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Book of Abstracts

Coupling in-host and between-hosts dynamics of infectious diseases

Maria V. Barbarossa

Institute of Applied Mathematics, Heidelberg University
barbarossa@uni-heidelberg.de

After a disease outbreak, recovered individuals constitute a large immune population, however their immunity is waning in the long term and they may become susceptible again. At the same time, the host's immune system can be boosted by repeated exposure to the pathogen, which is linked to the density of infected individuals present in the population. This prolongs the length of the host's immunity. Such an interplay of within host and population level dynamics poses significant challenges in rigorous mathematical modeling of immuno-epidemiology. In this talk we present a multiscale modeling approach for disease dynamics, monitoring the immune status of individuals and including both waning immunity and immune system boosting. A coupled system of ordinary and partial differential equations allows to investigate the temporal evolution of the distribution of immunities in a population, showing that different immune boosting mechanisms lead to very different stationary distributions of the immunity at the endemic steady state. Special cases of the general model will be considered, in particular a class of systems with constant and distributed delays.

Non-local cell adhesion models: Bifurcations, and boundary conditions

Andreas Buttenschön
Department of Mathematics, UBC
abuttens@math.ubc.ca

Cells interact with one another using adhesion proteins determining tissue fates, and outcomes of normal development, and cancer metastasis. Continuum models (PDEs) of tissues based on purely local interactions ignore important nonlocal effects, such as long-ranged adhesion forces. A mathematical description of cell adhesion had remained a challenge, until the introduction of an integro-partial differential equation (iPDE) model. Since then this approach has proven popular though many mathematical properties of these models are not yet well understood.I will focus on the analysis of steady-states and the formulation of no-flux boundary conditions for the non-local adhesion model. Combining global bifurcation results, equivariant bifurcation theory, and the mathematical properties of the non-local term, we obtain a global bifurcation result for the branches of non-trivial solutions. The significance of the steady-states is that they are observed in biological experiments (e.g. cell-sorting). I will construct various types of adhesive, repulsive, and no-flux boundary conditions for non-local adhesion models. In numerical simulations we consider adhesive, repulsive, and neutral boundary conditions, and show that the solutions mimic known behaviour of fluid adhesion to boundaries. At the end of the talk, I will discuss possible extensions of our work.

Joint work: Thomas Hillen.

Multiscale hybrid modeling and simulation of cancer growth within a 3D heterogeneous tissue

Alfonso Caiazzo
WIAS Berlin
caiazzo@wias-berlin.de

The goal of this talk is to present a hybrid approach for the modeling of cancer growth, obtained combining so-called continuous models (described by PDEs) and individual- or agent-based model. The individual-based approach is used to simulate the behavior of single cells, as well as to efficiently handle the presence of fibers and vascular structures within the tissue. The continuous model is used to describe the diffusion of nutrient (oxygen) from the vasculature within the tissue, and it is solved via a finite element method on a tetrahedral mesh. Each agent (a cell, a fiber, or a vessel) is fully realized within the model and interactions with other agent are primarily governed by mechanical (adhesion-repulsion) forces. Moreover, cancer cells react to the local oxygen concentration, which influences their biological behavior. We present preliminary results of the computational model, showing that it allows to efficiently simulate tumor growth around arbitrary vasculature structures, as well as interaction with the structure of the fibrous tissue.

Chemo-mechanical modeling of collective migration of neural crest cells

James J. Feng
Mathematics and Chemical and Biological Engineering, UBC
james.feng@ubc.ca

The collective migration of neural crest cells is central to early embryonic development of vertebrates. In vitro experiments have revealed two peculiar features. One is "spontaneous persistent migration" of a cluster in a largely 1D channel in the absence of a chemical gradient, where a single cell would have executed a random walk. The other is "group advantage": in a chemokine gradient too shallow to induce a single cell to chemotax, a cluster of cells can demonstrate robust chemotaxis up the gradient.

In this talk, I will describe a model that explains these behaviors from the biochemical interactions between Rac/Rho proteins. Through contact inhibition and co-attraction, the cells modulate each other's Rac1 and RhoA dynamics on their membranes and achieve a common polarity. This affords a group of cells much stronger persistence in their migration against ambient noise than for a single cell. Thus, an initial bias in the geometric setup can induce spontaneous collective migration that lasts for hours, and a cluster can respond robustly to a shallow gradient in a 2D space where a single cell cannot.

Joint work with Brian H. Merchant and Leah Keshet-Edelstein.

Mathematical modeling of the immune-mediated theory of metastasis

Thomas Hillen
Department of Mathematical and Statistical Science, University of Alberta
thillen@ualberta.ca

Accumulating experimental and clinical evidence suggests that the immune response to cancer is not exclusively anti-tumor. In fact, several pro-tumor effects of the immune system have been identified, such as production of growth factors, establishment of angiogenesis, inhibition of immune response, initiation of cell movement and metastasis, and establishment of metastatic niches.

