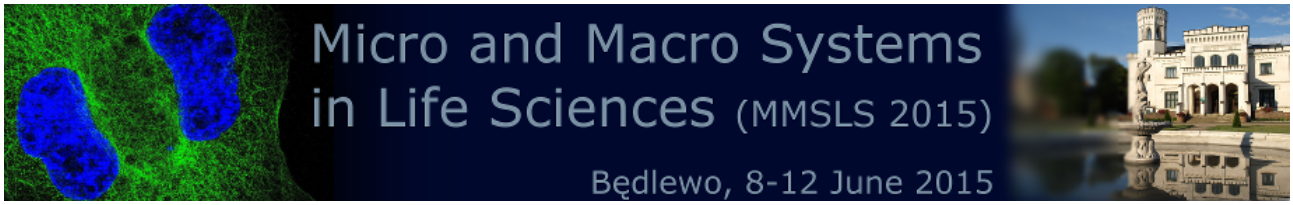

Book of Abstracts

Micro and Macro Systems in Life Sciences

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Mathematical Modeling of Disease Dynamics Based on Current Paradigms

Mathematical models that describe malignant behavior in the disease state are introduced and discussed. The models are then appraised and used to investigate the plausibility of current emerging paradigms regarding cancer evolution and development. Certain projections are then made and conclusions about the fight against cancer are drawn and placed in appropriate contexts.

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Metronomics Reloaded

Following the discovery of Gleevec's activity in the treatment chronic myelogenous leukemia, the paradigm of personalized therapy has gradually emerged and taken center stage in less than 2 decades, leading us to look at our traditional MTD chemotherapy as an old fashioned friend from the past. Indeed, the potential of target therapies to fight cancer without severe and frequent toxicities as well as the acknowledgment of the importance of microenvironment in the genesis, growth and resistance of tumors make chemotherapy less appealing. In this context, metronomic chemotherapy (MC) defined as the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, and with no prolonged drug-free breaks has been introduced in 2000. Since its inception in 2000, metronomic chemotherapy has undergone major advances as an anti-angiogenic therapy. The discovery its pro-immune properties and its direct effects on cancer cells has established the intrinsic multi-targeted nature of MC. Metronomics can be defined as the combination of MC and drug repositioning. Drug repositioning consists in using old drugs for new indications. The theoretical and pragmatic advantages to testing already established drugs for a potential effect on cancer cells are clear. The side-effects are known and have already been well documented,

so that, those drugs can immediately enter phase II studies to test their efficacy for cancer treatment. Some examples are available in the field of cancer with drugs such as celecoxib, valproic acid, statins, or more recently propranolol or metformin. Interestingly these agents display new mechanisms of action that can also be found in expensive new developed agents. Metronomics allow generating innovative, cheap, oral treatments that can target both cancer cells, cancer stem cells, as well as the microenvironement through an anti-angiogneic effect and restoration of anticancer properties of the immune system. After reviewing the anti-cancer mechanisms of metronomics and proposing additional mechanisms of action, we will consider the future of metronomics in the ever-changing landscape of anticancer treatment and current era of personalized therapy. More specifically we will show how metronomic chemotherapy can be combined with promising immune therapies such as AntiPD1/PDL1 or with target therapies both in adults and pediatric oncology. We will also reflect on the potential use of metronomics for patients living in low and middle income countries who cannot afford innovative and expensive molecules and who sometimes die of their disease at home with hardly any treatment to fight against their cancer.

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Joint work with: *S. Honoré, F. Hubert, M. Petit*

AGING OF MICROTUBULES AND EFFECT OF ANTIMICROTUBULE DRUGS

Microtubules (MTs) are long tube polymers of tubulin, found throughout the cytoplasm. They have highly dynamic behavior via their instability. MTs play important role in a number of cellular processes, including cell division and migration, that makes them attractive for targeted anticancer therapies.

The recent studies show that MTs age [1]. This feature might be very important in modeling of effects of anti-microtubule drugs on MT instabilities, since with their presence the effect of aging appears to be more perceptible. The aim of the work is to improve modeling of MT instability considering phenomenon of aging of MTs.

We propose a new deterministic mathematical model inspired by the work of P. Hinow et al. [2] to simulate the behavior of a MT population with presence of stabilizing and destabilizing drugs. The model couples transport equations with ordinary differential equations (ODE) with nonlocal terms endowed with suitable boundary conditions for both catastrophe and rescue. The mathematical model

takes into account results of biological observations provided by the pharmacologist of our interdisciplinary research group [3]. Numerical results are obtained in MATLAB by using upwind scheme with adaptive time step for the partial differential equations and the explicit Euler method for the ODE.

We obtain graphs for time evolution of the average total length of MTs in polymerization state and their caps and average length of MTs in depolymerization state (similar to data obtained by kymograph); concentrations of free GTP and GDP tubulin, total quantities of tubulin incorporated in MTs in polymerization and depolymerization states; time evolution of distribution of MTs in polymerization state.

Computational simulations describe diverse concepts of behavior of MT populations with and without impact of drugs. New model allows us to demonstrate the pharmacological action of some anti-microtubule drugs on MT population through their influence on MT aging and, thus, on MT instabilities. Numerical results are in a good agreement with biological observations.

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Modelling gene expression of a self-regulating protein

We analyze a model of gene transcription and protein synthesis. We take into account the number of sites on the protein's promoter at which the protein's dimers can bind blocking transcription of protein mRNA.

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Tree-free phylogenetic comparative methods: macroevolutionary dynamics on a branching process

Phylogenetic comparative methods are commonly used to analyze between species phenotypic data and therefore study phenomena on the macroevolutionary scale. They commonly assume that the evolutionary relationships between the species in question are known. With the current wealth of molecular information this most often can be the case but not always. Especially amongst the lower orders we are lacking phylogenies, we might be studying fossil data where the DNA signal has degraded and in fact we are still discovering new species (even among the higher orders). We consider a conditioned on the number of tip species birth-death process. The univariate trait evolving on top of it is modelled by a Brownian motion or Ornstein-Uhlenbeck process. We introduce the concept of the interspecies correlation coefficient which describes how quickly the tip species lose shared ancestral signal as we proceed from a Brownian motion (no drift) to OU processes with more and more drift. We show that there is a strong interaction between the speciation and adaptation rates. As new species start to appear slower each lineage starts to behave as an usual Ornstein–Uhlenbeck process. In fact a clear phase transition can be observed and we can show three distinct Central Limit Theorems for the contemporary sample average.

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On a fully discrete kinetic model of complex systems

Modeling approaches broadly based on kinetic theory reveal themselves very suitable towards the description of complex systems, like traffic flow or crowds dynamics. In order to capture the main features and simplify the description of such systems it is convenient to assume that the set of achievable velocities is a discrete one. In this poster we report some existence and uniqueness results as well as some numerical simulations for a class of discrete velocities models of pedestrians dynamics in which the spatial variable is discretized, too, in this way leading to a system of ordinary differential equations whose qualitative analysis is relatively more affordable that the corresponding continuous ones.

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Joint work with: *C. Lamont, L. Hlatky, P. Hahnfeldt*

A dynamical study of concomitant tumor resistance

Concomitant resistance is a biological process by which the presence of a tumor in the organism distantly inhibits the growth of a distinct neoplasm. We studied this phenomenon by using a combined experimental and theoretical approach. Three experimental settings were considered: a) simultaneous injection of two tumor implants, b) secondary injection after the primary implant had reached 100 mm3 and c) secondary injection after the primary implant had reached 500 mm3. In mice bearing two simultaneously injected tumors, growth of one (and only one) of the two tumors was significantly suppressed. To investigate this further, a modeling analysis was conducted using classical models of single tumor growth. No significant differences were obtained in any of the models' parameters, as compared to the control group. The only significant difference was in the time to reach a given volume threshold in the group of small tumors. Then, three theories of concomitant resistance were investigated: athrepsia (competition), direct inhibition of proliferation or indirect (angiogenesis-based) inhibition of proliferation. For each theory, several mathematical constructs were derived, relying on different structural forms of the tumor-tumor interactions. In each case, one minimally

parameterized, identifiable and biologically sound model was able to fit our data. Analysis of the parameters inferred from the fits allowed characterization of the quantitative impact of concomitant resistance on tumor growth.

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PDE/ODE models of motility in active biosystems

In the first part of the talk we present a review of our work on PDE models of swimming bacteria. First we introduce a stochastic PDE model for a dilute suspension of self-propelled bacteria and obtain an explicit asymptotic formula for the effective viscosity (E.V.) that explains the mechanisms of the drastic reduction of E.V.. Next, we introduce a model for semi-dilute suspensions with pairwise interactions and excluded volume constraints. We compute E.V. analytically (based on a kinetic theory approach) and numerically. Comparison with the dilute case leads to a phenomenon of stochasticity arising from a deterministic system. We develop a ODE/PDE model that captures the phase transition, an appearance of correlations and large scale structures due to interbacterial interactions. Collaborators: S. Ryan, B. Haines, (PSU students); I. Aronson, A. Sokolov, D. Karpeev (Argonne); In the second part of the talk we discuss a system of two parabolic PDEs arising in modeling of motility of eukaryotic cells on substrates. The two key properties of this system are (i) presence of gradients in the coupling terms (gradient coupling) and (ii) mass (volume) preservation constraints. We derive the equation of the motion of the cell boundary, which is the mean curvature motion perturbed by a novel nonlinear term and prove that the sharp interface property of initial conditions is preserved in time. This novel term leads to surprising features of the motion of the interface such as discontinuities of the interface velocity and hysteresis. This is joint work with V. Rybalko and M. Potomkin.

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Joint work with: *A. Quackenbush, H. Callender*

Implications of multiple sensitivity analysis techniques in stochastic models of focal adhesion dynamics

A cell's ability to move to the correct location at the correct time is vital for maintenance of homeostasis; improper movement is often indicative of a pathogenic phenotype. As such, it is critical to understand the molecular phenomena of motility. A key step in the process of cell motility is the development of focal adhesions, which are protein complexes involving cytoskeletal elements, membrane bound proteins, and extracellular matrix components. A fundamental part of a focal adhesion is integrin, the transmembrane receptor protein that links the actin cytoskeleton to extracellular matrix proteins. Here we develop and analyze a stochastic model of a nascent focal adhesion. The model captures the dynamics of the rate reactions over time between extracellular ligand molecules, intracellular adhesion proteins called talin, and integrins. We discuss results from a variety of sensitivity analysis techniques adapted for stochastic models. Such analysis is useful for improving the model and for developing theories about the underlying biological process of focal adhesion creation and of cell motility in general.

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Convergence of operator semigroups in models of mathematical biology.

We review some recent models of mathematical biology from the perspective of singular-perturbation theory for semigroups of operators. In doing this, we would like to argue that understanding biological models, such as these of gene expression, activity of kinases, activity of neurotransmitters, carcinogenesis or fish population dynamics, may lead to new and interesting theorems in pure mathematics.

