-Poisson stimulus-response models of neural spiking activity.* Journal of Neuroscience Methods **105** 25–37.

[5] J.P. Cunningham et al. (2008), *Inferring neural firing rates from spike trains using Gaussian processes.* Advances in Neural Information Processing Systems **20**.

[6] S. Koyama, & S. Shinomoto (2005) *Empirical Bayes interpretations of random point events.* Journal of Physics A - Mathematical and General **38** L531–L537.

[7] T. Shimokawa & S. Shinomoto (2009) *Estimating instantaneous irregularity of neuronal firing.* Neural Computation **21** 1931–1951.

[8] T. Shimokawa, S. Koyama, & S. Shinomoto (2010) *A characterization of the time-rescaled gamma process as a model for spike trains.* Journal of Computational Neuroscience **29** 183–191.

MINI-SYMPOSIUM 75

Noisy Cells

Saturday, July 2, 14:30, *Room*: **AM3**

Organizers: **Alexander Skupin, Rudiger Thul**

14:30–15:00

Thomas Höfer
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Ulfert Rand
Helmholtz Center for Infection Research Braunschweig
Melanie Rinas
Deutsches Krebsforschungszentrum Heidelberg
Hansjörg Hauser
Helmholtz Center for Infection Research Braunschweig
Mario Köster
Helmholtz Center for Infection Research Braunschweig

Noisy information processing in the innate immune response

The cellular recognition of viruses evokes the secretion of type-I interferons. in turn, interferons trigger an antiviral response that limits viral replication and spread. Combining the imaging of interferon induction and response in single cells with mathematical modeling, we uncovered strong cell-to-cell heterogeneity at multiple levels of regulation. The initiation of antiviral signaling, the induction of IFN genes and the expression of viral restriction factors all display large variability across a clonal, homogeneously infected cell population. We show that much of this variability is due to cell-intrinsic noise. We predict theoretically, and verify experimentally, that a small fraction of IFN-producing is sufficient to induce IFN target genes in the other, non-producing cells of the population. The coupling of the stochastic sensing of viral infections by the innate immune system with the paracrine amplification of protective responses has implications for our understanding of the biology of viral diseases.

15:00–15:30

Martin Falcke

Max Delbrück Center for Molecular Medicine
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Kevin Thurley
Max Delbrück Center for Molecular Medicine

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

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

15:30–16:00

Alexander Skupin
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Moritz Schütte
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Modeling the dynamics of enzyme-pathway coevolution

Metabolic pathways must have coevolved with the corresponding enzyme gene sequences. However, the evolutionary dynamics ensuing from the interplay between metabolic networks and genomes is still poorly understood. Here, we present a computational model that generates putative evolutionary walks on the metabolic network using a parallel evolution of metabolic reactions with their catalyzing enzymes. Starting from an initial set of compounds and enzymes, we expand the metabolic network iteratively by adding new enzymes with a probability that depends on their sequence-based similarity to already present enzymes. Thus, we obtain simulated time courses of chemical evolution in which we can monitor the appearance of new metabolites, enzyme sequences, or even entire organisms. We observe that new enzymes do not appear gradually but rather in clusters which correspond to enzyme classes. A comparison with Brownian motion dynamics indicates that our system displays biased random walks similar to diffusion on the metabolic network with long range correlations. This suggests that a quantitative molecular principle may underlie the concept of punctuated equilibrium as enzymes occur in bursts rather than by phyletic gradualism. Moreover, the simulated time courses lead to a putative time-order of enzyme and organism appearance. Among the patterns we detect in these evolutionary trends is a significant correlation between the time of appearance and their enzyme repertoire size. Hence, our approach to metabolic evolution may help understand the rise in complexity at the biochemical and genomic levels.

16:00–16:20

Tilo Schwalger
Max Planck Institute for the Physics of Complex Systems
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How stochastic adaptation currents shape interspike interval statistics of neurons - theory and experiment

Trial-to-trial variability and irregular spiking is an ubiquitous phenomenon throughout the nervous system. In many cases, the origin of this neural noise is not known and difficult to access experimentally. Here, we explore the possibility to distinguish between two kinds of intrinsic noise solely from the interspike interval (ISI) statistics of a neuron. To this end, we consider an integrate-and-fire model with spike-frequency adaptation in which fluctuations (channel noise) are either associated with fast ionic currents or with slow adaptation currents. We show by means of analytical techniques that the shape of the ISI histograms and the ISI correlations are markedly different in both cases: for a deterministic adaptation current, ISIs are distributed according to an inverse Gaussian density and the ISI correlations are negative. In contrast, for stochastic adaptation currents, the ISI density is more peaked than an inverse Gaussian density and the serial correlations are positive. We applied these measures to intracellular recordings of locust auditory receptor cells in vivo. By varying the stimulus intensity, we observed intriguingly similar statistics corresponding to both cases of the model. The results suggest

that stochasticity of slow adaptation currents may contribute to neural variability in sensory neurons.

References.

[1] Schwalger T, Fisch K, Benda J, Lindner B: How noisy adaptation of neurons shapes interspike interval histograms and correlations. PLoS Comput Biol 2010, 6(12): e1001026

MINI-SYMPOSIUM 76

Recent advances in infectious disease modelling I

Saturday, July 2, 11:00, *Room*: **CP3**

Organizers: **Robert Smith?, Elissa Schwartz, Stanca Cuipe**

11:00–11:40

Elissa Schwartz
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Immune Dynamics of Equine Infectious Anemia Virus

Equine Infectious Anemia Virus (EIAV) is a retrovirus that establishes a persistent infection in horses and ponies. The virus is in the same lentivirus subgroup that includes human immunodeficiency virus (HIV). The similarities between these two viruses make the study of the immune response to EIAV relevant to research on HIV. We developed a mathematical model of in-host EIAV infection dynamics that contains both humoral and cell-mediated immune responses. The model is parameterized using clinical, virological, and immunological data from horses infected with EIAV. Analysis of the model yields results on thresholds that would be necessary for a combined immune response to successfully control infection. Numerical simulations are presented to illustrate the results. These findings have the potential to lead to immunological control measures for retroviral infection.

11:40–12:00

Stanca M. Ciupe
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Antibody responses during Hepatitis B viral infection

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

12:00–12:20

Jonathan Forde
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Stanca Ciupe
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Reducing HIV Reservoirs by Induced Activation of Latently Infected Cells

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

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

12:20–12:40

Kasia Pawelek
Oakland University
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Modeling within-host dynamics of influenza virus infection including kinetics of innate and adaptive immune responses

Despite vaccines and antiviral agents, influenza infection remains a major public health problem worldwide. It is of great importance to study the biological events underlying virus replication and host immune response in order to develop more effective vaccines, treatments, and other prevention strategies. Here, we develop a new mathematical model to study the within-host dynamics of influenza infection. By comparing modeling predictions with both interferon and virus kinetic data, we examine the relative roles of target cell availability, innate and adaptive immune response in controlling the virus. This work provides a detailed and quantitative understanding of the biological factors that can explain the virus kinetics during a typical influenza infection.

12:40–13:00

Rachelle Miron
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Impulsive differential equations and their application to disease modelling

Many evolutionary processes are characterized by the fact that at certain moments of time they experience a change of state abruptly. These processes are subject to short-term perturbations which act instantaneously; that is, in the form of impulses. Thus, impulsive differential equations - differential equations involving impulse effects - appear as a natural description of observed evolution phenomena of several real-world problems. We will discuss how to solve linear homogeneous and non-homogeneous impulsive differential equations as well as non-linear autonomous impulsive differential equations. We will also give an overview of existence and uniqueness of impulsive systems as well as the issues that arise with stability. We illustrate using a model for HIV drug therapy.

MINI-SYMPOSIUM 77

Recent advances in infectious disease modelling II

Saturday, July 2, 14:30, *Room*: **AM9**

Organizers: **Robert Smith?, Elissa Schwartz, Stanca Cuipe**

14:30–15:10

Robert Smith?
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The impact of media coverage on the transmission dynamics of human influenza

There is an urgent need to understand how the provision of information influences individual risk perception and how this in turn shapes the evolution of epidemics. Individuals are influenced by information in complex and unpredictable ways. Emerging infectious diseases, such as the recent swine flu epidemic, may be particular hotspots for a media-fueled rush to vaccination conversely, seasonal diseases may receive little media attention, despite their high mortality rate, due to their perceived lack of newness. We formulate a deterministic transmission and vaccination model to invetigate the effects of media coverage on the transmission dynamics of influenza. The population is subdivided into different classes according to their disease status. The compartmental model includes the effect of media coverage on reporting the number of infections as well as the number of individuals successfully vaccinated. A threshold parameter (the basic reproductive ratio) is analytically derived and used to discuss the local stability of the disease-free steady state. The impact of costs that can be incurred, which include vaccination, education, implementation and campaigns on media coverage, are also investigated using optimal control theory. A simplified version of the model with pulse vaccination shows that the media can trigger a vaccinating panic if the vaccine is imperfect and simplified messages result in the vaccinated mixing with the infectives without regard to disease risk. The effects of media on an outbreak are complex. Simplified understandings of disease epidemiology, propogated through media soundbites, may make the disease significantly worse.

15:10–15:30

Axel Bonacic Marinovic
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Timeliness of intervention in epidemic outbreaks

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

15:30–15:50

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

Recently, the nationwide incidence of hepatitis C in Egypt has attracted much attention both in the scientific literature and mass media. Alarming new estimates exceeding 500 000 new cases per year (6.9/1000 per person-year) have been made based on data originating from the Egyptian Demographic and Health Survey performed in 2008. However, a more complete analysis of the hepatitis C epidemiology in Egypt, based on additional national-level as well as cohort-level data, reveals a very different story. First, it unveils a complex epidemic dynamics that violates the

simplistic methodological assumptions made for the incidence estimates; it thus becomes obvious that incidence has been overestimated. Second, a comparison with direct incidence measurements in rural cohorts suggests that the overestimation is by at least a factor of three. Accurate estimate of the hepatitis C incidence in Egypt remains a task for the future.

References.

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15:50–16:10

Bernhard Konrad
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Jessica M. Conway
The University of British Columbia
Alejandra Herrera
The University of British Columbia
Daniel Coombs
The University of British Columbia

Stochastic model-based predictions on post-exposure prophylaxis strategies for prevention of HIV infection

Antiretroviral treatment (ART) leads to a much lower viral load in HIV patients and thus improves quality and length of life. When used as a post-exposure prophylaxis (PEP) shortly after exposure to HIV, ARTs are also known to reduce the risk of infection. However, many aspects of the very early stages of HIV infection remain poorly understood because the associated low viral loads are difficult to measure clinically. We present a continuous-time branching process model of early HIV infection in order to capture dynamics of the small number of virus particles. Using the related Chapman-Kolmogorov differential equation and the associated probability generating function we derive an expression for the virus extinction probability which we solve numerically. This allows us to predict the efficacy of different PEP strategies, considering initiation time, duration, and multi-drug regimens. We also evaluate the risk of emergent drug resistance in the event of PEP

failure and then discuss how our results can be used to guide public health decisions on optimal PEP strategies.

16:10–16:30

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

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

MINI-SYMPOSIUM 78

Mechanical Models of Movement and Growth of Cells and Tissues I

Wednesday, June 29, 14:30, *Room*: **SP1**

Organizer: **Magdalena Stolarska**

14:30–15:10

Hans G. Othmer
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From Crawlers to Swimmers — Mathematical and Computational Problems in Cell Motility

Cell locomotion is essential for early development, angiogenesis, tissue regeneration, the immune response, and wound healing in multicellular organisms, and plays a very deleterious role in cancer metastasis in humans. Locomotion involves the detection and transduction of extracellular chemical and mechanical signals, integration of the signals into an intracellular signal, and the spatio-temporal control of the intracellular biochemical and mechanical responses that lead to force generation, morphological changes and directed movement. While many single-celled organisms use flagella or cilia to swim, there are two basic modes of movement used by eukaryotic cells that lack such structures – mesenchymal and amoeboid. The former, which can be characterized as 'crawling' in fibroblasts or 'gliding' in keratocytes, involves the extension of finger-like filopodia or pseudopodia and/or broad flat lamellipodia, whose protrusion is driven by actin polymerization at the leading edge. This mode dominates in cells such as fibroblasts when moving on a 2D substrate. In the amoeboid mode, which does not rely on strong adhesion, cells are more rounded and employ shape changes to move – in effect 'jostling through the crowd' or 'swimming'. Here force generation relies more heavily on actin bundles and on the control of myosin contractility. Leukocytes use this mode for movement through the extracellular matrix in the absence of adhesion sites, as does Dictyostelium discoideum when cells sort in the slug. However, recent experiments have shown that numerous cell types display enormous plasticity in locomotion in that they sense the mechanical properties of their environment and adjust the balance between the modes accordingly by altering the balance between parallel signal transduction pathways. Thus pure crawling and pure swimming are the extremes

on a continuum of locomotion strategies, but many cells can sense their environment and use the most efficient strategy in a given context. We will discuss some of the mathematical and computational challenges that this diversity poses.