Based on experimental data, we develop a mathematical model for the immune-mediated theory of metastasis, which includes anti- and pro-tumor effects of the immune system. The immune-mediated theory of metastasis can explain dormancy of metastasis and metastatic blow-up after resection of the primary tumor. It can explain increased metastasis at sites of injury, and the relatively poor performance of Immunotherapies, due to pro-tumor effects of the immune system. Our results suggest that further work is warranted to fully elucidate and control the pro-tumor effects of the immune system in metastatic cancer. (with Adam Rhodes)

Dare mathematics in medicine - mathematical modelling and simulation help to understand, diagnose and treat sepsis

Willi Jäger

Interdisciplinary Center for Scientific Computing (IWR)
Center for Modeling and Simulation in the Life Sciences (BIOMS), Heidelberg University
wjaeger@iwr.uni-heidelberg.de

Sepsis is a disease that can lead to the life-threatening collapse of the entire organ system. In Germany alone, about 279.000 people developed sepsis in 2013, and nearly one in four patients died. According to experts, many of these deaths would be avoidable. if it is possible to detect the diseases earlier, to better understand the possible causes and processes of sepsis, and to develop methods of prevention and therapy. Scientists in intensive care at the University Hospital Mannheim and the Interdisciplinary Center for Scientific Computing have been working for three years on the project Scientific Computing for the Improved Diagnosis and Therapy of Sepsis (SCIDATOS). Their goal is to contribute with quantitative concepts and methods to overcome the challenges of sepsis as a disease of the whole system. This requires

- mathematical modelling and simulation of the essential biophysical, biochemical and physiological processes, ranging from the cellular level to the system of the organs,
- to capture and analyze the required experimental and clinical data,
- to develop and deliver tools for efficient diagnosis and treatment proposals with the results obtained in the investigation.

This lecture gives a short survey on the mathematical modelling and simulation part and aims to stir discussions on analytical and numerical problems arising in the project.

Funding by the Klaus Tschira Foundation made it possible to start this interdisciplinary research and to achieve first important results. An application for its prolongation for another 3 years was approved just now.

Pattern formation in biological tissues - mechanisms, experiments and models

Moritz Mercker
Institute of Applied Mathematics, Heidelberg University
mmercker@gmx.de

Pattern formation is fundamental during embryogenesis and tissue development. Yet, the underlying molecular and cellular mechanisms are still elusive in many cases. Most current theories assume that tissue development is mainly driven by chemical processes: either as a sequence of chemical patterns each depending on the previous one, or by patterns spontaneously arising from specific chemical interactions (such as Turing-patterns). However, there is increasing evidence that other types of mechanisms are actively involved in patterning as well, such as tissue mechanics, cell-sorting, or bio-electrical processes. Firstly, we give a brief overview with respect to different mechanisms and models leading to self-organized pattern formation in tissues. Secondly, we focus on mechano-chemical patterning processes. Especially, we show that various interactions between chemical and mechanical processes in biological tissues spontaneously lead to robust and complex mechanochemical patterns. Joint work: Anna Marciniak-Czochra

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Advances in model order reduction for large scale or multi-scale problems

Mario Ohlberger
University of Münster
mario.ohlberger@uni-muenster.de

Model order reduction for parameterized systems has gained a lot of attention in recent years. Classical approaches such as the Reduced Basis Method, Balanced Truncation or Proper Generalized Decomposition are meanwhile well established for parameterized PDEs with a fast decay of the Kolmogorov width of the solution manifold. However, challenges still exist for problems with either a slow decay of the Kolmogorov width or for large scale or multi-scale problems, where the enormous computational and storage requirements of model reduction methods in the so called offline-phase are still prohibitive. Localization, with respect to both, parameter and space provide a path to solution for such problems in combining ideas from numerical multiscale methods, domain decomposition and model order reduction.

In this contribution we will discuss several applications from the life sciences and engineering that pose specific challenges with respect to an efficient numerical treatment. We will discuss suitable model order reduction methods with an emphasize on recent advances for localized model order reduction.

Spatio-temporal pattern formation in coupled bulk-surface reaction-diffusion systems

Frederic Paquin-Lefebvre

Department of Mathematics, UBC
paquin-lefebvre@math.ubc.ca

We discuss a class of systems for which passive diffusion in a bounded bulk domain is coupled to a nonlinear reaction-diffusion process on the boundary. Such a modeling paradigm has been employed to study various biological phenomena including intracellular pattern formation and cell polarization, as well as diffusion and quorum sensing within populations of diffusively coupled oscillators. We first consider the spatio-temporal patterns in a 2-D coupled bulk-membrane reaction-diffusion system with circular bulk geometry. We then briefly investigate the patterns of synchronization for two oscillators coupled via a 1-D bulk diffusion field. For each case, a multiple-time scale asymptotic analysis is employed to derive amplitude equations characterizing the local branching behavior of solutions near a variety of codimension-one (Hopf or pitchfork) and codimension-two bifurcation points. The key novel features of such weakly nonlinear analyses are the systematic treatment of arbitrary nonlinearities restricted to the boundaries, the bifurcation parameters arising in the boundary conditions, and the underlying spectral problem where both the differential operator and the boundary conditions involve the eigenvalue parameter.