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Joint work with: *A. Quackenbush, H. Callender*

General model of a cascade of reactions with time

The problem considered in this talk consists of a cascade of reactions with discrete as well as distributed delays, which arose in the context of Hes1 gene expression. For the abstract general model sufficient conditions for global stability are presented. Then the abstract result is applied to the Hes1 model.

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Mathematical model suggests a way to assess low grade glioma malignancy

Low grade gliomas (LGGs) are infiltrative and incurable primary brain tumours with typically slow evolution. These tumours usually occur in young and otherwise healthy patients, bringing controversies in treatment planning since aggressive treatment may lead to undesirable side effects. Thus, for management decisions it is essential to find a method to verify tumours aggressiveness and test their response to standard therapies with the lowest toxicity possible. Here we propose a mathematical model of LGG growth and its response to chemotherapy which agrees with patients' data. The model predicts, and our clinical data confirms, that the speed of response to chemotherapy is related to both proliferative potency of tumour and its resistance to therapy. Moreover, we provide estimated formula for time of tumour response to therapy, which can be used as a measure of tumour aggressiveness. Finally, we suggest propose chemotherapy fractionation scheme that might be therapeutically useful to predict the tumour growth and further prognosis.

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A stochastic model of high-grade serous ovarian cancer progression prior to treatment initiation

We seek to describe a putative mechanism of high-grade serous ovarian cancer recurrence in the presence of treatment: the probability of emergence of acquired and intrinsic revertant secondary mutations restoring BRCA1/2 function in platinum-resistant carcinomas. We first study HGSC tumor cell load by stochastically generating HGSC cell burden trajectories, using a stochastic version of Gompertz tumor growth. Second, we incorporate a cell-cycle dependent analysis in the stochastic Gompertz growth tumor burden model prior to therapy to estimate proliferative and quiescent subpopulation sizes. We then generate distribution functions accounting for the times until clinical detection and clinical lethal size of HGSC cell burdens are reached. We also correct for the time until a randomly chosen trajectory out of the generated HGSC cell trajectories reaches the detectability threshold by accounting for the fact that a tumor cell load becomes detectable at some unknown time after its actual progression. We assume either zero, uniformly distributed or normally distributed detection delays and study the differences between the distributions of detection times and lethal size times thus obtained and use these times of detection to estimate the probability that an intrinsic revertant BRCA1/2 mutation has already occurred in a proliferative cell prior to the estimated detection time.

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Joint work with: *N. Kronik*

Mathematical model of BCG treatment personalization for urinary bladder carcinoma

Due to the relatively low success rates of the combined surgical and adjuvant immunotherapy in the bladder cancer patients, we suggest a mathematically motivated strategy to improve these results. We use a schematic representation of the BCG-tumor-immune system and by estimating the different rates which control this system we construct a set of differential equations. The variables of the equation set are the number of tumor cells, bacteria cells, immune cells, and cytokines

participating in the tumor-immune response. We simulate this model over a clinically - relevant range of initial tumor sizes (distribution area) and tumor growth rates (tumor grade) using Matlab software. We use the indicators from biomarkers to input the initial conditions for immune system and tumor characteristics. Our model successfully retrieved previous clinical results for BCG induction treatment and BCG maintenance therapy with 82% complete response rate (CR) rate. Further, we designed alternative maintenance regimens using IL-2 given alone or concomitantly with BCG which improved success rates up to 86% and 100% of the patients without considering possible side effects. We suggest a flexible and versatile tool for physicians to plan new treatment protocols. Our results suggest that the subpopulation of non-responsive patients may be targeted for intensified combined BCG IL-2 maintenance treatment.

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Seeing the wood for the trees with mathematical modelling

The eye is a complex organ and, as such, represents a rich source of fascinating problems for applied mathematicians, interested in understanding its anatomy and physiology and how these change during ageing and in disease. In this talk attention will focus on photoreceptors, light-sensing retinal cells whose length fluctuates on a daily basis. I will start by presenting a simple mathematical model, formulated as a free boundary problem, which can be used to determine whether the observed fluctuations in healthy photoreceptors may be attributed to changes in oxygen demand during periods of light and dark. I will then focus on retinitis pigmentosa, a degenerative disease that targets the photoreceptors and causes progressive loss of visual function. I will present a second mathematical model developed in order to determine whether hyperoxia, exposure to elevated oxygen levels, may be responsible for the patterns of photoreceptor degeneration associated with retinitis pigmentosa.

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Joint work with: *W. Just, D. Lamar*

Infectious Diseases on Networks using NetLogo

We will first provide a brief introduction to models of disease transmission on contact networks. These models allow for exploration of stochastic effects and incorporation of more biological detail than the classical compartment-based ODE models. We then introduce a model we developed to simulate transmission on networks, for a variety of network types, using the agent-based platform of NetLogo. Finally, we will demonstrate how this model can help users explore how properties of the underlying contact network influence the disease dynamics. The primary focus of this talk is to illustrate how this model can be used as an aid in research of infectious diseases and also as a teaching tool for mathematical epidemiology.

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Mathematical modeling of tumor-driven angiogenesis. A mean field model.

In the mathematical modeling of tumor-driven angiogenesis, the strong coupling between the kinetic parameters of the relevant stochastic branching-and-growth of the capillary network, and the family of interacting underlying fields is a major source of complexity from both the analytical and computational point of view. Our main goal is thus to address the mathematical problem of reduction of the complexity of such systems by taking advantage of its intrinsic multiscale structure; the (stochastic) dynamics of cells will be described at their natural scale (the microscale), while the (deterministic) dynamics of the underlying fields will be described at a larger scale (the macroscale). In this presentation, starting from a conceptual stochastic model including branching, elongation, and anastomosis of vessels, we derive a mean field approximation of the vessel densities, leading to deterministic nonlinear partial differential equations for the underlying fields, driving the formation of the stochastic vessel network. Outcomes of relevant numerical simulations will be presented.

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Joint work with: *A. Benabdallah, M. Carrè, G. Chapuisat*

Optimal treatment for an heterogeneous in vitro tumor composed of resistant and sensitive cells

We propose to present a mathematical model of heterogeneous tumor growth based on experiments by M. Carré. This model is a competition ODE model and takes into account tumor cells sensitive or resistant to chemotherapy. The originality of the model relies in the control of the resistant cells by the sensitive cells when the chemotherapy only acts on the sensitive cells. First we prove that this simple model is able to simulate various situations that M. Carré has experimented in vitro. Specially metronomic (i.e. low-dose) chemotherapies are more efficient than the classical Maximum Tolerated Dose treatment. This confirms the hypothesis of M. Carré that metronomic therapy take better account of the complex relations of sensitive and resistant cells. Second, we study optimal treatments to control the global size of the tumor. Such optimal control problems can lead to singular controls of the tumor size. These mathematical results have to be confirmed by in vitro experiments, but this work will help in understanding the mode of action of metronomic chemotherapy and thus in calibrating them.

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Joint work with: *M. Ptashnyk, M. Sturrock*

Hopf Bifurcation in a Gene Regulatory Network Model: Molecular Movement Causes Oscillations

Gene regulatory networks, i.e. DNA segments in a cell which interact with each other indirectly through their RNA and protein products, lie at the heart of many important intracellular signal transduction processes. In this talk we analyse a mathematical model of a canonical gene regulatory network consisting of a single negative feedback loop between a protein and its mRNA (e.g. the Hes1 transcription factor system). The model consists of two partial differential equations describing the spatio-temporal interactions between the protein and its mRNA in a 1-dimensional domain. Such intracellular negative feedback systems are known to exhibit oscillatory behaviour and this is the case for our model, shown initially via computational simulations. In order to investigate this behaviour more deeply, we undertake a linearized stability analysis of the steady states of the model. Our results show that the diffusion coefficient of the protein/mRNA acts as a bifurcation parameter and gives rise to a Hopf bifurcation. This shows that the spatial movement of the mRNA and protein molecules alone is sufficient to cause the oscillations. Our result has implications for transcription factors such as p53, NF-κB and heat shock proteins which are involved in regulating important cellular processes such as inflammation, meiosis, apoptosis and the heat shock response, and are linked to diseases such as arthritis and cancer.

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Chemorepulsion, the role of a sign

I will review some of the results and open problems concerning global existence and boundedness of solutions to the fully parabolic chemorepulsion system. This system seems to be of interest in the biosciences community since it appears as a part of the models of cancer and Alzheimer's disease. From the mathematical point of view it is interesting, cause one sees the importance of the sign appearing in the equation. It seems that usual estimates do not give the required bound of

the solution. One needs to look for the estimates that can "see" the sign, sort of microscopic ones.

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Joint work with: *R. Chisholm, A. Escargueil, T. Lorenzi, A. Lorz, B. Perthame, E. Trélat*

Drug resistance in cancer: biological and medical issues, continuous modelling using structured population dynamics, and theoretical therapeutic optimisation

Considering cancer as an evolutionary disease, we aim at understanding the means by which cancer cell populations develop resistance mechanisms to drug therapies, in order to circumvent them by using optimised therapeutic combinations. Rather than focusing on molecular mechanisms such as overexpression of intracellular drug processing enzymes or ABC transporters that are responsible for resistance at the individual cell level, we propose to introduce abstract phenotypes of resistance structuring cancer cell populations. The models we propose rely on continuous adaptive dynamics of cell populations, and are amenable to predict asymptotic evolution of these populations with respect to the phenotypic traits of interest. Drug induced drug resistance, the question we are tackling from a theoretical and experimental point of view, may be due to biological mechanisms of different natures, mere local regulation, epigenetic modifications (reversible, nevertheless heritable) or genetic mutations (irreversible), according to the extent to which the genome of the cells in the population is affected. In this respect, the models we develop are more likely to be biologically corresponding to epigenetic modifications, although eventual induction of emergent resistant cell clones due to mutations under drug pressure is not to be completely excluded. From the biologist's point of view, we study phenotypically heterogeneous, but genetically homogeneous, cancer cell populations under stress by drugs. According to the cell populations at stake and to the exerted drug pressure, is drug resistance in cancer a permanently acquired phenotypic trait or is it reversible? Can it be avoided or overcome by rationally (modelguided) designed combinations of drugs (to be optimised)? These are some of the questions we will try to answer in a collaboration between a team of mathematicians and another one of biologists, both dealing with cancer and Darwinian evolution of cell populations.

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Joint work with: *A. Poskrobko*

On the age-dependent predator - prey model

We shall present the predator - prey model with age structure. This model is decribed by the system of partial differential equations.

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A kinetic approach to Darwinian dynamics

The talk will be devoted to the modeling, the qualitative analysis and simulation of Darwinian selection phenomena and their evolution.

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DNA melting model

We discuss the macroscopic version of microscopic DNA melting model corresponding to the mesoscopic model proposed in [1]. The experiments show (see e.g. [2]) that DNA bounds are not in two states (there is a bound or the bound is broken) as it was assumed previously [3], but can stretch out to some value making 'bubbles'. We show some analytical results and mostly numerical simulations how bubbles appears.