15:10–15:30

Guido Vitale
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Cellular Traction as an Optimal Control Problem

Force Traction Microscopy is the determination of the stress exerted by a cell on a planar deformable substrate on the basis of pointwise measured displacement. This classical inverse problem in biophysics is typically addressed inverting the displacement field using the Green functions of linear elasticity, under suitable regularizing conditions.

An alternative method formulates an adjoint problem for the direct two-dimensional plain stress operator by minimization of a convenient functional. The resulting coupled systems of elliptic partial dfferential equations (the forward and the adjoint problem) can then be solved by a finite element method. One advantage of such an approach is that can be extended to three dimensional case, including inhomogeneity and anisotropy and even finite displacements of the material.

This work deals with the rigorous statement of the inverse problem Some results of well posedness for the linear case are first given, using standard techniques. The theory is then extended to the less trivial case of pointwise observations with boundary control in 2D and 3D. The model is numerically approximated in 2D and a critical discussion of the results is addressed. Early results of the major biophysical problem of pointiwise observations with boundary control will be shown.

item Ambrosi D. et al. em Traction pattern of tumor cells, J Math Biol (2007) item Ambrosi D. em Cellular traction as an inverse problem, SIAM J Appl Math 66: 2049-2060 (2006) item Lions J.L. em Optimal control of systems, Springer Verlag (1971) item Casas E. em Boundary Control of a Semilinear Elliptic Equation with Pointwise state Constraint, SIAM J. Opt. Contr. (1996)

15:30–15:50

Magdalena A. Stolarska
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A mechanical model of cell motility and cell-subtrate interaction

Mechanical interactions between a cell and the substrate are vital for cell migration and are involved in various cellular processes, such as wound healing, embryonic development, a metastasis of cancerous tumors. In addition, experiments have shown that inter-cellular and cell-substrate mechanical interactions affect signal transduction pathways within the cell. As a result, understanding the nature of force generation by single cells and mechanical interaction of a cell with the substrate is extremely important.

In the talk, I will present a mathematical model of cell motility and cell-substrate interaction where the cell and substrate are modeled as elastic two-dimensional continua. The spatially and temporally dynamics cell-substrate attachments are treated as discrete spring-dashpot systems. A finite element implementation of the model of cell and substrate deformation is coupled to the equations governing the dynamics of the adhesions. The resulting simulations are used to better understand the oscillatory nature of amoeboid cell motility.

15:50–16:10

Katarzyna Rejniak
Moffitt Research Institute
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Forcing the way to metastasis: mechanical interactions between endothelial and circulating tumor cells

Metastasis to distant organs is an ominous feature of most malignant tumors, and it is the major cause of mortality. However, no more than 0.01% of circulating tumor cells is able to withstand all steps of a metastatic cascade, such as an escape from primary tumor mass into the blood stream, circulation with the blood flow and extravasation into the new site that can be subsequently colonized. The process of tumor cells extravasation, i.e., their ability to leave the circulation system under the physiological blood flow is still poorly understood. I will present a biomechanical model of circulating tumor cells and their interactions with endothelial cells forming the vascular wall. This model will be subsequently used to analyze various modes of tumor cell translocation under the blood flow: from circulation to rolling, to crawling, to transmigration.

16:10–16:30

Yangjin Kim
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The role of the microenvironment in tumor invasion: a mathematical model

Glioma cells tend to migrate from the primary tumor into the surrounding tissue. We develop a mathematical model which includes the role of adhesion and mechanical interaction between glioma cells and collagen network. Simulation results show cell migration behavior through the extracellular matrix using information from the complex fibrous structure. We also take into account the intracellular signals at each cell site for this cell migration through the ECM. We consider the detailed mechanical interactions between cells and between a cell and the collagen fibers in addition to reaction-diffusion of molecules.

MINI-SYMPOSIUM 79

Mechanical Models of Movement and Growth of Cells and Tissues II

Wednesday, June 29, 17:00, *Room*: **SP1**

Organizer: **Magdalena Stolarska**

17:00–17:40

Wolfgang Alt
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Mechanical feedback drives cell polarization, adhesion and migration

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

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

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

References.

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17:40–18:00

A model linking the lamellipodial actin cytoskeleton to cell shape and movement.

Dietmar Oelz
RICAM (Radon Institute for Compuational and Applied Mathematics), Vienna/Linz, Austria
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In this talk I will give an overview on a recent modelling effort concerning the lamellipodial Actin-cytoskeleton. In more detail I will outline the mechanical description of protein linkages and compare two different scaling aproaches that apply to either cross-linking proteins or adhesion complexes. The results are macroscopic, possibly nonlinear, friction coefficients. I wil also shortly mention analytic results that concern the interpretation these mathematical models.

18:00–18:20

Marco Scianna
Politecnico di Torino
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Multiscale model of tumor-derived capillary-like network formation

Solid tumors must recruit and form new blood vessels for maintenance, growth and detachments of metastases [**1**]. Vascularization is thus a pivotal switch in cancer malignancy and an accurate analysis of its driving processes is a big issue for the development of pharmacological treatments, giving rise to multiple experimental models. In particular, *tubulogenic* assays have demonstrated that tumor-derived endothelial cells (TECs), cultured in Matrigel (a commercial gelatinous protein mixture acting as basement membrane matrix), are able to autonomously organize in a connected network, which mimics an in vivo capillary plexus [**3**]. Such a process is promoted by the activity of the soluble peptide vascular endothelial growth factor (VEGF, [**2**]) as well as by the induced intracellular calcium signals [**5**]. We here

propose and discuss a multilevel hybrid model which reproduces the main features of the experimental system: it incorporates a continuous model of the microscopic VEGF-induced calcium-dependent regulatory cascades, and a discrete mesoscopic Cellular Potts Model (CPM, [**4**]) describing the phenomenological evolution of the single cells. The two components are unified and interfaced, and produce a multiscale framework characterized by a constant flux of information from finer to coarser levels: in particular, the molecular sub-cellular events realistically regulate the mesoscopic biophysical properties, behaviors and interactions of the simulated TECs. The model results are in good agreement with the analysis performed in published experimental data, allowing to identify the key mechanisms of network formation as well as to characterize its topological properties [**7**]. Moreover, by varying important model parameters, we are able to simulate some pharmacological interventions that are currently in use, confirming their efficiency, and, more interestingly, to propose some new therapeutic approaches, that are counter intuitive but potentially effective [**6**].

References.

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18:20–18:40

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Mechanistic cell-scale modelling of ductal carcinoma in situ (DCIS): impact of biomechanics in comedonecrosis

Ductal carcinoma in situ (DCIS)—a type of breast cancer whose growth is confined to the duct lumen—is a significant precursor to invasive breast carcinoma. The presence of a central necrotic core in one or more affected ducts (comedonecrosis) indicates poorer patient prognosis. Microcalcifications—calcium phosphate deposits that gradually replace necrotic cytoplasmic debris—are critically important to detecting DCIS by mammography. Nonetheless, most models only include necrosis as a simplistic volume loss term, and none have examined necrotic cell calcification.

We present a mechanistic, agent-based model of solid-type DCIS with comedonecrosis and calcification [1]. Each agent has a lattice-free position and phenotypic state. Cells move under the balance of biomechanical forces that are exchanged with other cells and the basement membrane. Each phenotypic state has a "submodel" of changes in cell volume and composition. Necrotic cells swell, lyse, and leak cytoplasmic fluid. Their nuclei degrade (pyknosis), and microcalcifications form in their cytoplasm and deteriorate over long time scales [2]. Phenotypic transitions from the quiescent state are regulated by proteomic- and microenvironment-dependent stochastic processes. The model is fully calibrated to patient data [3].

The model predicts that fast necrotic cell swelling and lysis account for the mechanical separation of the viable rim and necrotic core seen in histopathology—a feature often assumed to be an artifact of tissue preparation. Necrotic cell lysis is a major source of mechanical relaxation, directing proliferative cell flux towards the duct centre, rather than along the duct. Due to this necrotic "flux absorbing" effect, DCIS growth is linear, and growth is slower in larger ducts, with a minimum growth rate of 7.5 mm/year—in excellent agreement with mammography [4]. These results illustrate that well-calibrated, mechanistic cell modelling can provide quantitative insight on the biophysical phenomena that drive cancer progression.

References.

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18:40–19:00

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Jarosław Tyszka

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The particle-based model of foraminiferal morphogenesis

Foraminifera are a large group of single cellular organisms. About 275,000 species are recognized, both living and fossil. They produce shells made of calcium carbonate, agglutinated sediment grains and/or organic compounds. Shells are typically built from several chambers organized in very elaborated way. The question what govern their morphology to produce such great wealth of forms was unanswered for decades. Early suggestions come from D'Arcy Thomson (1919) who recongnised that simple physical forces associated with fluid dynamics are responsible for cell morphogenesis. First theoretical morphospace was defined over 40 year ago by Berger. His model included only simple geometrical operation (rotation, translation) and produced simple spiral form. Subsequent models used a similar approach and were able reproduce only narrow group of forms.

We showed that diversed shell patterns forms can be produced by using a simple optimization process. It is assumed that foraminifera locally optimizes the way of intracellular transport between the chambers. When every new chamber is formed, a new aperture is located at the shortest distance from the previous aperture. This simple formula produced several diversed forms. However, the model works well only for spheroidal chambers, it does not work for other shapes of chambers.

The next stage in research on the formation of foraminiferal shells is to build a low-level emergent model that can be able explained why "local optimization rule" was so accurate. We are searching for a model of processes that occur just before a new chamber is formed. Foraminifera create a "bubble" of cytoplasm attached to the shell which is mineralized preserving its shape. The "bubble" is not only deformed by external factors but mainly by internal organization of the cytoskeleton. We want to reflect this processes in the computer model and present its impact on final shapes of chambers. The cytoplasmic "bubble" is sourrounded by thin membrane made of lipid bilayer.

Lipid bilayer is an example of complex fluid phenomena so we employed the DPD (Dissipative Particle Dynamics) method. In this simulation technique a set of interacting particles is considered and their time evolution is governed by Newton's equation of motion. In our model lipid bilayer is modelled by two types of DPD particles: "A" which reflects hydrophilic heads and "B" for hydrophobic tails. Additional two types of particles denote extracellular fluid (water) and intracellular fluid (cytoplasm). Particles "A" and "B" are arranged into chained amphiphilic molecules by establishing constant "spring" connections. In order to avoid bending in chains of particles we apply force that streighten each triplet of connected "A" and "B" particles. Depending on types of particles that interact in pair we choose different potentials of interaction. In our simulation we study the behaviour of planar membranes affected by external forces.

Acknowldgements This research is supported by the Polish Ministry of Science and Higher Education, project no. 0573/B/P01/2008/34.

References.

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MINI-SYMPOSIUM 80

Mechanics of the cytoskeleton and cortical actin at the cellular level

Saturday, July 2, 08:30, *Room*: **AM1**

Organizers: **Wanda Strychalski, Guillaume Salbreux**

08:30–09:10

Guillaume Salbreux
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Role of the polar actin cortex in cytokinesis

During cytokinesis, the process of physical separation of the cell into two daughter cells, actin filaments accumulate at the cleavage furrow, producing the force for the equatorial constriction. A cortical network is however also present at the membrane of the two cellular poles. The actin network is dynamically polymerized and depolymerized, and myosin molecular motors generate internal stresses in the layer, putting the cortex under tension. Here we show that for a sufficiently large value of the polar cortical tension, the symmetric shape of the dividing cell is theoretically unstable, and oscillations of the volume of the cellular poles are expected to occur for a sufficiently slow actin turnover rate. Such oscillations of dividing cells are experimentally observed and are well described by the theoretical framework we propose.