Pattern selection in advective reaction-diffusion models of dryland vegetation

Eric Siero

Insitute of Mathematics, Oldenburg University
eric.siero@uni-oldenburg.de

Spatial vegetation patterns with different morphologies (gaps, stripes/labyrinths, spots) have been observed in many drylands worldwide. These patterns are thought to be caused by a water flux from bare to vegetated areas. Reaction(-advection)-diffusion models can help explain why these spatial patterns form. But how does the pattern morphology depend on the choice of model? And what does this imply for real ecosystems?

Understanding blood cancer dynamics using mathematical models

Thomas Stiehl
Institute of Applied Mathematics, Heidelberg University
thomas.stiehl@iwr.uni-heidelberg.de

Acute leukemias are cancerous diseases of the blood forming (hematopoietic) system. They are derived from a small population of leukemic stem cells (LSC) that out-compete hematopoietic stem cells (HSC) which are required for blood cell formation. Experiments suggest that differences in the interaction between healthy and malignant cells contribute to the observed inter-patient heterogeneity. These interactions include leukemic cell response to long-range feedbacks, e.g., hematopoietic growth factors and competition of stem cells for spaces in a supportive stem cell niche. We use a combination of analytical results, computer simulations and patient data analysis to provide insights into the following clinically relevant questions: (1) Do leukemic cells require growth factors to expand or do they grow indpendently of regulatory signals? Does this make a difference for the disease evolution? (3) How does HSC-LSC competition inside the stem cell niche affect diseasse dynamics? (4) How can we use mathematical models to assess patient prognosis?

Joint work: Anna Marciniak-Czochra, Anthony D. Ho, Wenwen Wang and Christoph Lutz.

Constructing mechanochemical patterns using geometric singular perturbation theory

Frits Veerman
Institute of Applied Mathematics, Heidelberg University
veerman@math.uni-heidelberg.de

Mechanochemical models present a new paradigm for biological pattern formation, where the interaction between domain curvature and pattern shape replaces the activator-inhibitor mechanism. Numerical simulations of a mechanochemical model formulated by Mercker&Marciniak-Czochra reveal a wide spectrum of novel patterning phenomena, which are as yet poorly understood from an analytical point of view. Our aim is to develop more analytical insight into the pattern formation process in mechanochemical models of this type. As a first step towards this goal, we show that one can employ methods from geometric singular perturbation theory to construct nonlinear, far-from-equilibrium patterns in a general class of mechanochemical models. This analysis reveals a direct relation between the biology –as encoded in the nonlinear interaction of model componens– and the type of (multiscale) patterns that can arise.

Analysis of Spatially Localized Diffusion Processes in 3-D

Michael Ward
Department of Mathematics, UBC
ward@math.ubc.ca

We analyze two diffusive problems involving spatially localized structures in a 3-D spatial domain. The analysis in 3-D is inherently different than in the well-studied 2-D case owing to the more rapid spatial decay of the free-space Green's function away from the localized structure.

Our first problem is to develop a hybrid asymptotic-numerical method to analyze the existence, linear stability, and slow dynamics of localized quasi-equilibrium multi-spot patterns of the Schnakenberg activator-inhibitor model with bulk feed rate A and inhibitor diffusivity D in the singularly perturbed limit of small diffusivity ϵ^2 of the activator component. In contrast to the 2-D case, we show that localized spot patterns only occur in the regime $D = \mathcal{O}(\epsilon^{-1})$. From the linear stability analysis we derive stability thresholds for spot self-replication and for competition instabilities. We also show that the slow spot dynamics can be closely approximated by a gradient flow involving the Neumann Green's matrix. The effect of spot-pinning due to a spatially-variable feed-rate $A(x)$ is also analyzed.

Our second problem in 3-D is to analyze the first passage time problem for a diffusing molecule in an enclosed region to hit a small spherical target whose surface contains many small absorbing traps. Using a matched asymptotic analysis in terms of small absorbing pore radius, we derive a high order expansion for the capacitance of the structured target which incorporates surface effects and gives explicit information on inter-pore interaction through a Coulomb-type discrete energy with additional logarithmic dependencies. In the large N dilute surface trap fraction limit, a single homogenized Robin boundary condition $\partial_n v + \kappa v = 0$ is derived in which κ depends on the total absorbing fraction, the characteristic pore scale, and parameters relating to inter-pore interactions.

Joint work: with A. Bernoff, A. Lindsay, T. Kolokolnikov, J. Tzou, and S. Xie

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Free boundary problems of active and driven hydrogels

Barbara Wagner
WIAS Berlin
Barbara.Wagner@wias-berlin.de

In this study we present a free-boundary problem for an active polar gel based on the Beris-Edwards theory that uses a tensorial order parameter and includes active contributions to the stress tensor to analyse the rich defect structure observed in applications such as the Adenosinetriphosphate (ATP) driven motion of a thin film of an actin filament network. Analytic expressions are derived that reveal the interplay of boundary conditions, film thickness and active terms and their control of transitions of flow structure.

In addition, aspects of free surface induced structure formation of a hydrogel that accounts for the interfacial free energy and finite strain due to the large deformation

of the polymer network during solvent transport across the free boundary are briefly sketched.