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Joint work with: *T. Lorenzi, M. Melensi*

Cancer cells and T-cells under immunotherapy

Competition between cancer cells and T-cells under immunotherapy: Evolutionary Biology and Mathematical Modelling How immunotherapies affects the evolutionary dynamics of cancer cells? Can we slow down cancer evolution by using immune boosters? Bearing these questions in mind, we present a mathematical model of cancer-immune competition under immunotherapies. The model consists of a system of structured equations for the dynamics of cancer cells and activated T-cells. Numerical results suggest that the selection of proper infusion schedules may play a key role in the success of anti-cancer therapies. In particular, we highlight how cancer evolution can be effectively slowed down by immunotherapeutic protocols relying on successive infusions of agents that boost the proliferation of activated T-cells and agents that enhance immune memory.

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Joint work with: *F. Nogueira*

Optimal Control for infectious diseases

We consider an optimal control problem with L_1 cost involving a SEIR model model for the control of a generic infectious diseases.

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Joint work with: *P. Manfredi*

Mathematical modelling of the spread of infectious diseases: beyond classical approach

Classical models of infectious diseases were based on statistical mechanics (SM). On the one hand classical tools of SM such as the mass-action law were heavy used in the first part of the life of mathematical epidemiology; on the other newer tools of SM, such as network theory, scale-free distributions etc... were adopted in recent years. However, all these approach fails to describe some scenarios because they abstract, in the first case, subjects as particles in random motion, in the second modelling scenario, as networks static or with autonomous changes. In reality human beings are complex active entities endowed by behaviours that impact on the disease spread. In turn, the behaviour is influenced by the available information on the epidemic spread. As a consequence epidemics feedback onto themselves passing through human behaviour. These considerations, expressed in various forms, led to the birth of a new discipline named behavioural epidemiology of communicable diseases (BE). Here we first briefly show some outstanding evidences of the relevance of these issues by means of examples taken from recent history and statistics. Then, we will review our personal contribution, by focusing on some issues concerning the modelling of changes in vaccine propensity and on mathematizing the intervention of public health authorities, and how to use in innovative way SM in BE.

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On optimal location of thermostats in a model of feedback control

I intend to discuss a problem of optimal choice of locations of thermostats in a certain model of feedback control of a reaction-diffusion process admitting a PDE representation. The idea of the control in matter is the following. The control bases on a thermostatic system, consisting of a given number of measurement and control devices. Each measurement device tracks the process in a certain location inside the process domain. The control devices react with respect to the data

obtained from measurement devices, delivering energy for process correction to given locations in the domain and thus complementing the feedback loop. The control aim is to pursue a prescribed target state.

The main point of my interest is the question on improving (optimizing) the choice of locations of the control and measurement devices, assuming that the control aim is given. A finite time horizon [0, T] is assumed for the model and the target function to be optimized is the gap between the process state and the reference state near the terminal time T. I will present both analytical and numerical results addressing this problem. This presentation will mostly base on my Ph.D. dissertation. Feedback controls of the above described type were considered earlier in the mathematical literature on PDEs, but the problem of optimal choice of locations of thermostats in the form as in my research seems to had not been addressed before.

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Joint work with: *T. Strohmer*

Identifying Changes in Brain MRI in Early Stages of Alzheimer's Disease

The goal of this study is to discriminate magnetic resonance imaging (MRI) of brains of patients with Alzheimer's Disease (AD) and brains of those without AD and then to identify changes in a brain MRI in the early stages of AD. A novel approach based on the diffusion map framework, which is considered to be one of the leading manifold learning methods, is used for this classification. Diffusion mapping provides dimensionality reduction of the data as well as pattern recognition that can be used to distinguish brains of patients with AD from brains of patients without AD. A new algorithm, which is an extension of diffusion maps, constructs coordinates that generate efficient geometric representations of the complex structures in the MRI. In addition, this method is adapted to the MRI and accounts for the variability in calibration of the MRI of different patients. The algorithm is tested on MRI data from patients who developed AD and those who did not. The algorithm is able to classify AD from normal data in an automatic, unsupervised method.

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Joint work with: *C. Engwer*

Simulations of actin-medicated polarity in yeast by a continuous reaction-diffusion-advection system

The yeast cell Saccharomyces cerevisiae provides an excellent model system to study the underlying mechanisms of cell polarity, a process fundamental to the function of many cell types. Two positive feedback loops are thought to contribute to the local polarization of the most important polarity regulator Cdc42, one actin-dependent and one actin-independent mechanism. A common model explains polarity by a Turing-type reaction-diffusion mechanism that can concentrate Cdc42 by a Bem1-mediated recruitment [2]. Since biological experiments show that cell polarity occurs even in the absence of Bem1, recent models emphasize the GDI-mediated exchange between the cytosol and the plasma membrane and the associated different diffusion rates [3]. However, these reaction-diffusion Turing-type models do not take into account the suggested actin-mediated feedback loop. Cdc42 orients actin cables, which in turn deliver secretory vesicles containing Cdc42. Vesicle trafficking models based on stochastic equations demonstrated that this mechanism can either reinforce [1] or perturb polarisation [4]. Following the approach proposed by [2], we present a minimal mathematical model based on reaction-diffusion-advection equations that, in addition to the diffusive transport, explicitly includes an advective term to simulate the actin-mediated vesicle transport. Vesicles move along actin cables, thus we additionally consider actin polymerisation and depolymerisation and incorporate exocytosis and endocytosis of Cdc42. Since we consider five substances, either cytosolic or membrane-bound, and model the full geometry we have a coupled bulk-surface problem. Thereby, our model does not rely on a Turing-type mechanism as it includes the actin-dependent advection of molecules and distinguishes between a cytosolic and membrane domain. Unlike [1] we further describe vesicle transport in a continuous model, which allows a deeper analysis. We present numerical results in 2D and 3D and compare those to experimental data. These show that the model is able to reproduce experimentally observed pathological cases and demonstrate how vesicle trafficking could reinforce polarization.

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Joint work with: *J. Banasiak*

Asymptotic state lumping in network problems

One of the aims of systems biology is to build multiple layered and multiple scale models of living systems which can efficiently describe phenomena occurring at various level of resolution. Such models should consist of layers of various microsystems interconnected by a network of pathways, to form a macrosystem in a consistent way; that is, the observable characteristics of the macrosystem should be, at least asymptotically, derivable by aggregation of the appropriate features of the microsystems forming it and from the properties of the network. In this talk we consider a general macromodel describing a population consisting of several interacting with each other subgroups, with the rules of interactions given by a system of ordinary differential equations, and we construct two different micromodels whose aggregated dynamics is approximately the same as that of the original macromodel. The micromodels offer a more detailed description of the original macromodel's dynamics by considering an internal structure of each subgroup. Here each subgroup is represented by an edge of a graph with diffusion or transport occurring along it, while the interactions between the edges are described by interface conditions at the nodes joining them. We prove that with an appropriate scaling of such models, roughly speaking, with fast diffusion, or transport, combined with a slow exchange at the nodes, the solutions of the micromodel are close to the solution to the macromodel.

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Nonlocal kinetic equations derived from stochastic dynamics of complex systems

We consider a number of nonlocal nonlinear kinetic-type equations whose solutions approximate densities of complex systems in the course of proper stochastic evolutions. The approximations were obtained using a mesoscopic scaling in the corresponding microscopic (nonequilibrium) dynamics which have applications to biological and life sciences. All equations were rigorously derived from the microscopic evolutions. We describe some properties of the solutions: stability of stationary solutions, travelling waves, long-time behaviour, aggregation etc. We present an overview of recent results in this area.

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Prostate Cancer Immunotherapy Model

We consider simple mathematical model that describes interactions between immune system and prostate cancer cells after vaccination. The model reflect the cascade of reactions that eventually leads to eliminations of cancerous cells. It occurs that asymptotic dynamics of the system can be simplified to the dynamics of one-dimensional system in which vaccinations are described as impulses. We propose conditions sufficient for cure and conditions for unsuccessful treatment.

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A free boundary problem associated with the risk of high cholesterol

Atherosclerosis is the leading cause of death in the United States and worldwide. The disease originates from a plaque that builds up on the artery, and may trigger heart attack or stroke. The growth of the plaque is initiated and maintained by LDL cholesterols which enter the plaque from the blood. In this talk I will describe a mathematical model, developed jointly with Wenrui Hao, of the growth of the plaque as a free boundary problem consisting a system of PDEs, with LDL and HDL cholesterol influxes from the free boundary. The risk of atherosclerosis will be visualized by a "risk map" in the (LDL, HDL)-plane. The existence, uniqueness, and asymptotic stability of small plaques have more recently been proved jointly with Wenrui Hao and Bei Hu.

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Optimization of spatiotemporal control for systems described by cellular automata

Cellular automata are frequently used to model dynamics of spatial systems. This work shows how a so-called adjoint sensitivity analysis may be applied to such systems. It is assumed that the cellular automaton has a continuous state, a spatiotemporal input and is characterized by one scalar objective function specified for example in a given optimization or parameter estimation problem. With this analysis it is possible to efficiently calculate a gradient of the objective function in a space of the spatiotemporal input of the automata. As an example, a model of avascular tumor growth with introduced spatiotemporal irradiation signal is analyzed. It is shown how to compute a gradient of a given objective function in the control space and how to use it in a gradient-descent optimization. The resulting suboptimal control is presented and compared to uniform irradiation protocol. This work was supported by Silesian University of Technology.

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Faractals and Cancer in the Era of System Biology

Despite progresses in our biological and clinical knowledge, human cancer remains one of the major public health problems throughout the world. Cancer is today recognized as a highly heterogeneous disease: more than 100 distinct types of human cancer have been described, and various tumour subtypes can be found within specific organs. It encompasses various pathological entities and a wide range of clinical behaviours, and is underpinned by a complex array of gene alterations that affect supra-molecular processes. This genetic and phenotypical variability is what primarily determines the self-progression of neoplastic disease and its response to therapy. Additionally, the asynchrony and self-progression of a cancer cell population suggests that the extent to which each neoplastic cell shares the properties of a natural cell may differ in time and in space. The complexity of alterations in cancer presents a daunting problem with respect to treatment: how can we effectively treat cancers arising from such varied perturbations? A tumour consists of genetically distinct subpopulations of cancer cells, each with its own characteristic sensitivity profile to a given therapeutic agent. Each cancer therapy can be viewed as a filter that remove a subpopulation of cancer cells that are sensitive to this treatment while allowing other insensitive subpopulations to escape. The conception of anatomical entities as a hierarchy of graduated forms and the increase in the number of observed sub-entities and structural variables has generated a growing complexity, thus highlighting new properties of normal cells and their tumoural counterpart. The need to tackle system complexity has become even more evident since completion of the various genome projects. One of the pre-eminent characteristics of the entire living world is its tendency to form multi-level structures of "systems within systems", each of which forms a Whole in relation to its parts and is simultaneously part of a larger Whole. Anatomical entities, when viewed at microscopic as well as macroscopic level of observation, show a different degree of complexity. The still unsolved central question is how to transform molecular knowledge into an understanding of complex phenomena in cells, tissues, organs and organisms. In order to understand cancer as a complex system that involves so many interacting components, we also need to determine the type of data that needs to be collected at each level of organization, the boundary conditions to use when describing the disease (i.e. a perturbed system), and the technologies and approaches best suited to reveal its underlying biological behaviour. Critical analysis of traditional clinical concepts is needed, as is reinterpretation of the clinical significance of failed therapies from the perspective of complexity. Two main con-

cepts, multi-scale causality and heterogeneity need to be considered when generating new medical interventions. The need to find a new way of classifying natural as well tumoural anatomical entities, and objectively quantifying their different structural changes, prompted us to investigate the Fractal geometry and the theories of complexity, and to apply their concepts to human cancer. It is known that mathematical methods have proved to be practical in oncology, but the current models struggle to resolve the 10-12 order-of-magnitude span of the timescales of systemic events, be they molecular, cellular or physiological. It is encouraging that mathematicians, biologists and clinicians contribute together towards a common understanding of cancer complexity. This multi-disciplinary approach may help to clarify old concepts, categorize the actual knowledge, and suggest an alternative approach to discover biomarkers with potential clinical value.