09:10–09:30

Andrew Harris
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Measuring the mechanical properties of cell monolayers

Cell monolayers are continuously exposed to mechanical stresses in development and normal physiological function. Mutations in cytoskeletal and cell-cell adhesion proteins lead to patient symptoms associated with increased tissue fragility, however a method for characterizing monolayer mechanics is lacking. We have developed

a novel system for tensile testing of monolayers which are suspended between two test rods. One of the rods is rigid acting as a reference whilst the other is flexible to allow for force measurement. Analysis of stress-strain curves during monolayer extension enables the determination of a monolayer in plane elastic modulus. The contribution of different cytoskeletal filaments to monolayer elasticity is ascertained by treatment with inhibitors. By depolymerising the actin cytoskeleton with Latrunculin B a substantial decrease in the elastic modulus can be observed.

09:30–09:50

Jean-François Joanny
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Cortical actin and cell instabilities

Cortical actin and cell instabilities. JF Joanny, J. Prost, G. Salbreux

We present a review of our work on cortical actin and of the instabilities of cells induced by cortical actin. We first show how we can apply our active gel theory to describe the properties of the acti-myosin cortex in a cell. We then discuss the stability of the cortical actin layer. The results are applied to three problems: the formation of belbs to discuss the experimetns of the group of E. Paluch in Dresden where the blebs are induced by photoablation; oscillations of non adhering cells to discuss the experiments of the group of P. Pullarkat in Bangalore; and the formation of contractile rings. In this last case, we discuss both wound healing formation in a xenopus embryo and the formation of a contractile ring during cytokinesis

09:50–10:10

Sundar Naganathan, Justin Bois, Guillaume Salbreux, Stephan W. Grill
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Actin binding proteins govern the range of polarizing cortical flows in *C. elegans* zygotes

Establishment of polarity is essential for conferring different developmental fates to the dividing cells of an embryo. In *Caenorhabditis elegans* one cell embryos, anteroposterior polarization is facilitated by long-ranged flow of the actomyosin cortex. Even though the flowing cortex contains many actin binding proteins (ABPs) that contribute to its structure and dynamics, there are only a limited number of mechanical properties that are important at large length and time scales relevant for polarization, for example contractility and cortical viscosity (Mayer, Bois, Depken,

Jülicher, Grill, 2010). Importantly, this suggests that there is only a reduced spectrum of cortical flow phenotypes that one might expect to obtain by modulating these few mechanical properties through different molecular mechanisms. To bridge the gap between molecular and cellular scales, we here sought to investigate which cell-scale mechanical properties are controlled by which ABPs. We devised a candidate RNAi screen of ABPs and found that several ABPs affect cortical flow. This was achieved by analyzing myosin foci size and density and several flow characteristics, such as peak velocities and spatio-temporal velocity-velocity correlations, for each ABP knockdown. The velocity-velocity correlations provided us with an estimation of the characteristic hydrodynamic length of cortical flow, which describes the extent to which flows are long-ranged. Interestingly, all those ABPs that displayed a detectable cortical flow phenotype did so through affecting this hydrodynamic length. RNAi either resulted in short-ranged flows, indicative of a less viscous cortex, or it resulted in flows that were longer-ranged than wild type, indicative of a cortex that is more viscous that under wild-type conditions. Our results suggest that the characteristic hydrodynamic length is a central physical property subject to precise regulation. They also point towards a type of "mechanical redundancy" in animal development, with many molecular mechanisms affecting the same cell-scale physical property.

10:10–10:30

Wanda Strychalski
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Robert D. Guy
University of California, Davis

Computational explorations of cellular blebbing

Blebbing occurs when the cytoskeleton detaches from the cell membrane, resulting in the pressure-driven flow of cytosol towards the area of detachment and the local expansion of the cell membrane. Recent interest has focused on cells that use blebbing for migrating through three dimensional fibrous matrices. In particular, metastatic cancer cells have been shown to use blebs for motility. A dynamic computational model of the cell is presented that includes mechanics of and the interactions between the intracellular fluid, the cell membrane, the actin cortex, and internal cytoskeleton. The Immersed Boundary Method is modified to account for the relative motion between the cytoskeleton and the fluid. The computational model is used to explore the relative roles in bleb formation time of cytoplasmic viscosity and drag between the cytoskeleton and the cytosol. A regime of values for the drag coefficient and cytoplasmic viscosity values that match bleb formation time scales is presented. The model results are used to predict the Darcy permeability and the volume fraction of the cortex. Applications of the model to blebbing-based cell motility are discussed.

MINI-SYMPOSIUM 81

Moving Organisms: From Individuals to Populations

Wednesday, June 29, 17:00, *Room*: **AM7**

Organizer: **Christina Surulescu**

17:00–17:40

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Cell dispersal: some nonparametric and multiscale aproaches

We provide a short overview of the current approaches to modeling cell motion through various media, thereby focussing on the model scales, ranging from the microscopic, intracellular level through the mesoscale of the joint action of population constituents toward the behavior of the entire population on the macroscopic level.

In this context we propose and analyze a multiscale model for bacterial motility in the framework of partial differential equations. Further we present an alternative approach which relies on stochastic processes accounting for the underlying motion phenotype and uses a nonparametric statistical technique in order to directly assess the macroscpic cell population density from data (if available) or numerical simulations of the cell trajectories. This nonparametric approach allows to handle detailed multiscale models in a complexity which in the context of PDEs is still prohibitive for the numerics.

We will also provide an outlook on the potential of the method for further interesting biomedical problems.

17:40–18:00

Franziska Matthäus[1]
Mario S. Mommer[2]
Marko Jagodič[3]
Tine Curk[4,6]

Jure Dobnikar[5,6]
[1] BIOMS, University of Heidelberg
[2] IWR, University of Heidelberg
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[6] Department of Chemistry, University of Cambridge, UK

Profits from noise: the example of E. coli motion and chemotaxis

E. coli bacteria propel themselves through flagellar rotation. The control of the flagella is given through a rather simple signaling pathway, involving only a very small number of enzymes. Despite its simplicity this signaling pathway regulates a number of complex behaviors like chemotaxis, adaptation, and even Lévy walks. A Lévy walk is a special type of a random walk, characterized by a power-law run length distribution. It has been proven to represent the optimal search strategy to find randomly located and sparse targets. Interestingly, in *E. coli* bacteria the Lévy walk is a result of noisy fluctuations affecting the signaling pathway. We use a model of the signaling pathway given in the form of differential and algebraic equations, augmented by a stochastic term, to study the influence of noise on the concentration dynamics and the behavior of single cells and populations. Based on the model we derive the power-law run length distribution analytically in dependence on and statistical properties of the noise and properties of the signaling pathway. Our expression yields a power-law exponent of -2.2 which coincides with experimental data. We also use the model to simulate chemotactic behavior of large populations in different chemical landscapes. We show that also chemotactic behavior profits from noise, as it increases bacterial motility and behavioral variability.

18:00–18:20

Jan Haskovec
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Radek Erban
OCCAM, University of Oxford

From individual to collective behaviour of coupled velocity jump processes: a locust example

A class of stochastic individual-based models, written in terms of coupled velocity jump processes, is presented and analysed. This modelling approach incorporates recent experimental findings on behaviour of locusts. It exhibits nontrivial dynamics with a phase change behaviour and recovers the observed group directional

switching. Estimates of the expected switching times, in terms of number of individuals and values of the model coefficients, are obtained using the corresponding Fokker-Planck equation. In the limit of large populations, a system of two kinetic equations with nonlocal and nonlinear right hand side is derived and analyzed. The existence of its solutions is proven and the systems long-time behaviour is investigated. Finally, a first step towards the mean field limit of topological interactions is made by studying the effect of shrinking the interaction radius in the individual-based model in the large population limit.

18:20–18:40

Danielle Hilhorst
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Masayasu Mimura
Institute for Advanced Study of Mathematical Sciences, Meiji University, 1-1 Higashi Mita, Tama-ku, Kawasaki, 214-8571 Japan

A nonlinear parabolic-hyperbolic PDE model for contact inhibition of cell-growth

We consider a parabolic-hyperbolic system of nonlinear partial differential equations which describes a simplified model for contact inhibition of growth of two cell populations. In one space dimension it is known that global solutions exist and that they satisfy the segregation property which reflects the inhibition mechanism: if the two populations are initially segregated - in mathematical terms this is translated into disjoint spatial supports of their densities - this property remains valid for all later times. In this talk, we use recent results on transport equations and Lagrangian flows to obtain similar results in the case of arbitrary space dimensions.

18:40–19:00

Jan Kelkel
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Integrin mediated Cell Migration: Multiscale Models, Analysis and Numerics

Invasion is a key property of cancer cells, whereby the contact with the surrounding tissue both enables the cells to move along tissue fibers and stimulates the production of proteolytic enzymes that destroy the tissue network, thus enhancing cell

migration. The product of the tissue degradation is seen as a chemotactic signal influencing the movement direction of the cells.

Existing models for the migration of tumor cells deal with the interactions of the cells with the environment but do not account for biochemical processes in the cell or on its surface. This processes are however very important, since the dynamics of receptors on the cell surface and the cytoskeleton structure are decisive in determining the speed of the cell as well as the secretion of proteolytic enzymes.

We present a model incorporating this subcellular mechanisms in a kinetic equation for cell movement, which is then supplemented by a reaction-diffusion equation for the chemoattractant along with an integro-differential equation for the tissue fibers. We then address the question of existence and uniqueness of solutions for this strongly coupled system of equations.

This strongly coupled and high dimensional model presents a real challenge for the design of a suitable simulation methodology. Selected simulation results illustrate important phenomena that arise in the model.

MINI-SYMPOSIUM 82

Semigroups of Operators in Mathematical Biology I

Wednesday, June 29, 08:30, *Room*: **AM9**

Organizers: **Horst Thieme, Adam Bobrowski**

08:30–08:55

Dariusz Wrzosek
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Do the aggregating cells attain a tight packing state?

We consider models of chemotaxis which take into account volume-filling effects such that an *a priori* threshold for the cell density corresponding to a tight packing state is taken into account (for more information we refer to a survey [2]). Our study concerns quasilinear parabolic systems with singular or degenerate diffusion of cells which include recent models by Wang and Hillen(2007) and Lushnikov (2008). It is proved in [3] that for some range of parameters describing the relation between the diffusive and the taxis part of a cell flux there are global-in-time classical solutions which in some cases are separated from the threshold uniformly in time. Existence and uniqueness of global in time weak solutions as well as the set of stationary states are studied as well. In the recent preprint [1] it is proved for parabolic-elliptic version of the model that if the taxis force is strong enough with respect to self-diffusion and the initial data are chosen properly then there exists a classical solution which reaches the threshold in finite time provided the diffusion of cells is non-degenerate.

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08:55–09:20

Anna Marciniak-Czochra
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Structured population models in metric spaces

Time evolution of a heterogeneous population parametrised by the dynamically regulated properties of individuals can be described by so called structured population models, which are first order hyperbolic equations defined on $\mathbb{R}^+$.

In this talk a new framework for the analysis of measure-valued solutions of the nonlinear structured population model is presented. Existence and Lipschitz dependence of the solutions on the model parameters and initial data are shown using the properties of nonlinear semigroups in suitably chosen metric spaces. The estimates for a corresponding linear model are obtained based on the duality formula for transport equations. The results are discussed in the context of applications to biological data. In particularly, the new framework is applied to describe a process of cell differentiation, which involves discrete and continuous transitions.

The presentation is based on joint works with Piotr Gwiazda (University of Warsaw) and Grzegorz Jamroz (University of Warsaw/University of Heidelberg).

09:20–09:45

Piotr Gwiazda
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Split-up algorithm in the metric space for the equations of structured population dynamics

The talk is based on the joint research with Jose Carillo, Rinaldo Colombo, Anna Marciniak-Czochra and Agnieszka Ulikowska. As the example of the structured population equations we mean the equation of so-called age-structured model (transport equation in a half space with non-local boundary conditions) or size structured model (transport equation with an integral term in space on the right hand side), see for more details B. Perthame "Transport equations in mathematical biology" 2007. From the biological reason there is a need for using initial data in the space of Radon measures. Using the Lipschitz-bounded distance (flat metric) we prove Lipschitz dependence of the solutions to linear and nonlinear system w.r.t. initial data and coefficients of equations. Significant simplifications of the calculations is done by using the split-up algorithm, dealing separately with a semigroup of transport and a semigroup of an integral kernel operator.

09:45–10:10

Robert Service
University of Helsinki, Department of Mathematics and Statistics
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Finite populations conditioned on non-extinction

It is well known that stochastic models of the dynamics of finite populations tend to fall into two categories (when the system is closed): those that allow for unlimited growth of the population with positive probability and those for which extinction of the population in the long run is certain.