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A "universal" model of metastatic cancer: What can one learn from site-specific volumes of metastases?

We develop a methodology for estimating unobservable characteristics of the individual natural history of metastatic cancer from the volume of the primary tumor and site-specific volumes of metastases measured before, or shortly after, the start of treatment. In particular, we address the question as to what information about natural history of cancer can and cannot be gained from this type of data. Estimation of the natural history of cancer is based on parameterization of a very general mathematical model of cancer progression accounting for primary tumor growth, shedding of metastases, their selection, latency and growth in a given secondary site. This parameterization assumes Gompertz (and, as a limiting case, exponential) growth of the primary tumor, exponential growth of metastases, and exponential distribution of metastasis latency times. We find identifiable parameters of this model and give a rigorous proof of their identifiability. As an illustration, we analyze a clinical case of renal cancer patient who developed 55 lung metastases whose volumes were measured through laborious reading of CT images. The model with maximum likelihood parameters provided an excellent fit to this data. We uncovered many aspects of this patient's cancer natural history and showed that, according to the model, onset of metastatic disease occurred long before primary tumor became clinically detectable.

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Multiscale modeling of the impact of ECM ligand density and cell-cell adhesion on the onset of EMT

Epithelial-mesenchymal transition plays a pivotal role in multicellular invasion phenomena, such as wound healing or tumor spreading. Here, we focus on the onset of cell migration as a key process of EMT. In particular, we develop a simple mechanical model of single cell migration based on the forces exerted by focal adhesion and cytoskeletal contration. Our main question is the relationship between available ECM ligand density (e.g. integrins) and the onset of single cell migration. Then, we integrate the above results to a multicellular modeling framework (LGCA) to study the impact of cell-cell adhesion and the competition for ECM ligands on the onset of EMT at the macroscopic level.

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Joint work with: *A. Swan, K. Painter*

Using anisotropic diffusion to model glioma spread

Anisotropic diffusion describes random walk with different diffusion rates in different directions. In context of glioma invasion, we can obtain directional information in the brain through diffusion tensor imaging (DTI).

In my talk I will derive a tumor invasion model from basic biological principles, including the directional DTI information. I will analyse some of the mathematical behavior of the resulting model and show how it can be used to model glioma spread as well as wolf movement (if time allows).

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Mathematical Modelling of the Tumor Growth Paradox and more...

The tumor growth paradox describes the effect that a tumor after incomplete treatment grows larger than it was before treatment. A possible explanation is the presence of cancer stem cells (CSC). CSC are less sensitive to treatments and can repopulate the tumour. On my poster I present a basic CSC model to explain the tumor growth paradox. If combined with immune interactions we find that the immune system selects for CSC. Since CSC are known to be less sensitive to treatments such as chemotherapy and radiation therapy, we investigate the benefit gained by a differentiation promoter combined with radiation. We find that a differentiation promoter can have a drastic effect, allowing us to reduce the radiation dosage. Ongoing work relates to a non-local PDE version of the model to investigate spatial CSC distributions and invasions.

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Mathematical modeling of the microtubule dynamic instabilities

The aim of our group is to design some pertinent mathematical /computational models of the pharmacological effects of microtubule-targeted drugs, which are powerful anti-mitotic drugs used in human cancers. Those drugs induce important perturbations on microtubule dynamic instabilities. As these instabilities play a key role in cancer progression: i.e cell proliferation/division and cell migration, any contribution on the comprehension of their effects could be helpful.We will focus in this talk in the modeling of microtubules targetting drugs.

Harsh Jain

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Endothelial-tumor cell crosstalk and its implications for therapy

We will focus in this talk in the modeling of microtubules targetting drugs.

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Influence of gene copy number on gene expression

Gene copy number variation may significantly influence gene expression level in live cells. We study the relationship between the number of copies of an auto-regulated gene, and the properties of the protein number distribution.

Even for identical gene copies, in the presence of gene regulation, our model predicts deviations from linear dependence of the average protein concentration on gene copy number, characteristic for unregulated genes. In a wide range of the model parameters we observe that various measures of gene expression noise (standard deviation, coefficient of variation and Fano factor) depend in a non-monotonous manner on the number of gene copies. We also analyse a situation when different copies of a given gene resulting from mutations in the gene promoter region are no longer identical, although still coding for the same protein. We discuss possible effects of both gene copy number variation and mutations affecting transcription factor binding on the cell growth rate (fitness function).

The presented analysis is based on the graphical method of geometric construction, which allows to predict various properties of the system. Our theoretical predictions can be tested experimentally and therefore may be of relevance for both genetic engineers and evolutionary biologists.

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Transmission of infectious diseases and of catchy ideas

Transmission of ideas in human populations is not unlike transmission of infectious diseases and can be modeled in a similar way. Moreover, knowledge or beliefs about a certain disease may induce a behavioral response that can modify the probability of infection. There has been growing interest in the recent literature in modeling the interplay of the spread of a disease, the spread of awareness about the disease, and the behavioral response triggered by the awareness. This talk will highlight some research on this topic, including recent joint work of the authors.

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Coevolutionary dynamics of host and parasite

Host-parasite coevolution can have profound impacts on a wide range of ecological and evolutionary processes including population dynamics, the maintenance of genetic diversity, and the evolution of recombination. To examine the coevolution of quantitative traits in hosts and parasites, we present and study a fully coevolutionary model of a host-parasite system that incorporates (1) ecological dynamics that feed back into the coevolutionary outcome; (2) parasite that can be obligatory or facultative; and (3) Holling Type II functional responses between host and parasite, which are suitable for brood parasitism since parasites need to search for host and spend some time handling resources. We perform both local and global analysis for the coevolutionary model and the corresponding ecological model. In the absence of evolution, our analysis on the ecological model implies that the extremely small value of the death rate of parasite due to hunting/searching for all potential host species can drive host extinct globally while the extremely large value of the death rate can drive parasite extinct globally. The facultative parasite system can have one, two, or three interior equilibria while the obligated parasite system can have either one or three interior equilibria. Multiple interior equilibria result in rich dynamics with multiple attractors. Particularly, the ecological

system can exhibit bistability between the facultative parasite only boundary attractor and the coexistence interior attractor when it has two interior equilibria. Our analysis on the coevolutionary model provide important insights on how coevolution can change the ecological and evolutionary outcomes of host-parasite interactions. Most interesting findings suggest that: (a) Host and parasite can select different strategies that result in local extinction of one species. However, these strategies can have convergence stability (CS) but they may not be evolutionary stable strategies (ESS); (b) Host and facultative (or obligated) parasite can have ESS strategies that drive host (or obligated parasite) extinct locally; (c) Trait functions play an important role in the CS of both boundary and interior equilibria as well as their ESS strategies; and (d) The small variance of the trait difference that measures the parasitism efficiency can destabilize the coevolution system, thus generate evolutionary arms-race dynamics with different host-parasite fluctuating patterns.

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Light as a biomarker: computer-assisted reconstruction and analysis of genetic properties of cells from their microscopic images

In my talk I will discuss the recent developments and the major challenges in noninva-sive computer-assisted study of living specimen based on the information extracted from their microscopic images. In particular, I will pay attention to the correlation be-tween optical and genetic properties of cells (e. g., chromosome number and mass). The primary impact of the proposed research is in the fields of embryology and evolu-tionary biology. One of the major applications of this research is in viability assess-ment of human embryo cells, which cannot be stained and thus can be observed via specific microscopic modalities during the IVF treatment. I will also discuss a possi-ble extension of our approach to analysis of cancer biopsies.

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Stationary Waves on the Sphere

We investigate stationary waves on the sphere using the bistable reaction-diffusion system. The motivation of this study arises from a model of activation waves in immune systems (see [1],[2]). We establish analytically: (i) the existence and uniqueness of stationary waves; (ii) the limiting wave profile for diffusion coefficients tending to zero; and (iii) the (non) stability of the constructed stationary waves. The stability result may justify the critical role of stationary waves in the determination of initial data for initiating propagating waves on the sphere, which is consistent with the numerical results for B-cell activation model.

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Flexing Protein muscles: How to Pull with a "Burning Rope"

The segregation of chromosomes during cell division is accomplished by kinetochore machinery that uses depolymerizing microtubules to pull the chromosomes to opposite poles of the dividing cell. While much is known about molecular motors that pull by walking or push by polymerizing, the mechanism of how a pulling force can be achieved by depolymerization is not resolved. In this talk, I will describe a new model for this type of molecular motor, the depolymerization motor,

that is used by eukaryotic cells to segregate chromosomes during mitosis. In the process, I will explore the use of Huxley-type models (i.e. generalizations of Huxley's model of muscle crossbridge kinetics) to study several different examples of processes governed by the binding and unbinding of flexible proteins. The main consequence of this study is new insight into how to pull with a "burning rope".

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Joint work with: *I.-K. Choi, J. Crivelli, J. Gevertz, J. Wares, A. Yoon, C.-O. Yun*

Cancer-immune dynamics of oncolytic virotherapy and dendritic cell vaccines

Recent experiments with engineered oncolytic adenovirus have caused substantial reduction in growth rates of tumors in mice. We develop ordinary differential equation (ODE) models based on the data from five different treatments: (Ad) oncolytic adenovirus, (Ad/4-1BBL) Ad virus co-expressing the molecule 4-1BBL, (Ad/IL-12) Ad virus co-expressing the cytokine IL-12, (Ad/4-1BBL/IL-12) Ad virus co-expressing both 4-1BBL and IL-12, and Ad/4-1BBL/IL-12 in conjunction with dendritic cell (DC) vaccines. By fitting time series data of tumor growth to our ODE models, we attempt to elucidate the underlying cancer-virus and cancer-immune dynamics to clarify the strengths and limitations of oncolytic virotherapy combined with DC vaccines. Using modeling, we consider how different treatment strategies can be used to (1) rapidly kill the tumor with a goal of complete elimination or (2) maintain the tumor long-term at low levels. We also describe the problem of improving the delivery of oncolytic virus into tumors. Images show that viruses seem to penetrate hardly more than a few millimeters from the site of injection and only infect isolated and sparse clusters of cells, rather than dispersing comprehensively throughout the tumor. Understanding the kinetics of virus delivery into a tissue and the extracellular matrix poses a useful problem that could require the formulation of partial differential equation or other spatial models.

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Strategies of eradicating glioma cells

The cellular dispersion and therapeutic control of glioblastoma, the most aggressive type of primary brain cancer, depends critically on the migration patterns after surgery and intracellular responses of the individual cancer cells in response to external biochemical and biomechanical cues in the microenvironment. Recent studies have shown that a particular microRNA, miR-451, regulates downstream molecules including AMPK and mTOR to determine the balance between rapid proliferation and invasion in response to metabolic stress in the harsh tumor microenvironment. Surgical removal of main tumor is inevitably followed by recurrence of the tumor due to inaccessibility of dispersed tumor cells in normal brain tissue. In order to address this multi-scale nature of glioblastoma proliferation and invasion and its response to conventional treatment, we propose a mathematical model of glioblastoma that analyses spatio-temporal dynamics at the cellular level, linking individual tumor cells with the macroscopic behaviour of cell organization and the microenvironment, and with the intracellular dynamics of miR-451-AMPK-mTOR signaling within a tumour cell. The model identifies a key mechanism underlying the molecular switches between proliferative phase and migratory phase in response to metabolic stress and biophysical interaction between cells in response to uctuating glucose levels in the presence of blood vessels (BVs). The model predicts that cell migration, therefore efficacy of the treatment, not only depends on oxygen and glucose availability but also on the relative balance between random motility and strength of chemoattractants. Effective control of growing cells near BV sites in addition to relocalization of invisible migratory cells back to the resection site was suggested as a way of eradicating these migratory cells.

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Evolution of States of a Spatial Ecological Model: Micro- and Mesoscopic Descriptions

There is studied an infnite system of point entities in R^d which reproduce themselves and die, also due to competition. In the microscopic approach, the systems states are probability measures on the space of confgurations of entities. The mesoscopic description is based on a version of the Vlasov scaling. The evolution of states is obtained from a BBGKY-type equation for the corresponding correlation (moment) functions k_t. It is proved that: (a) the equation has a unique classical solution k_t, $t < T$, for some $T < 1$; (b) for each t, there exists a unique sub-Poissonian state m_t for which k_t is the correlation function; (c) in the Vlasov scaling limit the rescaled k_t converges to the correlation functions of the time-dependent Poisson point feld the density of which solves the kinetic equation obtained from the equation for the correlation functions. A number of properties of the solutions of the kinetic equation are established and the role of the competition is carefully analyzed.

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Dynamical models of prostate cancer treatment

We formulate and use clinical data to validate a mathematical model of prostate cancer growth to study the complex dynamics of androgen suppression therapy and the production of prostate-specific antigen (PSA), a clinical marker for prostate cancer. Our model also accurately describes the oscillatory androgen dynamics as observed.

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Self-organization: From microscopic to macroscopic

The macroscopic limits of the kinetic model of interacting agents are studied. The kinetic model is one–dimensional and agents are characterized by their position and orientation with interaction controlled by a sensitivity parameter. The macroscopic limits of the kinetic 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 approximations. The interesting generalizations are discussed.

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Modeling and Optimization of Metronomic Chemotherapy: More Questions Than Answers

There is growing evidence that how a drug is administered can significantly affect the outcome of treatment. Metronomic chemotherapy is the administration of cytotoxic drugs at a lower dose, constant or varying in time, without significant rest periods. In recent years, this has become an interesting alternative to the traditional MTD (maximum tolerated dose) approach at the same time attesting that "more is not necessarily better". Although medical data in support of this approach are mounting, there still are more questions than answers. These interesting questions provide challenges to modelers as well as to experts working in optimization theory on how to give some mathematical insights into what is called a "biologically optimal dose" which takes into account the complexity of the nonlinear interactions describing biological phenomena. In this talk, we will present a simple, minimally parametrized model that includes the cancer cells, the carrying capacity of the vasculature and an immunocompetent cell density under a single agent treatment which exhibits cytotoxic, antiangiogenic and pro-immune

effects. The dynamical system features of this model will be discussed as well as some partial answers will be given concerning optimality of the treatment. An analysis as optimal control problem indicates the optimality of singular controls which would point to lower dose, metronomic administration schedules as optimal. The connection with some medical studies concerning metronomic chemotherapy will be addressed.

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Newton's method for nonlinear stochastic wave equations

We consider nonlinear stochastic wave equations driven by time-space white noise:

$$\frac{\partial^2 u}{\partial t^2} - \frac{\partial^2 u}{\partial x^2} = f\left(t, x, u|_{C_{t,x}}\right) + g(t, x, u|_{C_{t,x}})\dot{W} \quad \text{on } [0, T] \times R,$$

where $C_{t,x}$ is the wave cone with vertex (t, x). The existence of solutions is proved by means of direct iterations. Next we apply Newton's method. The main result concerning its first-order convergence is based on Cairoli's maximal inequalities for two-parameter martingales. Moreover, a second-order convergence in a probabilistic sense is demonstrated.

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The role of the autologous immune response in chronic myelogenous leukemia

Tyrosine kinase inhibitors (TKIs), such as imatinib (IM), have significantly improved treatment of chronic myelogenous leukemia (CML). However, the majority of patients are not cured for undetermined reasons. It turns out that many patients who otherwise responded well to IM therapy still show variations in their

BCR-ABL transcripts. To investigate this phenomenon, we developed a mathematical model that integrates CML and an autologous immune response. Our modeling results suggest that IM therapy drives the leukemic population into the "immune window", allowing the patient's autologous immune cells to expand and eventually mount an efficient recognition of the residual leukemic burden. This response drives the leukemic load below this immune window, allowing the leukemic population to partially recover until another weaker immune response is initiated. Thus, the autologous immune response may explain the oscillations in the BCR-ABL transcripts observed in patients on IM. This is a joint work with G. Clapp, T. Lepoutre, and F. Nicolini.

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Genetic consequences of range expansion under climate change

Range expansion is a crucial population response to climate change. The genetic consequences are not well understood but are clearly coupled to ecological dynamics that, in turn, are driven by shifting climate conditions. We model a population with a reaction–diffusion system, coupled to a heterogeneous environment that shifts with time due to climate change. We decompose the resulting traveling wave solution into neutral genetic components to analyze the spatio-temporal dynamics of its genetic structure. Our analysis shows that range expansion under slow climate change preserves genetic diversity. However, diversity is diminished when the climate change occurs too quickly. We show that populations with intermediate dispersal ability are best for maintaining genetic diversity during shifting climatic conditions. Our study also provides new analytical insight regarding dynamics of traveling wave solutions in heterogeneous environments. This work is joint with Jimmy Garnier (CNRS).

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Joint work with: *M. Czerkies, Z. Korwek, W. Prus, S. Błoński, J. Jaruszewicz, M. Kochańczyk, B. Tian, M. Kimmel, A. Brasier*

NF-κB and IRF3 crosstalk signaling in MEFs

NF-κB, IRF3 and AP-1 are most potent transcription factors controlling innate immune responses to pathogens. Combining single cell and population techniques with mathematical modeling we analyzed crosstalk of these pathways in mouse embryonic fibroblasts in response to LPS and poly(I:C). We found that both LPS and poly(I:C) activate mediating kinases IKKα/β and TBK1; interestingly, only poly(I:C) stimulation leads to activation of IRF3 (activated by TBK1) and triggering of transcription of IFNβ, IRF7, and RIG-1 and other interferon regulated genes. LPS stimulation leads to transient or oscillatory (in some cells) responses of NF-κB, in contrast to switch-like responses (preceded by one or two pulses in a fraction of cells) to poly(I:C) stimulation, with fraction of switched-on cells increasing with the stimulation dose. As suggested by the experiment in which cells are costimulated by LPS and IFNβ, the difference in NF-κB responses is caused by IFNβ para- and autocrine regulation that leads to activation of EIF2AK2 (PKR) and OAS1A, which results in suppression of NF-κB inhibitors synthesis. Correspondingly the blockade of INFβ receptor causes attenuation of response to poly(I:C) at latter time points. Overall this suggests that autocrine regulation breaks the negative regulation of NF-κB (and IRF3) leading to build up of nuclear NF-κB and IRF3, followed by apoptosis in a fraction of cells (not observed in the case of LPS stimulation). The IRF3 activation is stabilized by positive feedback involving strongly upregulated STAT1/STAT2 and RIG-1 (which is STAT1/STAT2 responsive). We confirmed by mathematical modeling the dynamically divergent responses to LPS (mimicking bacterial infection) and to poly(I:C) (mimicking viral infection). NF-κB is known for exhibiting oscillatory responses to TNFα, which are replaced by switch-like responses in A20-deficients cells. Here, we found that activation of the IRF3 pathway, or INF stimulation leads to the similar effect on NF-κB signaling, possibly due to inhibition of translation of NF-κB inhibitors. The switch-like behavior, frequently associated with cell fate decisions, is associated with bistability arising here due to the positive feedbacks in IRF3/IFNβ/STAT1/STAT2 regulation.

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Joint work with: *H. Behar, N. Brenner, G. Ariel*

Fluctuations-induced coexistence in public goods dynamics

Cooperative interactions, their stability and evolution, provide an interesting context in which to study the interface between cellular and population levels of organization. Such interactions also open the way for the discovery of new population dynamics mechanisms. We have studied a version of the public goods model relevant to microorganism populations actively extracting a growth resource from their environment. Cells can display one of two phenotypes – a productive phenotype that extracts the resources at a cost, and a non-productive phenotype that only consumes the same resource. We analyze the continuous differential equation model as well as simulate stochastically the full dynamics. It is found that the two sub-populations, which cannot coexist in a well-mixed environment, develop spatio-temporal patterns that enable long-term coexistence in the shared environment. These patterns are solely fluctuation-driven, since the continuous system does not display Turing instability. The average stability of the coexistence patterns derives from a dynamic mechanism in which one sub-population holds the environmental resource close to an extinction transition of the other, causing it to constantly hover around its critical transition point, forming a mechanism reminiscent of self-organized criticality. Accordingly, power-law distributions and long-range correlations are found. When a time scale separation occurs between two dynamic parameters is defined, a structurally unstable point emerges and any small perturbation of the dynamics with additive noise leads to an equilibrium distribution in which both species coexist in context of additive but not multiplicative noise.