In practice one often expects extinction times to be sufficiently long that useful conclusions such as stabilisation of population structure can be drawn from deterministic population models. The talk is about work, old and new, aiming to justify such conclusions rigorously.

10:10–10:30

Horst Thieme
Arizona State University
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Iterative approximation of the spectral radius of a positive operator

In population models with infinite dimensional structure, the basic reproduction number often is the spectral radius of an appropriate positive linear operator on an infinite-dimensional ordered Banach space. This operator is called next generation operator in case a biological interpretation is available. Since a closed expression for its spectral radius can only be obtained in special cases, there is renewed interest in the approximation and estimation of the spectral radius. Quite a few results are available in the operator theory and and computational/numerical literature. It is the purpose of this talk to review some of these and give them a new twist.

MINI-SYMPOSIUM 83

Semigroups of Operators in Mathematical Biology II

Saturday, July 2, 11:00, *Room*: **AM9**

Organizers: **Horst Thieme, Adam Bobrowski**

11:00–11:25

Jozsef Farkas
University of Stirling
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Wentzell semigroups in biology

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

11:25–11:50

, Peter
József Z. Farkas
Department of Computing Science and Mathematics, University of Stirling, Stirling, FK9 4LA, United Kingdom
Peter Hinow
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Structured and unstructured continuous models for *Wolbachia* infections

Wolbachia is a maternally transmitted bacterium that lives in symbiosis with many arthropod species. We introduce and investigate a series of models for an infection of a diplodiploid host species by Wolbachia. The continuous models are characterized by partial vertical transmission, cytoplasmic incompatibility and fitness costs associated with the infection. A particular aspect of interest is competitions between mutually incompatible strains. We further introduce an age-structured model that takes into account different fertility and mortality rates at different stages of the life cycle of the individuals. With only a few parameters, the ordinary differential equation models exhibit already interesting dynamics and can be used to predict criteria under which a strain of bacteria is able to invade a population. Interestingly, but not surprisingly, the age-structured model shows significant differences concerning the existence and stability of equilibrium solutions compared to the unstructured model.

Keywords: *Wolbachia*, endosymbiosis, cytoplasmic incompatibility

11:50–12:15

Mirosław Lachowicz
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Some Markov Jump Processes in Mathematical Biology

The general approach that allows to construct the Markov processes describing various processes in mathematical biology (or in other applied sciences) is presented. The Markov processes are of a jump type and the starting point is the related linear equations. They describe at the micro–scale level the behavior of a large number N of interacting entities (particles, agents, cells, individuals,...). The large entity limit ("$N \to \infty$") is studied and the intermediate level (the meso–scale level) is given in terms of nonlinear kinetic–type equations. Finally the corresponding systems of nonlinear ODEs (or PDEs) at the macroscopic level (in terms of densities of the interacting subpopulations) are obtained. Mathematical relationships between these three possible descriptions are presented and explicit error estimates are given. The general framework is applied to propose the microscopic and mesoscopic models that correspond to well known systems of nonlinear equations in biomathematics.

12:15–12:40

Radosław Bogucki
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Adam Bobrowski
Politechnika Lubelska

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

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

12:40–13:00

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

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

MINI-SYMPOSIUM 84

Epidemiology, Eco-Epidemiology and Evolution

Saturday, July 2, 11:00, *Room*: **AM8**

Organizers: **Ezio Venturino, Nico Stollenwerk**

11:00–11:40

Ezio Venturino, Alessandro Castellazzo, Andrea Mauro, Claudia Volpe
Dipartimento di Matematica "Giuseppe Peano",
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On an age- and stage-dependent epidemic model.

A very general epidemic model will be introduced in which the disease spreads by contact among a population which is age-dependent. A stage structure is introduced in the disease, to describe its progression. The model formulation thus hinges on a system of highly nonlinear hyperbolic partial differential equations. The well-posedness is discussed. Numerical simulations reveal the occurrence of recurrent epidemic outbreaks, under suitable circumstances.

11:40–12:00

Caterina Guiot[1], Ilaria Stura[2], Ezio Venturino[2], Lorenzo Priano[1,3], Alessandro Mauro[1,3]
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[1]Dipartimento di Neurologia e Neuroriabilitazione,
IRCCS Ist. Auxologico Italiano, Piancavallo (VB), Italy.

Multi-scale modelling of human sleep

Sleep is a complex dynamic process, regulated both by "long time" circadian and homeostatic rhythms and the alternance between Rapid Eyes Movement (REM) and non REM (NREM) sleep and by the occurrence of peculiar "short-time" transient Electro Encephalo Graphics (EEG) events, namely Transient Synchronized EEG Patterns (TSEP), which are thought to be expression of synchronous cortical neuron discharges and are supposed to play the main role in the building-up of NREM sleep and flexible adaptation against perturbations. Our study aims at collecting, analyzing and modeling the time series of TSEP related to the achievement, maintenance and interruption of NREM sleep, in physiological conditions.

12:00–12:20

Philip Gerrish
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Genomic mutation rates that cause extinction: general evolutionary predictions

When mutation rates are low, increasing the mutation rate can give rise to an increase in adaptation rate. If mutation rate is increased further, however, a point may be reached at which fitness declines despite continued adaptive and/or compensatory evolution. If fitness decline persists, it intuitively culminates in population extinction. Mathematical formalization of this criterion for extinction gives rise to a simple relation that puts a dynamic upper limit on viable mutation rates. The particular mathematical guise of this relation suggests encompassing generality, which we confirm using individual-based simulations. Additionally, we re-derive the classical "error threshold" formula and show, by proxy, that it is similarly general when used dynamically an attribute not previously recognized. Finally, we demonstrate the utility of the insights gained from these developments with an example application to immunology.

12:20–12:40

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An epidemic model on computer networks

We study failure spread scenarios in computer/communication networks. A general epidemic model of type *Susceptible-Infected-Disabled* is analyzed and takes into account two levels of failure caused by the attack of a virus or a worm for instance. The first level takes place when the failure can be repaired without disconnecting the node, preserving the connections passing through this node. The second failure level involves that the node must be replaced and, consequently, the connections are dropped.

The dynamic process is given by a Markov chain in continuous time according to the transmission and recovery processes. Several results on both types of steady states, disease-free and endemic, are given and an epidemic threshold is stated. Here the network features are summarized by the largest eigenvalue of the weighted adjacency matrix of the network.

On the other hand, a second model is presented according to the heterogeneous mean-field approach. In this case, the network features are given by both the node degree distribution and the conditional probabilities (i.e. the connections of the neighbours of each node).

We have carried out several stochastic simulations using different network topologies (e.g. *scale-free* generated via Barabási-Albert, *random* generated via Erdős-Rényi, *homogeneous*, ...). Finally, a complete-parameter comparison is performed in order to evaluate the theoretical approaches presented.

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12:40–13:00

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Chaos and noise in population biology

In several epidemiological and ecological case studies, the often subtle interplay between typical non-linear structures like co-existing attractors or dynamical saddles attracting in some state space directions and repelling in others and the effect of noise in these case will be investigated. Examples are dengue fever, seasonal influenza and retrospective measles studies as well as from classical predator-prey models. The findings in part come from empirical data analysis, here mainly from epidemiology due to the better data situation than in ecology, and also have impact on parameter estimation in such epidemiological systems.

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MINI-SYMPOSIUM 85

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits I

Wednesday, June 29, 14:30, *Room*: **AM4**

Organizer: **Anja Voss-Boehme**

14:30–15:10

Jenny Bloomfield
Heriot Watt University
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The effect of nonlocal cellular interactions on pattern formation

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

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

15:10–15:30

Richard Gejji[1,2], **Pavel M. Lushnikov**[3] **and Mark Alber**[1]
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Macroscopic model of self-propelled bacteria swarming with regular reversals

Periodic reversals of the direction of motion in systems of self-propelled rod shaped bacteria enable them to effectively resolve traffic jams formed during swarming and maximize their swarming rate. In this paper, a connection is found between a microscopic one dimensional cell-based stochastic model of reversing non-overlapping bacteria and a macroscopic non-linear diffusion equation describing dynamics of the cellular density. Boltzmann-Matano analysis is used to determine the nonlinear diffusion equation corresponding to the specific reversal frequency. Macroscopically (ensemble-vise) averaged stochastic dynamics is shown to be in a very good agreement with the numerical solutions of the nonlinear diffusion equation. Critical density p_0 is obtained such that nonlinear diffusion is strongly suppressed for $p < p_0$. An analytical approximation of the pairwise collision time and semi-analytical fit for the total jam time per reversal period are also obtained. It is shown that cell populations with high reversal frequencies are able to spread out effectively at high densities. If the cells rarely reverse then they are able to spread out at lower densities but are less efficient to spread out at higher densities.

15:30–15:50

Andras Czirok
University of Kansas Medical Ctr
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Vasculogenesis and collective movement of endothelial cells

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

15:50–16:10

Reuben O'Dea
Nottingham Trent University
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Multiscale analysis of pattern formation and wave propagation in a discrete cell signalling model

It is well known that cell-scale interactions can have profound effects on macroscale tissue growth. I will discuss two approaches to analysing such phenomena within a continuum framework, allowing their inclusion within macroscale models of tissue growth.

Firstly, a multiscale asymptotic method with which to analyse fine-grained patterning patterning in cellular differentiation within a continuum framework is introduced, based on a generic discrete signalling model. Most applications of such methods are to continuous systems, while here discreteness on the short lengthscale must be taken into account.

An important feature of such systems is the progression of pattern-forming modulated travelling waves across the discrete lattice. Such phenomena have been widely studied within discrete diffusion equations for monotone waves; employing a WKBJ technique in place of the standard travelling wave ansatz, I show how analysis of such waves is greatly simplified and highlight the crucial dependence of wave propagation on the underlying lattice geometry. In addition, I extend this analysis to the modulated travelling waves exhibited in cell signalling models.

16:10–16:30

Robert Rovetti
Loyola Marymount University
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Periodicity, spatial correlations, and waves in a probabilistic lattice model of the cardiac cell.

Cardiac cells have a surprisingly complex internal architecture, and dynamic instabilities of the calcium signaling within them may lead to ventricular fibrillation, the leading cause of sudden cardiac death. We study a system of locally-coupled stochastically-excitable elements in a 2D automata lattice that replicates physiological features of the cardiac cell, including threshold excitation, refractory period, global periodic forcing signal, and spatial nearest-neighbor interactions. We first derive a simple mean-field difference equation which models the expected excitation rate at each beat, and find conditions under which it can undergo a bifurcation to period-2 behavior (mimicking the pathological condition known as "alternans"). Using a local structure approximation to account for pairwise (and higher-order) correlation, we show these conditions are dependent on the nature of the neighbor-to-neighbor coupling, as well as the geometry of the cell itself. We finally consider the continuous-time case, which allows for cascading spatial interactions, resulting in the formation of excitation waves.

MINI-SYMPOSIUM 86

The dynamics of interacting cell systems: from intercellular interaction to tissue-level traits II

Wednesday, June 29, 17:00, *Room*: **AM4**

Organizer: **Anja Voss-Boehme**

17:00–17:40

Fernando Peruani
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Understanding the spatial organization of bacteria

The spatial self-organization of bacteria can be understood by thinking of bacteria as self-propelled rods that interact by pushing each other. Despite the simplicity of the model, it is possible to show that the combination of these two ingredients, self-propulsion and volume exclusion, is enough to reproduce the phenomena observed in experiments: collective motion, clustering, and aggregation. Interestingly, the combination of self-propulsion and volume exclusion can induced a surprisingly rich variety of self-organized patterns which is not limited to the above mentioned patterns. As a proof of principles, it will be shown that when volume exclusion induces stagnation of cells, a new phenomenology driven by the jamming of cells emerges.

17:40–18:00

Anja Voss-Boehme
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Interacting cell system models for cell sorting and collective motion

Biological structure and function in cell populations often result from the complex interaction of a large number of components. In particular when cells that are in direct physical contact or located close to each other are known to interact, possibly in a type-specific manner, one is interested in concluding characteristics of the global, collective behavior of the cell configurations from the individual properties of the cells and the details of the intercellular interaction. To understand the determinants of these processes and to conclude the tissue level traits, it is necessary to design and analyze appropriate mathematical models.

It is argued that the model class of interacting particle systems is well-suited for this task. For two exemplary problems, cell sorting and collective motion of oriented cells with ferromagnetic alignment, cell based lattice models are developed which describe the major details of the respective intercellular interaction. If suitably simplified, these models are analytically tractable. Several results concerning the long-time behavior and the emergence of structure are presented and interpreted in biological terms. Challenging mathematical problems that require further theoretical developments are identified.

18:00–18:20

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

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

Here we give two examples of experimental situations where a macroscopic mathematical model for the population of cells was derived (in a non-rigorous way) from postulated microscopic interactions. In both cases, the aim is two-fold. Since the models succeed in reproducing the experiments, they can make predictions about more complicated, or even unattainable, experimental conditions. On the

other hand, in a context where the microscopic mechanisms at stake are difficult to investigate directly, the quantitative match of the macroscopic models with the experiments indicate that the underlying microscopic hypotheses may be true.

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

18:20–18:40

Thomas Zerjatke, Nico Scherf, Ingmar Glauche, Ingo Roeder
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Knowing their neighbours - correlation structures in the development of related stem cells

Time lapse video microscopy enables the tracking of stem cell development in bioengineered culture conditions on a single cell level. The resulting cellular genealogies retain information on cellular characteristics, divisional history, and differentiation. Analysing the topology, the dynamical features, and the correlation structure within these pedigree-like genealogies provides information about underlying processes such as migration, cell growth, and differentiation.

For a systematic analysis of cellular genealogies we compare experimental data for different hematopoietic stem cell cultures with a single- cell based, mathematical model of hematopoietic stem cell organisation. In particular we illustrate how ancestral relation between cells influences their current behaviour and decision making. Furthermore we derive emerging contact networks based on spatial positioning of the cells within the time lapse video data. In particular we analyse whether ancestral information is conserved within the community structure of these networks and whether these mutual interactions between cells correlate with secondary read-outs such as cell cycle distribution or the occurrence of cell death events.

The presented framework for a comprehensive description and analysis of cellular development on the level of individual cells and their progeny is an important advancement to support experimental single cell tracking approaches. By combining experimental and modeling data our results demonstrate that the analysis of cellular genealogies and corresponding interaction networks can provide valuable insights into processes of cellular development and differentiation that can not be obtained on a population level.

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18:40–19:00

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Stochastic modelling of cell migration

Cell migration is a central process in normal human tissue development as well as in numerous disease states. Metastatic spread of cancer tumours occurs as a direct result of changes in cell migration, and further insight into the mechanisms behind cell migration is of great importance in cancer research. CMACs (cell-matrix adhesion complexes) are at the heart of the migratory system of the cell; elucidation of CMAC behaviour is essential in understanding cell migration [1] [2]. In this work, quantitative time-series live cell microscopy data are used together with existing knowledge to develop a stochastic model describing the behaviour of the CMAC population of the wild-type cell with respect to CMAC areas and the number of CMACs. New CMACs are born according to a Poisson process and then the subsequent multiplicative growth and decline of CMAC area and final death is described by means of a random walk with a Markov process regime. Analytical results are derived and simulations are performed to validate model performance. It is shown that the model is able to mimic CMAC behaviour with respect to most aspects of the properties described above, and also is able to predict the behaviour of new perturbed experimental conditions.

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MINI-SYMPOSIUM 87

Multi-scale mathematics of the liver: From intracellular signaling to intercellular interaction

Wednesday, June 29, 08:30, *Room*: **AM4**

Organizers: **Anja Voss-Boehme, Andreas Deutsch**

08:30–09:10

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Constructive Algorithms for Modeling Realistic Vascular Structures

The liver is the major metabolic organ in the human body as it fulfills a huge variety of vital metabolic tasks. The most important link between the liver and the rest of the organism is the blood flow through the three vascular systems (hepatic artery, portal vein, hepatic vein). In order to properly model the function of the liver, it is crucial to have an appropriate model of the blood transportation systems.

In vivo 3D CT imaging and subsequent image processing provides the structure of vascular systems with limited resolution far from the scale of individual lobule, sinusoids and liver cells on which the metabolic functions of the liver take place. To bridge this gap in resolution, models for vascular structures can be used. In the talk, we present an extension of the Constrained Constructive Optimization (Schreiner et al.) and the Global Constructive Optimization (Georg et al.) approach for hepatic blood vessels. Based on topological and geometrical analyses of many different human hepatic vascular structures, we evaluate these two algorithms. We introduce parameters and adapt them such that the generated vascular systems geometrically closely resemble natural ones. This resemblance is quantified by a statistical comparison to the geometric properties of real human hepatic vascular structures.

09:10–09:35

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

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

References.

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09:35–10:00

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Modelling Endocytosis - from the Molecules to the Liver Cell

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

Simulation results identify critical regulatory steps that control efficient cargo flux which is essential for liver cells.

References.

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

10:00–10:25

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From hepatocyte polarization to canalicular network formation: a multiscale approach

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

on the polarity and tissue morphology of murine hepatocytes in *in vitro* sandwich cultures.

MINI-SYMPOSIUM 88

Fractals and Complexity I

Wednesday, June 29, 14:30, *Room*: **CP1**

Organizer: **Przemyslaw Waliszewski**

14:30–15:10

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Origins of Allometric Growth: A Contemporary Perspective

The theoretical allometry relation (AR) between the size of an organism Y and that of an organ within the organism X is of the form $X = aY^b$ and has been known for nearly two centuries. The allometry coefficient a and allometry exponent b have been fit by various data sets over that time. In the last century the phenomenological field of allometry has found its way into almost every scientific discipline and the ARs have been reinterpreted with Y still being the size of a host network and X a function of the network. For example, in biology the measure of size is often taken to be the total body mass and the function is the metabolic rate, or heart rate, breathing rate, or longevity of animals. Most theories purporting to explain the origin of ARs focus on establishing the proper value of b entailed by reductionist models, whereas a few others use statistical arguments to emphasize the importance of a.

On the other hand, statistical data analysis indicates that empirical ARs are obtained with the replacements $X \to \langle X \rangle$ and $Y \to \langle Y \rangle$ and the brackets denote an average over an ensemble of realizations of the network and its function. Networks in which these empirical ARs are established include the metabolism of animals, the growth of plants, species abundance in econetworks, the geomorphology of rivers, and many more. The resulting empirical AR can only be derived from the theoretical one by averaging under conditions that are incompatible with real data. Consequently another strategy for finding the origin of ARs is required and for this we turn to the probability calculus and fractional derivatives.

We assume that the statistics of living networks can be described by fractional diffusion equations (FDEs) and hypothesize that FDEs can explain the origin of ARs. We obtain the Fourier-Laplace transform of the general solution to the FDE that contains both historical information and nonlocal influences on the dynamic variables, that is, fractional derivatives in both time and phase space, complexity commonly found in living networks. The scaling properties of the resulting solution to the FDE enable us to interrelate the network's size and function by means of

the mechanism of strong anticipation. The analysis shows that strong anticipation and scaling taken together support the hypothesis and is sufficient to explain the origin of empirical ARs.

15:10–15:30

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Using a mix of cellular automata in tumor margin analysis

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

References.

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15:30–15:50

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Fractality of chromatin

The extension of the fractal concept towards biology and medicine has improved our understanding of functional properties and the dynamics of physiological phenomena in living organisms Fractals are very useful to characterize properly the complexity of tissues by describing relevant underlying design principles [1]. Fractality has evolutionary advantages. Structures with fractal features can be built by simple, iterative programs. Fractal banching is a simple and efficient way for the construction of complex connections resulting in short distances for transport. Fractal foldings of membranes permit to create a large surface area within a very

small volume. Power law organization of physiological systems increase the capacity of adaptation in the case of changes in the environment [1]. Therefore we can expect that fractality can also be found in the organization of the genome and the epigenome. Several investigators showed the presence of self-similarity in DNA sequences. Experimental data support the concept of a fractal organization of chromatin. In intact interphase chicken erythrocytes, spectra obtained by small angle neutron scattering. revealed a constant fractal dimension of the protein component, and a biphasic DNA organization, with a fractal dimension on lower scales and a different one on the larger scales [2]. Fractal structures can be created in polymers by iterative processes for instance by repeated folding during condensation. Thus a polymer can be packed in a small volume without entanglements, facilitating rapid unravelling when necessary. Recent experiments suggest that this process applies also to chromatin leading to a genome organization in form of a spatial segregation of open and closed chromatin with knot-free fractal globule formations[3]. All these studies support the concept of a fractal nature of DNA, nuclear chromatin and the surrounding nucleoplasmic space, i.e. a fractal organization of the nucleus. Morphologists, using light and electron microscopy, are demonstrating indirect evidence for the fractal organization of chromatin for nearly two decades . They differentiate basically two distinct chromatin conformations: the uncondensed euchromatin and the much denser and darker heterochromatin, which is usually considered to be transcriptionally less active. Alterations of the nuclear architecture reflect genomic and non-genomic changes, which are very common in tumor cells. Genomic changes may be point mutations translocations, or amplifications or alterations of the chromosomal position. Furthermore malignant tumors show widespread epigenetic changes including global hypomethylation, as well as focal hypermethylation of multiple CpG island gene regulatory regions. Hypomethylation is associated with decondensing of the chromatin structure and induces chromosomal instability. A more aggressive behaviour is usually observed in genetically unstable neoplasias with an increasing number of genetic or epigenetic changes. Therefore unstable tumors are expected to show a more complex chromatin rearrangement, with a mixture of many chromatin areas with varying density (lighter and darker), equivalent to a higher fractal dimension in the computerized image analysis[1]. Clinico-pathologic studies demonstrated that an increased fractal dimension of chromatin at diagnosis was an independent adverse prognostic factor for survival of patients with different malignant neoplasias, such as multiple myeloma , squamous cell carcinoma of the oral cavity squamous cell carcinoma of the larynx , and malignant melanoma of the skin [4-7]. Therefore we may conclude that the complexity of the chromatin architecture in neoplastic cells may reveal important prognostic information. In summary, fractal characteristics of the nucleus are essential for its function and are reflected in its chromatin structure, which may accompany pathologic processes , such as carcinogenesis and tumor progression.

References.

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15:50–16:10

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Lacunarity analysis and classification of microglia in neuroscience

Fractal analysis in the neurosciences has advanced over the last twenty years to include measures such as lacunarity. Lacunarity assesses heterogeneity or translational and rotational invariance in an image. In general, measures of lacunarity correspond to visual impressions of uniformity, where low lacunarity conventionally implies homogeneity and high lacunarity heterogeneity. It is now necessary to review some of the new permutations of this analysis technique and what it can tell the neuroscientist. This paper outlines methodological considerations associated with three different types of lacunarity analysis applied to the classification of microglial cells.

16:10–16:30

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On dynamics of growth of prostate cancer; Towards the objective fractal system of tumor grading

Cellular growth is the fundamental biological phenomenon. A mathematical model shows that the emergence of simplistic macroscopic dynamics of growth, such as Gompertzian dynamics results from a coupling of a number of events at the microscale level. The coupling is associated with the emergence of at least three features, i.e. fractal structure of space-time, in which growth occurs, conditional probability of events, which eliminates sensitivity to the initial conditions, and a temporal function of entropy. The latter one is dependent on macroscopic dynamics of growth, and determines a capability of the supramolecular system for coding or transfer of biologically relevant information. Indeed, experiments with growth of prostate cancer spheroids suggest that both intra- and intercellular interactions play a significant role in fractal dynamics of growth.

The pattern of growth during tumor angiogenesis changes. Growth in space results in formation of the spatial fractal tissue structures as reflected by the spatial fractal dimension. The spatial fractal dimension for the normal-appearing prostate epithelium was 1.451 (018) (n=18 cases), for the Gleason 3 pattern 1.469 (022) (n = 15 cases), for the Gleason 4 pattern 1.601 (019) (n=18 cases), and for the Gleason 5 pattern 1.769 (011) (n=10 cases). In addition, different areas of the same tumor possessed a similar value of the spatial fractal dimension. With regards to the morphometric cell analysis, the minimal cell radius, aspect ratio, cell roundness and compactness were all statistically different across all Gleason score cases (ANOVA $p<0.05$). Sphericity, solidity shape and circularity were statistically different between cases with Gleason score 3, and those with a score of 4 and 5 (ANOVA $p<0.05$). However, these parameters were not different between cases with a Gleason score of 4 and 5. Based on the cellular morphology parameters, discriminant analysis with leave one out showed that 60% of Gleason score 3 and 4 cases, 63% of Gleason score 4 and 5 cases and 62% of Gleason score 3 and 5 cases could be correctly classified. This dropped to 45% when all the three groups were analyzed.