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Quasi-stationary and shadow limits of multiscale reaction-difusion-ode models of biological pattern formation

This talk is devoted to a problem of model reduction for a class of reaction-diffusion-ode systems. Such systems of equations arise, for example, in modeling

of interactions between cellular processes and diffusing growth factors. Taking into account different time and space scales of the underlying processes leads to singularly perturbed problems. We develop an approach leading to a higher order approximation of such problems using the renormalization group (RG) method. We focus on two types of approximation: a quasi-stationary (Tikhonov-type) model reduction in case of fast non-diffusive variables and a shadow limit for systems with large diffusion. Both approximations are shown to preserve pattern formation mechanisms. We discuss them on examples of models exhibiting different types of spatio-temporal structures: Turing patterns, dynamical spike patterns and stationary patterns with jump discontinuities.

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Mean-field approximation in gene regulation and evolutionary games

Many natural and social processes can be modeled by systems of interacting objects. One may then try to derive their global behavior from individual interactions between their basic entities such as protein molecules in gene regulation and signaling pathways in cells, animals in ecological and evolutionary models, and people in social processes. Although interactions in such models are usually local, they propagate in space and time and this makes the rigorous mathematical analysis of such systems very difficult if not impossible. We would like to present here a method of self-consistent mean-field approximation. The core idea is as follows. The force exerted on a given object, coming from its neighbors, is replaced by an unknown mean force - a mean field. Given the mean field, we can easily calculate the expected value of the state of the object in the equilibrium (a stationary state of an appropriate dynamics). Now one can compute the value of the mean field which should be consistent with the unknown value introduced in the beginning. We will apply a mean-field method in simple stochastic models of gene regulation, signaling pathways in cells, and spatial evolutionary games. This enables us to obtain approximate analytical expressions for the expected value and variance of the number of molecules of a given type in stationary states of our systems.

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Deterministic description of random biological structures

Frequently, random biological structures (sets of bacteria, biological tissue etc) can be considered as random two-phase geometric structures described by probabilistic distributions, for instance, by correlation functions. This talk is devoted to a new computationally effective approach to study such structures in terms of the generalized Eisenstein-Rayleigh sums. The results yields the constructive RVE theory (VM 2006) much more effective than vague statistical approaches. We give precise and computationally instant answers such questions as isotropy of structure and its macroscopic behavior which can be detected as normal or anomalous. For instance, the method is applied to the collective behavior of bacteria.

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Joint work with: *L. Berlyand, V. Rybalko, L. Zhang*

Motility of keratocyte cells: asymptotic and numerical analysis via a phase field model

The study of crawling eukaryotic cells has been of recent interest to biologists and mathematicians. Their motion is modeled by a 2D phase field consisting of a scalar Ginzburg-Landau PDE coupled with a vectorial parabolic reaction-diffusion equation. In the sharp interface limit, the normal velocity of the cell's boundary is defined implicitly by a non-linear and non-local equation. To prove short-time existence of curves propagating via this evolution we equivalently prove existence of solutions of a fully non-linear PDE. To numerically study the sharp interface equation, we develop an algorithm which resolves the difficulty of non-local volume preservation, and we present examples of asymmetric geometry interacting with non-linearity to produce motion of the cell's center of mass. This work is completed with Ph.D. adviser Leonid Berlyand in collaboration with Volodymyr Rybalko and Lei Zhang.

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On some PDE models related to tumor

This talk is devoted to the analysis on some PDEs models related to tumor. The main feature of the models is that they have transport terms like chemotaxis or haptotaxis. I will focus mainly on the long time behavior of the models. I will show also some numerical simulations to corroborate the theoretical results.

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Joint work with: *M. Tabaka*

Binary to graded response conversion in autoregulated genes: transcriptional leakage vs. noise

The response of a gene to a signal of increasing strength is binary when the protein distribution changes its shape from unimodal through bimodal to unimodal. Graded response occurs when the protein distribution remains always unimodal.It became a common knowledge that positive autoregulation of genes is utilized by by cells as an evolutionary way of obtaining bimodal expression, whereas negative autoregulation is preferred for precise, unimodal response. But what if the cells need to adapt from the environment where binary response was beneficial to the environment where graded response is favored? The change of the nature of the gene regulation from positive to negative may not be the optimal way because it requires multiple mutations. We present a stochastic model model of the response of an autoregulated gene to signal molecules over a range of their possible concentrations. Using this model, we show that another, simpler mechanism is possible for the conversion between binary and graded response: fine-tuning of transcriptional leakage. We show that noise due to translational bursting and transcriptional leakage have the opposite effects in a positively autoregulated gene: Whereas an increase in the noise converts the response from graded to binary, an increase in the leakage converts the response from binary to graded. It seems that the change in the leakage level can be achieved by single mutations and therefore we hypothesize that it may be more probable than the change of the nature of

feedback from positive to negative. Our results highlight the previously underappreciated phenomenon of transcriptional leakage, which is a common phenomenon in wild-type genes but has largely been treated as an unfavorable effect disrupting tight gene regulation. Our results suggest that its existence may be justified by an evolutionary strategy.

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Joint work with: *D. Kajunguri, J. Hargrove*

Modelling the control of Trypanosoma brucei rhodesiense through mass chemoprophylaxis and insecticide-treated cattle

Background: In Uganda, cattle are considered to be an important reservoir of Trypanosoma brucei rhodesiense (Tbr), a parasite that causes human trypanosomiasis, transmitted by tsetse flies Glossina fuscipes fuscipes. Recent studies show that, when tsetse flies feed predominantly on cattle, control of sleeping sickness could be achieved by treating 20Aim: Our aim is to investigate here the effects and costs of interventions using a combination of trypanocides and ITC, rather than exclusive use of either treatment. Methodology/Principal Findings: We use a mathematical model for the transmission of T.b. rhodesiense in humans and cattle to evaluate the impact of the simultaneous use of trypanocides and ITC on the control of T. b. rhodesiense in Tororo district, Uganda. Assuming that this district is closed to tsetse immigration, we derive an analytical expression of the model's basic reproduction number, , and investigate its sensitivity to the model's key parameters. The sensitivity analysis shows that the basic reproduction number is more sensitive to the proportion of cattle kept on insecticides than to that of cattle treated with trypanocides. Numerically, we determine, for different proportions of cattle treated with tryoanocides and proportions of tsetse flies' feeds on cattle, the minimal proportion of ITC required for the disease to be eradicated as well as the corresponding time to eradication and cost. The model is further extended and analysed to investigate the effects of fly immigration on the disease dynamics. Speaker: Rachid Ouifki

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Long time behaviour of the stochastic model of stem cells differentiation with switching

Differentiation and self-renewal of stem cells are essential processes to maintain a supply of well-specialized cells for every tissue. The promising medical applications and the complexity of those processes encourages to implement numerical and mathematical methods to understand better the mechanisms which regulate stem cells behaviour. Environmental or internal perturbations may have an influence on the death rate, proliferation rate and on the fraction of self-renewal at every stage of differentiation. We investigate a piece-wise deterministic Markov process based on the deterministic model of multistage cell lineages proposed by Anna Marciniak-Czochra. The long-time behaviour of the two-dimensional version of the model is well discovered, asymptotic stability of the related Markov semi-group is proved.

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Joint work with: *J. Bhattacharyya*

Spatial interactions in a population dynamics involving Allee effect and chemical defense

The toxic effect of macroalgae on herbivorous reef fish is studied by means of a spatiotemporal model of population dynamics with a nonmonotonic toxin-determined functional response. We assume that the growth rate of macroalgae is mediated by Allee effect. We see that under certain conditions the system is permanent in presence of all the organisms. Conditions for local stability of the system is obtained with weak and strong Allee effects. It is observed that in presence of Allee effect, under certain conditions, the model exhibits complex dynamics including Hopf bifurcation and saddle-node bifurcation. It is also observed that the system does not exhibit diffusion-driven instability.

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Nutrient and toxic stressors in food chain models

Bioaccumulation of toxic compounds in aquatic food chains can pose risk to ecosystem conservation as well as wildlife and human health. Ecotoxicological modeling aims to predict how contaminants cycle through aquatic food systems. There is increasing evidence that considering resource stoichiometry and nutrient availability will improve risk assessment protocols in ecotoxicology. We developed stoichiometric aquatic food chain models that investigate co-occurring nutrient and toxic stressors in order to improve our understanding of the processes governing the trophic transfer for nutrients, energy, and toxins. These modeling efforts offer insight on the importance of elemental food quality in ecotoxicological testing protocols for assessing risk of exposures to toxins.

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Mathematical Modeling of Calcium Induced Calcium Influx Waves

The existing theories of calcium waves are based on the assumption that the calcium is released in the autocatalytic process from the internal stores located inside the cell. These sort of waves are named by L. F. Jaffe as calcium induced calcium released (CICR) waves in contrast to another possible (much faster) type of waves - calcium induced calcium influx (CICI) waves supported by the influx of calcium through the membrane. Such fast waves are indeed observed in experiments. We propose a mathematical theory of fast calcium waves of CICI type. According to the suggestion of L. F. Jaffe [1], these waves are supported by the influx of calcium from the intercellular space by the stress activated ion channels located in the cell membrane. The local stretching of the membrane is evoked by a thin cross-linked actin network, the cortex, attached to the cell membrane. Myosin motors in this network are responsible for the appearance of contractile forces, depending on the calcium concentration. The thickness of the cortex is of the order of 100 nm, which is very small in comparison with the size of typical cells (10-20μm). Cells are also equipped with the systems of pumps pumping out the

excess of calcium. The competition between these two processes and the diffusion lead to the appearance of the travelling waves. The model is based on a system of reaction diffusion equations for calcium and buffer proteins coupled with the mechanical equations for the traction forces produced by the cortex. The important feature of the proposed system is the dynamic boundary condition which is responsible for the influx of calcium from the extracellular space. It is interesting that the theory leads to homoclinic travelling waves (as observed in reality) without postulating additional equation for so called recovery variable as it is usually done.

References:

[1] L.F. Jaffe, Stretch-activated calcium channels relay fast calcium waves propagated by calcium-induced calcium influx, Biol. Cell 99, 175-184 (2007)

Acknowledgments. The main part of the work was completed before 2015 when the first author was still working at Institute of Applied Mathematics and Mechanics, The University of Warsaw.

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The immune system-tumour interactions model with discrete time delay: model analysis and validation

We consider a mathematical model describing the interactions between malignant tumour and immune system with discrete time delay incorporated into the system. Time delay represents the time required to generate an immune response due to the immune system activation by cancer cells. The basic mathematical properties of the considered model, including the stability of stationary solutions and the possibility of stability switches, are investigated when the time delay is treated as a bifurcation parameter. Considered model is validated with the experimental data and additional numerical simulations are performed to illustrate and extend the analytical results.