Tumor growth in time during angiogenesis is not of Gompertzian nature anymore. The long-term temporal evolution of PSA in 50 prostate cancer patients during growth ($b>0$) or decay ($b< 0$) phase describes the exponential function of the algebraic form $p(t) = p0\exp(bt)$ with the coefficient of non-linear regression $R > 0.95$ and the Poisson probability distribution, in which p(t) stands for PSA concentration, p0 is the initial PSA concentration in time t0, b stands for the coefficient, t denotes scalar time. Such evolution suggests a decay of intercellular interactions. Those results define clinically relevant prostate cancer as the first order dynamic system. The novel approach based upon the parameters p0, p' and b can be used to compare objectively dynamics of growth of different prostate cancers or to identify cancer recurrence. The spatial fractal dimension allows the objective and numerical grading of prostate cancer.

MINI-SYMPOSIUM 89

Fractals and Complexity II

Wednesday, June 29, 17:00, *Room*: **CP1**

Organizer: **Przemyslaw Waliszewski**

17:00–17:40

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uate School of Medical and Dental Science, Niigata University, Niigata, Japan

Fractal Geometry in the Assessment of Oral Epithelial Dysplasia Grading System

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

Materials and Methods: Eighty images of haematoxylin and eosin stained dysplasia images (mild (25), moderate (27), severe (28)) were analyzed to extract the epithelial connective tissue interface (ECTI) profiles using different thresholding methods. Box counting, local and local connected fractal geometry techniques were

then applied to assess the complexity of the ECTI profiles. The spatial distribution of a set of dysplasia cell nuclei were also assessed in different dysplasia grades. Statistical analyses to compare the different grades of dysplasia were performed.

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

Conclusion: The initial results of this study agree with our previous findings [4,5] and provides further evidence that the traditional classification of dysplastic changes into three grades might not represent accurately the morphological characteristic of the premalignant change This emphasizes the problems of using methods that have elements of subjectivity. A quantitative classification system is therefore a much preferred options. The use of quantifiable methods such as different measures of fractal geometry might be of use in establishing new, reproducible systems.

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17:40–18:00

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Fractal Dimension of Anal Intraepithelial Neoplasia (AIN)

AIN is a precancerous condition that is interrelated to infections by human papillomaviruses (HPV) and HIV. The histological classification of AIN is getting more and more important, due to increasing HPV infection rates throughout human population. Distinct grades of neoplasia are known, whereas high grades indicate a high risk for a tumor progression. Nevertheless, the grading diagnosis of histological slides is not always clear because of varying subjective conditions. In addition to

subjective diagnoses, quantitative classification methods would be attractive but sophisticated solutions have not quantitatively been developed so far. Therefore, this study intends to evaluate digital images of AIN tissues by incorporating nonlinear morphological analysis. AIN tissues were H&E stained and digitally photographed with a standard microscope. Three distinct grades were diagnosed by a well trained pathologist in order to get a reference. The fractal dimensions of the images grey value landscapes using Fourier transformation were calculated and compared to the subjective diagnoses. Distinct grades of AIN led to distinct and well separated values of the fractal dimension. Higher grades of AIN yielded higher values of the fractal dimension. The conclusion is that fractal geometry is well suited for the diagnosis of AIN. The fractal dimension reflects the roughness of the images grey value distribution and is in accordance with the grading. Therefore, the fractal dimension is a quantitative value that may routinely support subjective diagnoses.

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

18:00–18:20

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Mathematical model of box-counting analysis in the human dentate nucleus during development

Many disorders of the cerebellum may be developmental in origin. In order to recognize impaired development and better to understand the etiology of various neurological disturbances of the cerebellum, a precise timetable of the cellular events that take place during normal development is needed. Therefore, the binary and skeletonized two dimensional neuronal images of Golgi impregnated sections of the human dentate nucleus at various gestational periods were subjected to fractal analysis in order to investigate the morphology of these cells during development. Since the results showed that both parameters increased during gestation, a mathematical model which quantitatively describes changes in morphology of neurons from the human dentate nucleus during development is proposed. While the binary fractal dimension linearly increased with gestational time, the skeletonized fractal dimension increased with time exponentially. The findings of the present study are generally in accordance with previous qualitative data and provide better understanding of the formation of the neuronal circuitry of the human dentate nucleus.

18:20–18:40

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Applying Fractal Dimension in Analysis of Biosignals and of Medical Images

We present applications of fractal analysis of EEG and HRV signals, as well as of medical images, for supporting medical diagnosis and for assessment of influence of chemical and physical agents on living systems. We will show examples of stress assessment, sleep analysis, measuring the depth of anesthesia, classification of tumors based on Higuchis fractal dimension.

18:40–19:00

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Fractal analysis in irregular regions of interest

Fractals have been successfully applied in many areas of science and technology. One of the most prominent applications is fractal analysis in medicine, especially in analyses of different kinds of images. For medical images diagnostically important information often lies in the texture. Fractal dimension may be used as an index of irregularity. In this paper we describe the application of the intensity difference scaling method for assessment of the fractal dimension in the irregular regions of interest (irregular ROI-s). Near boundary between different tissues or structures the values of fractal dimensions changed significantly. The values of fractal dimensions

were calculated on synthetic fractal textures which ranged in fractal dimension from 2.05 to 2.95 (2.05, 2.10, 2.20, 2.30, 2.40, 2.50, 2.60, 2.70, 2.80, 2.90, 2.95). For each value of fractal dimension thirty 64-by-64 images were obtained. The mean squared error (MSE) for the 330 samples for each algorithm was assessed. We tested 7 methods of computing of fractal dimension of surfaces: rectangular prism surface area method (MSE = 0.0054), triangular prism surface area method (MSE = 0.0098), power spectral density method (MSE = 0.0241), method based on mathematical morphology (MSE = 0.0093), variogram analysis (MSE = 0.0054), intensity difference scaling method (MSE = 0.0020), and our adaptation of intensity difference scaling method in irregular ROI-s (MSE = 0,0017). Our experiments for dental radiovisiographic images, pantomograms and nuclear medicine scans showed that it is difficult to fit the entire regular region of interest within the examined organ with simultaneous inclusion of the relevant fragment avoiding the influence of boundaries and other kinds of unnecessary structures at the same time. Our method of assessment of fractal dimension in irregular regions of interest solves these difficulties.

MINI-SYMPOSIUM 90

Mathematical modelling of physiological processes in patients on dialysis

Saturday, July 2, 11:00, *Room*: **CP2**

Organizer: **Jacek Waniewski**

11:00–11:40

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Physiology-based approach to modeling of dialysis

Physiologically based pharmacokinetic models attempt to utilize basic physiological, biochemical, biophysical, and physicochemical information to describe the distribution, disposition, conversion, and elimination of a given substance. More specifically, such models require information about organ volumes, physiological blood flow rates, solute generation rates, enzymatic reactions, as well as information on thermodynamic characteristics such as solubilities, dissociation constants, partition coefficients, diffusivities, and membrane permeabilities. Teorell was among the first to present a physiologically based pharmacokinetic model more than 70 years ago [1].

The distribution volume, the number of compartments, and the exchange of solute between compartments are important components of a kinetic model. Models for hemodialysis are characteristic for assuming a change in compartment volume because of ultrafiltration. On the other hand, rate constants describing the exchange between compartments, the generation and the elimination of solute are generally assumed as constant.

Parameters of physiologically based models have an important meaning. For example, transport within and between compartments is described by convection and diffusion through the cardiovascular system. Two limiting cases of transport may be distinguished: Flow-limited transport for solutes with high diffusivity and membrane permeability such as urea, and diffusion-limited transport for solutes with low membrane permeability such as creatinine. Notice that transport of solutes between organs is determined by convection irrespective of solute diffusivity. The importance of organ perfusion for solute kinetics in hemodialysis was first recognized by Dedrick [2]. Thus, even if diffusion across cell membranes is almost instantaneous for substances such as urea, the equilibration throughout the whole body during the typical post-dialysis urea rebound takes about 30 min because of differences

in regional perfusion [3]. Surprisingly, a similar time course is observed for other solutes such as creatinine which, unlike urea, have much reduced membrane permeability. The kinetics for both urea and creatinine (and possibly other solutes) can be described by a unified model combining flow-limited transport between organs and diffusion-limited transport within organs [4]. The assumption of constant exchange rates between compartments must be questioned when hemodialysis and ultrafiltration-induced changes in blood volume are known to affect cardiovascular control and regional blood flow distribution [5, 6].

Indicator dilution has a long tradition in physiology to model characteristics of solute transport and to identify important model parameters inaccessible to direct measurement [7, 8]. In hemodialysis, the focus of indicator dilution is on measuring blood flows such as access blood flow and cardiac output, and distribution volumes such as central blood volume and lung water [9, 10]. A variant of indicator dilution is the modeling of ultrafiltration-induced changes in blood volume and vascular refilling in the microcirculation for the purpose of understanding fluid balance during hemodialysis [11, 12].

Physiologic models are more complex and require more data that usually cannot be obtained in the single experiment. It is often impossible to analyze various tissues relating to specific compartments, especially in man, and one has to rely on in-vitro or animal data. In addition to data acquisition problems, the models are often composed of complex sets of nonlinear differential equations that must be solved numerically. Also, the expansion of compartments has been criticized as an addition of arbitrary parameters to artificially improve the model fit whereas in reality each additional compartment represents a constraint that can be checked against real data should they become available [13].

Physiologically based kinetic models can be used to identify meaningful physiological parameters inaccessible to direct measurements such as volumes, flows, and permeabilities. Unlike statistical models extrapolation of mechanistic models outside the range of data is possible with some confidence. In hemodialysis this is important when scaling the treatment with regard to treatment duration, treatment frequency, and body size [14, 15].

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11:40–12:00

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Mathematical modeling of peritoneal dialysis

Peritoneal dialysis (PD) is a treatment option for patients with kidney failure that is available in most countries around the world. Its main goal is to remove waste metabolic product and excess water to the fluid infused into the peritoneal cavity that is finally drained out. The increasing usage of PD required special tools that would allow for the estimation of treatment efficiency. In particular, mathematical models allow for the quantitative description of bidirectional water and solute peritoneal transport.

Three types of mathematical models can be used for the modeling of the peritoneal transport: the classical membrane model, the three-pore model, and the distributed model. The first two models (typically applied in clinical and experimental research) use phenomenologically derived parameters that characterize peritoneal transport. However, their relative simplicity does not allow for the derivation of the information on the fundamental physiological processes that govern fluid and solute transport during peritoneal dialysis. Therefore, the distributed approach is used to provide detailed information on the peritoneal physiology and more realistic description of the complexity of the peritoneal anatomy and transport system. This approach is based on the local tissue and microcirculatory physiology and its parameters are derived from the local structure and properties of the tissue and microvasculature.

In order to describe bidirectional fluid and solute transport, the two-phase structure of the interstitium was taken into account, based on the previous experimental findings (Guyton et al, 1969). The two-phase system contains a water-rich, colloid-poor region (Fluid Phase, F), where fluid transport is driven by the hydrostatic pressure, and a colloid-rich, water-poor region (Colloid Phase, C). In general,

Phase C corresponds to the matrix of macromolecules that makes up the interstitial ground substance. The system of nonlinear partial differential equation was solved numerically for the tissue layer of the muscle of 1 cm width with uniformly distributed capillary and lymphatic beds and an interstitial layer (0.015 cm) on the peritoneal surface free from cells and blood vessels using a distributed model. The model parameters were adjusted to provide a description of a typical single exchange with hypertonic glucose 3.86% solution. Diffusive and convective solute transport was analyzed on the example of plasma protein (albumin) and glucose (osmotic agent).

Numerical results of the developed model described the bidirectional water and protein transport in agreement with the data about flows and clearances from clinical studies. Computer simulation suggested that two-phase structure of the tissue allows for the separation of opposite fluid flows: fluid transport from the peritoneal cavity into the tissue (absorption) occurs mainly through the Fluid Phase, whereas the Colloid Phase is used for the water transport in the opposite direction (ultrafiltration). Moreover, the model predicted that glucose transport (mainly diffusive), occurs across both phases. In contrast, the peritoneal transport of albumin, which leaks by convection to the peritoneal cavity, occurs mainly through the Colloid Phase.

12:00–12:20

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New exact solutions of mathematical models describing peritoneal transport

Mathematical description of fluid and solute transport between blood and dialysis fluid in the peritoneal cavity has not been formulated fully yet, in spite of the well known basic physical laws for such transport. Recent mathematical, theoretical and numerical studies introduced new concepts on peritoneal transport and yielded better results for the transport of fluid and osmotic agent [1]–[4]. However, the problem of a combined description of osmotic ultrafiltration to the peritoneal cavity, absorption of osmotic agent from the peritoneal cavity and leak of macromolecules (proteins, e.g., albumin) from blood to the peritoneal cavity has not been addressed yet. Therefore, we present here a new extended model for these phenomena and investigate its mathematical structure. The model is based on

a three-component nonlinear system of two-dimensional partial differential equations with the relevant boundary and initial conditions. In the particular case, this model produces one, which was studied earlier in papers [1]–[3]. The non-constant steady-state solutions of the model obtained are studied. The realistic restrictions on the parameters arising in the model were established with the aim to obtain exact formulae for the non-constant steady-state solutions. As result, the exact formulae for the density of fluid flux from blood to tissue and the volumetric flux across the tissue were constructed, and two linear autonomous ordinary differential equations to find the glucose and albumin concentrations were derived. The analytical results were checked, whether they are applicable for the description of the glucose-albumin transport in peritoneal dialysis.

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12:20–12:40

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Modeling of glucose-insulin system in patients on dialysis

One of the most common causes of end-stage renal disease (ESRD) worldwide is diabetes mellitus. According to the US Renal Data System in 2005 above 44% of new ESRD patients were diabetics. The process of regulation of glucose concentration in blood is complicated and can be substantially affected by uremia and dialysis, which both may have an impact on secretion and clearance of glucose and insulin, and on insulin resistance leading to hypo- or hyperglycemia. Low levels of blood glucose may cause shock and death, while too high levels are toxic. Thus, it is essential that glucose levels must be tightly regulated and an analysis of the effects of dialysis (peritoneal dialysis with glucose-based solution and hemodialysis) on plasma glucose and insulin concentration is of great importance. A mathematical model describing glucose-insulin regulation was based on the models proposed by Stolwijk and Hardy (1974) and Tolic et al (2000). Two different sources of glucose were taken into account: hepatic glucose production and an external source (e.g. food digestion, intravenous glucose infusion or transport between dialysis fluid in the peritoneal cavity and blood). There are three types of glucose utilization: 1) glucose leaves blood to enter most cells through facilitated diffusion (insulin independent glucose utilization), 2) in certain types of cells (e.g. muscle and adipose tissue) insulin helps to stimulate the facilitated diffusion process (insulin dependent glucose utilization), 3) glucose can be also excreted by the kidneys. As regards insulin, two sources are taken into account: pancreatic insulin production controlled by the glucose concentration and external source of insulin (e.g. injection). Insulin is degradated through a reaction involving the insulinase at a rate proportional to insulin concentration in blood. All these assumptions are used in the mass balance equation describing the blood concentration changes of glucose and insulin during dialysis (peritoneal dialysis and hemodialysis). The clinical parameters of the glucose-insulin system, insulin sensitivity index and glucose effectiveness at basal and zero insulin (GEZI) were also estimated using clinical data from: 1) six hour peritoneal dialysis dwells with glucose 3.86% solution performed in 13 stable, fasting, non-diabetic patients, and 2) hemodialysis with a bolus of 33% glucose infused into blood in 8 stable, non-diabetic maintenance hemodialysis patients during their regular dialysis treatment. Computer simulations based on the model were performed for each patient and each dialysis session to estimate the model parameters. The mean values and standard deviations of the parameters were calculated and compared for both studies. There were statistically significant differences between hemodialysis and peritoneal dialysis patients especially in the parameters describing insulin regulation such as the insulin catabolism rate and the maximal level of insulin generation. Clinical and modeling results demonstrated high interpatient variability in glucose and insulin concentration profiles during a peritoneal dwell and during hemodialysis, and in the parameter values of the glucose-insulin system. The proposed model was able to adequately reproduce the clinical data on glucose and insulin transport and plasma levels and to distinguish patients with and without abnormalities in glucose regulation.

12:40–13:00

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Compartmental modeling and adequacy of dialysis

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

MINI-SYMPOSIUM 91

Modelling biofilms: from gene regulation to large-scale structure and function

Wednesday, June 29, 17:00, *Room*: **AM5**

Organizers: **John Ward, Fordyce Davidson**

17:00–17:40

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Cell differentiation in bacterial biofilms

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

One of the most striking examples of bacterial cell differentiation is within a *biofilm*: a multicellular sessile community of bacteria encased within a self-produced polymeric matrix. It is thought that over 90% of bacterial colonies in the natural environment exist in this form. Biofilms are important in all sectors of our economy with examples ranging from human health (e.g. they form the basis of chronic infections) to bioremediation (e.g. they are required for the effective treatment of sewage). The Gram positive bacterium *Bacillus subtilis* is extensively used in an industrial context to produce enzymes for cleaning products and has growing potential as an alternative and environmentally friendly pesticide. It has recently been shown that within biofilms of *B. subtilis*, only a subpopulation of the isogenic cells produce the extracellular matrix which surrounds all of the cells, while a different subset retain their flagella (and therefore remain motile) and a further subset will undergo sporulation. We discuss a regulatory network that may shed some light

on component processes in cell differentiation in *B. subtilis*. In particular we focus on the phosphorylation of the response regulator DegU and its control of cell fate, detailing how a non-unimodal distribution of "on" cells within a population does not necessarily come from a classical bistability in the underlying dynamics of the regulatory network.

17:40–18:00

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Modelling approaches for Quorum sensing in *Pseudomonas putida* and its observation in a biofilm compartment

More and more bacterial species are found to regulate gene expression via extracellular signals called autoinducers. By that mechanism, usually called Quorum sensing (QS), they check for the environmental conditions as population density and diffusion limitation. *Pseudomonas putida*, a rhizosphere bacterium, has one such QS regulation system. Expression of a fluorescence protein (GFP) allows for direct monitoring of induction behaviour on single cell level, but uses as second autoinducer receptor which perturbs the original system to some extent. An ODE model allows to estimate this perturbation and helps to interpret the observed behaviour.
In an experimental approach the dynamics of upregulation was observed under flow and non-flow conditions. A two compartment model was set up and fitted to the experimental data. By that, several hypotheses could be checked, giving a clear hint on a growing layer which is not directly accessible by the flow compartment, probably a biofilm.
A second interesting topic concerns an QS-induced (delayed) production of an autoinducer-degrading enzyme. We introduce a delay differential system, analyse its behaviour and compare it to simpler models. Transferred to a spatial model (as part of a reaction-diffusion equation) it allows to consider the ecological consequences for single bacteria in a biofilm.

18:00–18:20

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Early stages of biofilm formation of Pseudomona syringae on leaves surfaces

Bacterial aggregates observed on leaf surfaces can be compared to biofilms in aquatic and medical environments due to their nutrient heterogeneity, and constantly changing water conditions. Bacteria on leaves surface are found forming aggregates of a wide range of sizes. A localized high level of density of cells may foster genetic and metabolic exchange; furthermore epiphytic survival of bacteria during desiccation is likely enhanced when they are aggregated. Aggregates may also locally facilitate coordinated bacterial population responses for traits expressed in a density-dependent manner through quorum sensing. We developed a stochastic model to describe the frequency, size, and spatial distribution of the gram-negative bacterium Pseudomonas syringae aggregates on bean leaf surfaces. Our model, a logistic birth-death model with migration (time-homogeneous Markov process), is able to elucidate two factors fostering aggregate formation: migration and variability of the leaf surface environment. Our results successfully explain quantitative experimental data available. We discuss how to analyse the joint distribution of the numbers of aggregates of different sizes at a given time and explore how to account for new aggregates being created, that is, the joint distribution of the family size statistics conditional on the total number of aggregates. Through simulations we examine several migration regimes in order to find out how this affects the aggregates size distribution. We discuss the ecological significance of the large aggregates formed on leaves as early stages of biofilm formation. Aggregation formation is thought to be the first step towards pathogenic behaviour of this bacterium; understanding aggregate size distribution would prove useful to understand the switch from epiphytic to pathogenic behaviour.

References.

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18:20–18:40

Niels Chr Overgaard
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A new necessary condition for coexistence of species in equilibrium states of the Wanner-Gujer-Kissel biofilm model

We consider the classical Wanner-Gujer-Kissel 1D-model [1,2] in the case of two bacterial species competing for space and a single limiting substrate in a biofilm of a given fixed thickness. We focus on the model's ability to describe equilibrium states in which the two species coexist. If we let $f(z,t) = (f_1(z,t), f_2(z,t))$, $0 \le z \le L$, $t \ge 0$, denote the volume fractions of the two species and $S(z,t)$ the concentration of the limiting substrate, then the model consistes of the following system of non-linear PDEs:

$$f_t + (vf)_z = A(S)f, \quad f_1(z,t) + f_2(z,t) = 1, \quad v(0,t) = 0, \tag{1}$$

and

$$S_t - DS_{zz} + \lambda^T A(S)f = 0, \quad S_z(0) = 0, \quad S(L) = S^0, \tag{2}$$

along with appropriate initial data. Here $v = v(z,t)$ is a (scalar) velocity field, $A(S) = \mathrm{diag}(a_1(S), a_2(S))$ the growth matrix, and S^0 the bulk concentration of the substrate at the biofilm-water interface $z = L$. Moreover, D denotes diffusivity and λ is a vector containing reciprocal yield coefficients. More about mathematical biofilm modelling can be found in a recent overview by Klapper and Dockery [3]

In this work we derive a new necessary condition, in the form of an inequality, for the existence of coexistence equilibrium states to the model (1) and (2). This condition is used in numerical experiments to locate model parameters which exibit coexistence states, something which would be difficult otherwise. The equilibrium is computed using a robust numerical method developed by the author and presented at the ECMTB 2008 in Edinburgh. It is hoped that our necessary condition could be a stepping stone in the search for a mathematically rigorous proof of the existence of coexcistence equilibrium states for biofilm models of this class.

A motivation for this work is a recent article by Klapper and Szomolay [4], where an exclusion principle for ruling out occurence of certain coexistence equilibrium states is presented. While this principle is correct, it is exemplified with a biofilm system, of the kind studied here, for which the authors seem to imply that a coexistence equilibrium may occur only for one special value of the applied substrate bulk concentration S^0. Our investigations indicate that the situation is far more favorable, and that coexistence equilibria actually exists for a whole range of values of S^0, and that for each such value, the system is actually attracted to a coexistence equilibrium state.

References.

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18:40–19:00

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

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

MINI-SYMPOSIUM 92

Mathematical modeling and simulations of angiogenesis I

Wednesday, June 29, 08:30, *Room*: **UA3**

Organizers: **Xiaoming Zheng, Trachette Jackson, Roeland Merks**

08:30–09:10

Rafał Wcisło
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Complex Cellular Automata based on particle dynamics as a framework for modeling solid tumor growth and angiogenesis

To simulate the growth dynamics of tumor in both its avascular and angiogenic phases we propose a novel computational paradigm based on, so called, complex automata approach (CxA). It combines the cellular automata modeling (CA) with off-grid particle dynamics coupled by continuum reaction-diffusion equations. The particles represent both tissue cells and fragments of vascular network. They interact with their closest neighbors via semi-harmonic central forces simulating mechanical resistance of the cell walls. The particle dynamics is governed by both the Newtonian laws of motion and the cellular automata rules. The rules represent cell life-cycle stimulated by various biological processes such as carcinogenesis and diffusion-reaction processes involving nutrients and tumor angiogenic factors. We discuss the main advantage of CxA model such as its ability of simulating mechanical interactions of tumor with the rest of the tissue. We show that our model can reproduce realistic 3-D dynamics of the entire system consisting of the tumor, normal tissue cells, blood vessels and blood flow. We conclude that the CxA paradigm can serve as an efficient and elegant general framework of more advanced multiple-scale models of tumor coupling microscopic in-cell processes with its macroscopic evolution. Finally, we discuss the main requirements and design components of an interactive visualization engine based on CxA paradigm. Such the system can be used as a valuable tool for educational purposes and, in the nearest future, for in silico experiments, which can play the role of angiogenesis assays in planning cancer treatment.

09:10–09:30

Amina Qutub
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Characterizing Endothelial Cell Behavior and Adaptation During Brain Capillary Regeneration by Rule Oriented Modeling

Cell-cell communication defines how blood vessels regenerate through a process called angiogenesis. Growth factors like vascular endothelial growth factor (VEGF) and brain-derived growth factor (BDNF) guide angiogenic sprouting in the brain, in conditions of hypoxia, such as during a stroke or in brain cancer. Here, we present a computational strategy to characterize the sequence and magnitude of cell-cell interactions, allowing us to quantify how each endothelial cell behavior inhibits or augments each other. We introduce a novel rule-oriented agent-based programming method to allow rapid testing and comparison of multiple hypotheses in silico to in vitro angiogenic experiments. Results show the interaction of tip and stalk endothelial cells, and predict how migration, proliferation, branching, elongation and quiescence states inhibit or enhance one another to form capillary structures within an in vitro 3D matrix, leading to distinct capillary phenotypes in the presence of VEGF and BDNF. This quantitative understanding of how cells move as a function of molecular stimuli, and form vessels, will be used to help guide small molecule drugs and tissue engineering therapies targeting the brain microvasculature.