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Joint work with: *Mariusz Nieć*

A hybrid model of tumour induced angiogenesis in 3D

Angiogenesis is the physiological process of growth of new blood vessels from existing vasculature. It is a fundamental step in the transition of tumours from benign to the malignant state (so called angiogenic switch). The growth of endothelial cells forming vessels is stimulated by factors released by tumour cells that are under hypoxic conditions. One of the major factors is the vascular endothelial growth factor (VEGF). We have developed a hybrid model consisting of continuous and discrete part describing the dynamics of tumour growth and sprouting angiogenesis in three-dimensional spatial domain. Continuous part of the model is based on the multiphase model, and it is represented by a set of advection equations for different types of the cells. It is complemented by reaction-diffusion equations for oxygen and VEGF. The discrete part of the model is necessary for modelling the angiogenesis. It enables modelling growth and sprouting of the new vessels, creation of functional vessel loops and simulation of the blood flow through it. A number of simulations were performed with different model parameters in order to check the model suitability. Generated vascular networks may differ in for example vessel tortuosity or density of vessels. Simulation results were compared to the results of the models that do not take into consideration spatial dependencies, generally to the models of Hahnfeldt type.

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Understanding the dynamics and complexity of the interstitial drug transport in pancreatic tumors: integration of in-silico and in-vivo experiments

Delivery of anti-cancer drugs to solid tumors is a complex process involving biochemical, mechanical, and biophysical factors. In particular, the cellular, fibril and metabolic heterogeneity in the tumor tissues, such as in pancreatic cancers, can create an intricate extracellular microenvironment, which significantly limits the interstitial transport and optimal drug exposure. Mathematical modeling provides a means through which one can unravel this complexity by examining interactions

between contributing components in a systematic way via computational simulations and quantitative analyses. We use a combination of in-vitro and in-vivo experiments to calibrate our biomechanical in-silico model of microenvironmental pharmacodynamics, microPD, and investigate the interstitial drug transport in pancreatic tumors. We use this model to evaluate the behavior of targeted imaging agents and hypoxia-activated drugs, and dynamical reciprocal changes in both the tumor and its microenvironment. Our computational simulations show various ways to overcome barriers to drug transport and to enhance drug efficacy. We envision that this work will contribute to the development of quantitative measures of drug and imaging agent design in order to optimize cancer treatment.

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Joint work with: *J. T. Tien*

Stochastic Model of Ebola Epidemic

We develop a realistic, but at the same time mathematically tractable and statistically predictive dynamic model of the recent west Africa epidemic of Ebola. We expand the traditional model of an SIR stochastic epidemic on a graph with a given degree distribution to account for the Ebola-specific features. These include, among others, a class of individuals at high risk of infection (e.g., health workers), and a dynamic network structure that reflects how contacts with different segments of the population change over the course of infection within host. Joint work with Joseph Tien at OSU

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Joint work with: *R. Bartsch, T. Fischer, E. Schalk, S. Sager*

Modelling of Neutropenia after AML treatment

Introduction Neutropenia is one of the most harmful side effects during leukaemia treatment, since neutrophils are crucial in protecting patients against bacteria and fungi. Mathematical modelling can form a basis for advanced patient-specific analysis and decision support tools. Such a mathematical model must be able to

reproduce qualitatively and quantitatively patterns of leukocytes and neutrophils during chemotherapy treatment.

Methods: For our study Optimal Control of Clinically Relevant Cancer Chemoherapy Schedules in Patients with Acute Myeloid Leukaemia (AML) - with Special Emphasis on Neutropenia (MARTINA), we used data of leukocytes and neutrophils during and after chemotherapy treatment (cytarabin and daunorubicin, cycle 1-5) of 3 different patients contracting AML. In order to describe the dynamics of leukocytes and neutrophils, we used a published model by Quartino et al. (Invest New Drugs 30:833-845), which we modified with respect to the pharmacokinetics and pharmacodynamics of the applied agents. We fitted the parameters to our measurements using least square terms and compared them among patients and treatment cycles. In this study, we also investigate the qualitative and quantitative dependence of neutropenia duration against different dose levels and chemotherapy schedules.

Results: After modifying the original model we were able to simulate typical patterns of leukocyte and neutrophil dynamics and the typical length of neutropenia (approximately 3 weeks). We then reproduced personal cell patterns of the 3 treated AML patients by parameter fitting. Patient-specific parameters were able to explain differences in patient-specific cell dynamics. As a second step, a comparative analysis of different chemotherapy schedules was conducted using the patient-specific model parameterisations. This analysis indicated that the length of neutropenia depends not only on the dose and timing of the chemotherapy, but also on physiological characteristics of the patients.

Conclusions: The presented model is able to simulate neutrophil dynamics in response to chemotherapy treatment and allows taking patient-specific characteristics into account. As soon as this approach is combined with detailed information about the dynamics of leukaemic cells, a new framework can be designed for the development of optimal chemotherapy schedules that maximises lethal effects on cancer cells and minimises the risk of neutropenia and infectious complications at the same time.

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Joint work with: *L. Edelstein-Keshet, A. Vardi, I. Koren*

Algae blooms

Models for the interactions of Algae blooms and viruses will be presented and compared to experimental data.

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Rigorous derivation of nonlinear scalar conservation laws from follow-the-leader type models via many particle limit

We prove that the unique entropy solution to a nonlinear scalar conservation law with strictly monotone velocity and nonnegative initial condition can be rigorously obtained as the large particle limit of a microscopic follow-the-leader type model, which is interpreted as the discrete Lagrangian approximation of the nonlinear scalar conservation law. More precisely, we prove that the empirical measure (respectively the discretised density) obtained from the follow-the-leader system converges in the 1-Wasserstein topology (respectively in L^1_{loc}) to the unique Kruzkov entropy solution of the conservation law. The initial data are taken in L^∞, nonnegative, and with compact support, hence we are able to handle densities with vacuum. Our result holds for a reasonably general class of velocity maps (including all the relevant examples in the applications, e.g. in the Lighthill-Whitham-Richards model for traffic flow) with possible degenerate slope near the vacuum state. The proof of the result is based on discrete BV estimates and on a discrete version of the one-sided Oleinik-type condition. In particular, we prove that the regularizing effect $L^\infty \to BV$ for nonlinear scalar conservation laws is intrinsic of the discrete model.

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Piecewise deterministic Markov processes in biological models

We present a short introduction into the framework of piecewise deterministic Markov processes. We illustrate the abstract mathematical setting with a series of examples related to dispersal of biological systems, cell cycle models, gene expression, physiologically structured populations, as well as neural activity. General results concerning asymptotic properties of stochastic semigroups induced by such Markov processes are applied to specific models like gene expression and size-structured models.

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Joint work with: *T. L. Stepien, Y. Kuang, and E. J. Kostelich*

Data-Validated Model of Glioblastoma Tumor Growth

Glioblastoma Multiforme is an extremely aggressive form of brain cancer, with a mean survival time with treatment on the order of one year. We present a mathematical model for the growth and spread of glioblastoma in murine brains. This model is compared to experimental data in order to estimate model parameters and validate model assumptions.

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Optimization for Clinical Decision Support

Physicians need to make many important decisions per day. One clinical example is the scheduling and dosage of chemotherapy treatments. A second example is the discrimination of atrial fibrillation from atypical atrial flutter, based on ECG data.

Such important and complex decisions are usually based on expert knowledge, accumulated throughout the life of a physician and shaped by subjective (and sometimes unconscious) experience. It is not readily transferable and may be unavailable in rural areas. At the same time, the available imaging, laboratory, and basic clinical data is abundant and waits to be used. This data is not yet systematically integrated and often single data-points are used to make therapy decisions.

More and more clinical decision making tasks will be modeled in terms of mathematical relations. I propose a systematic approach that supports and trains individual decision making. The developed ideas, mathematical models, and optimization algorithms will be generic and widely applicable in medicine and beyond, but also exploit specific structures, resulting in a patient- and circumstance-specific personalized medicine.

This allows, e.g., a physician to first simulate the impact of his decisions on a computer and to consider optimized solutions. In the future, it will be the rare and unwanted exception that an important decision can not be backed up by consultation of a model-driven decision support system or based upon a systematic model-driven training.

We will present mathematical algorithms, mathematical models and encouraging preliminary results from a transfer to clinical practice for different diseases.

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Joint work with: *U. Ledzewicz and A. Friedman*

An Epidemiological Model for the Spread of an Infectious Disease with Quarantine

Physicians need to make many important decisions per day. One clinical example is the scheduling and dosage of chemotherapy treatments. A second example is the discrimination of atrial fibrillation from atypical atrial flutter, based on ECG data. Such important and complex decisions are usually based on expert knowledge, accumulated throughout the life of a physician and shaped by subjective (and sometimes unconscious) experience. It is not readily transferable and may be unavailable in rural areas. At the same time, the available imaging, laboratory, and basic clinical data is abundant and waits to be used. This data is not yet systematically integrated and often single data-points are used to make therapy decisions.

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This allows, e.g., a physician to first simulate the impact of his decisions on a computer and to consider optimized solutions. In the future, it will be the rare and unwanted exception that an important decision can not be backed up by consultation of a model-driven decision support system or based upon a systematic model-driven training.

We will present mathematical algorithms, mathematical models and encouraging preliminary results from a transfer to clinical practice for different diseases.

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Joint work with: *T. Silva and J. Tiago*

Mathematical modeling of the early stages of atherosclerosis

Atherosclerosis, the major cause of cardiovascular disease, is a chronic inflammation that starts when LDL (low-density proteins) cholesterol enter the intima of the blood vessel where they are oxidized. The anti-inflammatory response of oxLDL triggers the response of monocytes that are transformed into macrophages and foam cells, leading to the production of inflammatory cytokins and further recruitment of monocytes. This complex process leads to the formation of an atherosclerotic plaque (atherogenesis) and possibly to its rupture. Several theories have been developed to explain the pathogenesis of atherosclerosis but none of them can explain the whole process due to the large number of factors involved. On the other hand, mathematical models should account for these complex multiphysics phenomena. They are described by nonlinear reaction- diffusion equations, coupled with fluid and structure equations and only a few results exist for some simplified models. This talk is devoted to the well-posedness of simplified models capturing essential features of the early stage of atherosclerosis development. Numerical simulations to illustrate the mathematical results will also be presented. The influence of hemodynamic factors in the atherosclerotic plaque growth will be discussed.

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Joint work with: *U. Ledzewicz*

Adjoint Sensitivity Analysis and Optimal Control: Mathematical Model of Vicodin Abuse

Vicodin is the most commonly prescribed pain reliever in the United States, and about two million Americans are currently abusing it. The goal of this research is to reevaluate the previous sensitivity analysis done by Caldwell et. al. on their models of this abuse. Through the incorporation of a terminal payoff term, motivated by optimal control, a more streamlined and accurate method of determining the normalized sensitivity indices is derived. The outcomes of this new method are the same for the parameters but provide new insight for the sensitivity with respect to the initial populations. Moreover, the connection between sensitivity analysis and optimal control is examined, bridging the two theories.