09:30–09:50

Heiko Rieger, Michael Welter
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Blood vessel network remodeling during tumor growth

With the help of a theoretical model the process in which a growing tumor transforms a hierarchically organized arterio-venous blood vessel network into a tumor specific vasculature is analyzed. The determinants of this remodeling process involve the morphological and hydrodynamic properties of the initial network, generation of new vessels (sprouting angiogenesis), vessel dilation (circumferential growth), blood flow correlated vessel regression, tumor cell proliferation and death, and the interdependence of these processes via spatio-temporal changes of blood flow parameters, oxygen / nutrient supply and growth factor concentration fields. The emerging tumor vasculature is non-hierarchical and compartmentalized into different zones. It displays a complex geometry with necrotic zones and "hot spots" of increased vascular density and blood flow of varying size. The origin of

these hot spots is discussed. The blood vessel network transports drug injections efficiently, but the computation of the interstitial fluid flow shows that most of the drug is quickly washed out from the tumor after extravasation.

09:50–10:10

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Petros Koumoutsakos
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Image Driven Computational models of Cell migration

Cell migration has been identified as one of the fundamental mechanisms driving embryogenesis, organ development, angiogenesis and tumor invasion. We develop computational models of cell migration and tissue infiltration to assist related experimental studies. Continuum models are developed to capture migration of cell agglomerates at the tissue level resolution and a discrete particle model enables for the exploration of cell migration on a cellular scale.

The models are validated against a set of in-vitro and in-vivo model systems. In order to facilitate the validation process, we develop a set of computational tools that allow for the extraction of relevant statistical metrics on biological experiments. Curvelet based image reconstruction is used for vessel network and cell membrane segmentation and Particle Image Velocimetry (PIV) on in-vitro experiments to register mass transport in migrating cell layers. We combine these methods and present a robust algorithm for in-vitro cell shape tracking of multiple cells.

References.

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[2] P. Koumoutsakos, B. Bayati, F. Milde, G. Tauriello, *Particle Simulations of Morphogenesis* Math Model Meth Appl Sci. *accepted.*

10:10–10:30

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Parameter sensitivity investigation of a mathematical model of glioma angiogenesis via Latin hypercube sampling.

Malignant glioblastoma multiforme (GBM) is a relatively rare cancer with a very poor prognosis. It is unique among cancers in that the tumors are quite diffuse and infiltrative, but do not metastasize out of the CNS. This diffuse nature, as well as its location in the brain, presents many challenges for treatment and disease monitoring. Following the development of anti-angiogenic agents in the past few years, there has been much hope that this form of treatment might make great strides in the treatment and management of malignant glioma, but clinical response to date has been disappointing. Patients often show a strong initial response on MRI, with imageable tumor receding relatively soon following treatment initiation. However, after some time they all progress, often with more diffuse, wide-spread disease than prior to anti-angiogenic treatment. To better understand the role of angiogenesis and anti-angiogenic therapy in GBM patients, we have created a proliferation-invasion-hypoxia-necrosis-angiogenesis (PIHNA) mathematical model of glioma growth with angiogenesis and have adapted it to simulate anti-angiogenic therapy. Based on our clinically validated, extensive work with the proliferation-invasion (PI) model of glioma growth (1, 2, 3) this model was developed to simulate the effects of hypoxia on vascular recruitment in glioma. It has been correlated with FMISO PET imaging data (4), and provides a basis from which we can better understand the effects of anti-angiogenic treatment on vascular recruitment, as well as the tumor environment. Here we present our use of a sensitivity analysis technique incorporating latin hypercube sampling (LHS) to vary parameters against each other and determine which parameters in the model have the most significant influence on hypoxic burden and how treatment parameters fit in. This knowledge allows us to better assess the significance of anti-angiogenic therapies on tumor growth patterns and give insight into the relationships between these factors and the tumor microenvironment to enhance combat and control of the disease.

References.

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MINI-SYMPOSIUM 93

Mathematical modeling and simulations of angiogenesis II

Wednesday, June 29, 11:00, *Room*: **UA3**

Organizers: **Xiaoming Zheng, Trachette Jackson, Roeland Merks**

11:00–11:30

Roeland M. H. Merks
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Cell-based modeling of angiogenic blood vessel sprouting: cell-ECM interaction and tip-cell selection

Angiogenesis is a topic of intensive experimental investigation so its phenomenology and the molecular signals contributing to it have been well characterized. Yet it is poorly understood how the biological components fit together dynamically to drive the outgrowth of blood vessels. Cell-based simulation models of angiogenesis describe endothelial cell behaviour in detail, help analyze how cells assemble into blood vessels, and reveal how cell behaviour depends on the microenvironment the cells themselves produce. Our previous simulation models, based on the Cellular Potts model, have shown that the elongated shape of endothelial cells is key to correct spatiotemporal in silico replication of vascular network growth [**1**]. We also identified a new stochastic mechanism for angiogenic sprouting [**2**]. Here I will briefly discuss new insights into the role of cell shape and stochastic motility during vascular branching. Then I will present recent results on the role of tip cells, suggesting that tip cell-stalk cell interactions accelerate angiogenic sprouting. I will also discuss our recent cell-based modeling studies of cell-extracellular matrix interactions during angiogenesis.

References.

[1] Merks, R.M.H., Brodsky, S.V., Goligorsky, M.S., Glazier J.A. *Cell elongation is key to in silico replication of in vitro vasculogenesis and subsequent remodeling.* Developmental Biology **289** 44–54, 2006.

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11:30–12:00

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

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

12:00–12:30

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Using mathematical modeling to assess the efficacy of oxygen for problem wounds: use of hyperbaric or topical oxygen therapies

We extend a previously developed mathematical model [1] for acute wound healing to investigate the application of hyperbaric and topical oxygen therapies to treat acute, delayed, and chronic wounds. In this talk, I will present the model, a sensitivity analysis of the model, and simulation results for treating the wound with hyperbaric and topical oxygen therapies.

References.

[1] R.C. Schugart, A. Friedman, R. Zhao, C.K. Sen, *Wound angiogenesis as a function of tissue oxygen tension: a mathematical model* PNAS USA **105** 2628–33.

12:30–13:00

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A model for anti-angiogenic therapy

Since the proposal by J. Folkman in the 70's to use tumoral neo-angiogenesis as a therapeutic target, important efforts lead to the development of various anti-angiogenic drugs now used in the clinic. Though, the practical results obtained by these so-called "targeted therapies" are quite poor up to now and anti-angiogenic drugs are far from replacing the classical, very toxic, chemotherapies. In some cases, angiogenic drugs can even exhibit paroxystic effects such as metastatic acceleration [**3**]. It seems that the way of administering the drug, its *scheduling* is of fundamental importance and determining the best schedules for anti-angiogenic drugs alone or in combination with cytotoxic drugs is a clinical open question.

In order to give insights on these questions, we developed the model of [**2**] and included a module to incorporate the metastases [**1**]. We will present interesting simulations studying and optimizing efficient temporal administration protocols, and describing the paradoxal effect observed in [**3**].

In particular, we can give answers in an emerging area of clinical oncology named metronomic chemotherapy (or anti-angiogenic therapy) [**4**]. It consists in delivering the chemotherapy at doses below the maximum tolerated doses, with a frequent schedule and is based on the assumption that such a schedule would have an anti-angiogenic effect.

References.

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MINI-SYMPOSIUM 94

Systems Biology of Development

Saturday, July 2, 14:30, *Room*: **AM1**

Organizers: **Walter de Back, Lutz Brusch, Andreas Deutsch**

14:30–14:55

Johannes Jaeger
EMBL/CRG Research Unit in Systems Biology, Centre de Regulació Genòmica (CRG), Barcelona, Spain
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Reverse-Engineering the Evolutionary and Developmental Dynamics of the Gap Gene Network

Evolutionary developmental biology tries to close the gap between molecular evolution and phenotypic change. This requires a quantitative systems-level understanding of the gene networks underlying development across multiple levels from the molecular to the organismic. Obtaining such an understanding is challenging due to the large number of factors involved. We depend on computational models for this task. I present a reverse-engineering approach, where gene regulatory interactions are inferred from quantitative expression data, using data-driven mathematical models (called gene circuits). Gene circuit models of the gap gene network of Drosophila reproduce observed gene expression with high precision and temporal resolution and reveal a dynamic mechanism for the control of positional information through shifts of gap gene expression domains. We are extending this approach to a comparative study of the gap gene network between different species of dipterans (flies, midges and mosquitoes). I present preliminary results on data quantification and modeling for gap genes in the scuttle fly Megaselia abdita, and the moth midge Clogmia albipunctata. Our approach yields predictions of how changes of gene regulatory feedback affect the timing and positioning of expression domains. These predictions will be tested experimentally using RNA interference in all three species. No such quantitative systems-level analysis of an evolving gene regulatory network has been achieved to date.

14:55–15:20

Margriet M. Palm

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Cell elongation and cell adhesion suffice for vascular network formation

The formation of blood vessels is crucial in many biological processes including embryonic development, wound healing and cancer. Vascular networks form by migration of endothelial cells and their interaction with the ECM. A multitude of computational models explain vascular network formation by means of chemotaxis driven aggregation. However, experiments suggest that vascular networks may form also without secreted chemoattractants [1].

Previously, we have highlighted cell length as a key property for vascular-like network formation [2]: a cell-based, Cellular Potts model indicated that chemotaxis and cell elongation, together, suffice for forming stable, regular networks. We have now analyzed the dynamics of this model in absence of chemotaxis, and find that cell elongation and cell adhesion alone suffice for forming network-like structures.

The deformability of cells and their adhesion to the ECM turn out to be key to network formation. Flexible, adherent cells form blobs with individual cells packed closely together. More rigid, elongated cells cannot assume their ideal shape inside a blob, making network-like structures the preferred configuration. Without chemotaxis, network-like patterns form in a narrow region of parameter space; chemotaxis dramatically widens this region and sharpens the phase transitions between blobs and networks. Concluding, vascular network formation does not necessarily require chemotaxis or similar, midrange attractive forces between cells, although such forces make network-like patterning more robust.

References.

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[2] Roeland M.H. Merks *et al*, *Cell elongation is key to in silico replication of in vitro vasculogenesis and subsequent remodeling* Dev Biol 2006

15:20–15:45

Julio Belmonte
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Susan D. Hester
J. Scott Gens

Sherry Clendenon
James A. Glazier
Biocomplexity Institute, Indiana University, USA

Multi-cell, Multi-scale Models of Vertebrate Somitogenesis

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

15:45–16:10

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Paracrine vs Autocrine Regulation of Early Vascular Patterning

During embryonic vasculogenesis, the earliest mechanism of blood vessel morphogenesis, isolated vascular cell progenitors called angioblasts assemble into a characteristic network-like pattern. So far, however, the mechanisms underlying the coalescence and patterning of angioblasts remain unclear.

We consider a hybrid cell-based approach similar to that used for a similar *in vitro* process [1,2]. However, contrary to previous mathematical models that assume chemotaxis towards an autocrine signal [1,2,3,4], we favour an alternative mechanism based on matrix-binding of paracrine signals. Detailed morphometric analysis of simulated vascular networks and confocal microscopy images obtained from *in vivo* quail embryos reveals our model can reproduce the vascular patterns with high accuracy.

The work to be reported has been made in collaboration with W. de Back, J. Starruß and A. Deutsch (Center for High Performance Computing, Technische Universität Dresden), M. A. Herrero (Department of Applied Mathematics and IMI, Universidad Complutense de Madrid) and A. Mattiotti and J. M. Pérez-Pomares (Laboratory of Cardiovascular Development and Angiogenesis, Universidad de Málaga).

References.

[1] Merks RMH, Brodsky SV, Goligorksy MS, Newman SA and Glazier JA (2006) , *Cell elongation is key to in silico replication of in vitro vasculogenesis and subsequent remodeling*, Dev Biol **289**: 44-54.

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16:10–16:30

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The role of Wnt3 in early Hydra head regeneration

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

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

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

References.

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Index of authors