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Joint work with: *N. Komarova*

The role of tissue architecture in the context of tumor evolution

Understanding the unique microenvironment and the architecture of the stem cell niche and its surrounding neighbors is crucial to determine the origins of cancer. Moreover, knowledge of the division patterns of cells, both healthy and malignant, can suggest ways of altering the microenvironment of the tissue, with the aim of controlling the growth rate of the cells, and possibly minimizing the size of the tumor. We have developed a class of stochastic models of a renewing tissue, and addressed the optimization problem of tissue architecture in the context of tumor evolution and progression. Several mathematical models have been introduced in order to understand the dynamics of cells in the tissue. These works concentrated on mutations in stem cells, because of their crucial role in the cancer initiation and progressions.

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The role of the stem cell niche in delaying cancer

We propose a class of general stochastic models to simulate the dynamics of the stem cell niche. We consider two stem cell groups; one stem cell group S1 responsible for the numbers of Transit-Amplifying (TA) cells and Stem Cells (SCs), and the other stem cell group S2 regulating the total number of stem cells. We examine this model in the context of double-hit mutant generation, and discover that such a cooperative pattern in the stem niche leads to the minimum probability of double-hit mutant generation under symmetric division of SCs. It turns out that symmetric divisions are compatible with the lowest rates of double-hit mutant production. Furthermore, we find the optimal architecture (which minimizes the rate of double-hit mutant production).

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Joint work with: *D. F. M. Torres*

Optimal control and cost-effectiveness analysis for a tuberculosis model

Tuberculosis prevention, diagnosis and treatment represents a worldwide scale challenge. We propose an optimal control problem that consists in analyzing how two tuberculosis post-exposure interventions should be implemented, for a certain time period, in order to reduce the number of active infected individuals, while controlling the intervention implementation costs. We introduce some summary measures to describe how the optimal solutions change when varying transmission intensity and protection against reinfection. A cost-effectiveness analysis is done, to compare the application of each of the control measures, separately or in combination.

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On differences between experimental and real-life models

Biological experiments, used as a basis for development of mathematical models, are performed using various techniques. Some of them involve plasmid transfection. While it has been known that transfection itself may significantly alter experimental results, there is little research into how knowledge about experimental procedures can be employed to build better models or improve the quality of conclusions that can be drawn.

In this work we show that mathematical models describing dynamics of intracellular processes should include usual molecular players as well as those introduced artificially by means of transfection. Otherwise, the dynamics captured by the model might be much different from the dynamics of the processes it is supposed to capture.

As an example a simple regulatory module involving two types of mRNA and two types of miRNA regulating their levels is considered. Additionally, plasmids that are used to report activity of miRNA are taken into account. Since the efficiency of transfection vary from cell to cell, the amount of plasmids that entered a cell is sampled from a normal distribution.

Results of numerical simulations indicate that cellular responses change not only quantitatively, which should be expected, but also qualitatively. A phase shift may appear in oscillations, which should be taken into account in experiment planning. Usually, the same time instants are chosen in experiments involving transfection as in other procedures. This might lead to a completely disturbed view on cellular behavior. Therefore, specific character of experimental procedures should be taken into account in model building.

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A stochastic micro-macro model for cancer cell proton dynamics

Tumor spreading and migration through the surrounding tissue is a crucial stage in cancer development and a highly complex phenomenon, involving processes on several different space and time scales. Most tumors are characterized by regions of acidity and hypoxia. The acidic environment promotes apoptosis of normal cells, while cancer cells can survive and proliferate, which facilitates invasion. In spite of the increased acidity in the environment the intracellular pH level of cancer cells is at the alkaline side of neutrality, since tumor cells are capable to maintain their intracellular pH level through several membrane based ion transport systems. We discuss a micro-macro model for cancer cell proton dynamics. Random effects are taken into account in the subcellular proton dynamics and modelled by a stochastic differential equation on the microscale. The equation is coupled with a classical reaction-diffusion equation describing the dynamics of extracellular protons on the macroscale.

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Mathematical Modeling and Analysis of Glioblastoma Tumor Growth

Glioblastoma multiforme is an aggressive brain cancer that is extremely fatal. Gliomas are characterized by highly diffusive growth patterns, which makes them impossible to remove with surgery alone. To give insight on the mechanisms most responsible for tumor growth and the difficult task of forecasting future tumor behavior, numerical and analytical results from various reaction-diffusion models are compared to experimental data.

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Multiscale models for glioma invasion: proliferation and therapy aspects

Gliomas are rarely curable brain tumors arising from abnormal glial cells in the brain. In particular, the most agressive type, glioblastoma multiforme, has a poor prognosis with a median survival rate less than one year. Complex therapy approaches including surgical resection of neoplastic tissue, radio- and chemotherapy can still not ensure healing and are part of ongoing research. We present a multiscale modeling approach for describing glioma invasion in white brain matter. The models consist of kinetic transport equations coupled with (integro-) differential equations and account for the evolution of glioma density (mesoscale) in interplay with subcellular dynamics (microscale) of integrin binding to the surrounding tissue. Particular attention is payed to proliferation and tumor heterogeneity. We also deduce effective equations for the tumor evolution on the macroscopic level and propose a framework to assess a treatment approach involving resection followed by radiotherapy with concurrent and adjuvant chemotherapy.

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Mathematical Modeling of the Dynamics of the Cellular Cytoskeleton

Actin-driven motility of eucaryotic cells plays a crucial role in many biological processes and has therefore been under intense experimental and theoretical investigation. In this talk a minimal model for the polymerization and depolimerizaton of actin filaments is discussed, which consists of four hyperbolic conservation laws describing the evolution of densities of actin filament tips and one parabolic equation for the dynamics of the actin monomer concentration. For this coupled hyperbolic-parabolic system a free boundary problem is formulated, which models the directed motion of the cell. Short time well posedness is proved and several

mechanisms are discussed for which the solutions may break down for large times. In particular, possible blow-up phenomena are given, both analytically and numerically. The cease of existence of solutions indicates the emergence of actin polymerization fronts, as they are observed during the directed motion of cells.

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On a multiscale model involving cell contractivity and its effects on tumor invasion

Invasion of tumor cells is an important step for metastasis and is governed by several subcellular processes. A number of them affect the contractivity, by which we describe the ability of the cancer cells to adapt their shape and orientation according to the surrounding tissue. We derive a multiscale model focusing on the influence of the cell contractivity on tumor cell migration. It takes into account both the subcellular level, where changes of contractivity are initiated, and the macroscopic level of the cell population. The resulting PDE-ODE system involves in particular haptotactic and chemotactic cross-diffusion as well as a temporal delay. We provide the local existence of a unique solution in a general framework, prove the global existence of solutions for a slightly more specific setting and present numerical simulations to illustrate the effect of contractivity on the migration of cancer cells in our model. These are joint works with G. Meral (Zonguldak), C. Surulescu (Kaiserslautern) and M. Winkler (Paderborn).

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Oncolytic Virotherapy to Treat Cancer and Immune System Effects

Oncolytic viruses are a form of cancer treatment used to target tumor cells without harming healthy cells. These viruses have been engineered to specifically infect

and kill cancer cells. Maximizing oncolytic potential of replicating viruses, however, has not been found to be an optimal strategy, as opposed to maximizing viral spread through the tumor. An ordinary differential equation system represents the interactions of infected tumor cells, tumor cells infected by the virus, and virus specific antigens, with the effects of the immune response. Here, the thresholds between replicating viruses parameters are explored to find the most optimal outcome towards the minimization of tumor cells.

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Controllability and Sensitivity of Models of Combined Anticancer Therapy

We analyze sensitivity of sufficient conditions for local controllability for a class of models of treatment response to combined anticancer therapies. The combined therapy is understood as combination of direct anticancer strategy e.g. chemotherapy and indirect modality (in this case antiangiogenic therapy). Controllability of the models in the form of semilinear second order dynamic systems enables to expect that different objectives of treatment could be reached. We discuss the effect of different models of cancer growth (Gomperztian vs. logistic) and supporting vascular network growth. The important finding presented in the paper is that sufficient conditions of local constrained controllability for the simple models of combined therapy are satisfied that is generally not true when antiangiogenic therapy as a single treatment is used. In the case of the original Hahnfeldt model the sufficient condition of local constrained controllability for monotherapy is not satisfied at all and for its modification proposed by d'Onofrio and Gandolfi its satisfaction needs additional constraints on the system parameters. The conditions are independent of the type of growth equation used for description of the cancer growth dynamics (Gompertzian or logistic ones). The third model of this class presented in the paper proposed by Ergun et al could be treated in similar way. we can study the effect of time delays in control variables on the controllability conditions. In the case of delays, introduced to the growth models in order to describe PK/PD effects, we limit our discussion to relative controllability, the conditions are satisfied similarly as before and the conclusions are also almost the same.

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Mathematical modelling of the intracellular protein dynamics: the importance of active transport along microtubules

We propose a spatio-temporal model of intracellular protein dynamics, i.e. protein and mRNA transport inside a cell, that takes into account the active transport along microtubules in cytoplasm as well as diffusion and is able to reproduce the oscillatory changes in protein concentration observed in many experimental data. The proposed model is generic, built with a focus on the possibility of its adaptation to specific signalling pathways. On the basis of numerical simulations, we formulate a new hypothesis that the oscillatory dynamics is allowed by the mRNA active transport along microtubules from the nucleus to distant locations.

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On a two species chemotactic system

We consider a system of three equations modeling the behavior of two biological species moving attracted by a chemical factor. The system contains second order terms in the first two equations modeling the chemotactic effects. We consider different cases: when the two species compete for the resources and when the interaction between the species is relegated to the chemical production. We present results on global existence of solutions and the stability of the steady states.

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Entropy of Protein Networks in Malignant Cells

We describe a strategy for the selection of protein targets suitable for drug development against neoplastic diseases taking the particular case of breast cancer as an example. Hubs of protein connectivity were combined with transcriptome data from malignant and control cell lines because highly connected proteins that are up-regulated in malignant cell lines are expected to be suitable protein targets for chemotherapy with a lower rate of undesirable side effects. We show that the protein targets effectively identified by the combination of protein connectivity and differential expression are known as suitable targets for the successful drug therapy of breast cancer. We found that the entropy of the protein interaction network exhibits significant correlation according to the type of drug that is used to control their growth. The correlation between malignant cell sensitivity to target specific drugs is negative. By reference to protein network entropy, we show that the treatment benefit to the patient due to the inactivation of top-5 up-regulated protein hubs can be expected to be 1-2

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Microtubule Organization in the Presence of Motor Proteins

Microtubules (MTs) and motor proteins interact in vivo and in vitro to form organizations such as asters and bundles. In vivo, MT organization depends on cell type and the cell-cycle stage, and so understanding these organizations is an important part in understanding normal cellular function. Here, we construct a novel nonlocal transport model that describes the evolution of MTs as they interact with motor proteins. Our model takes into account motor density, directionality, processivity, and motor cross-linking capability. An advection-type term accounts for directed MT transport (due to either MT treadmilling or MT sliding), and an integral term accounts for the reorientation of MTs due to their interactions with cross-linking motor proteins. Simulations of our model with a single motor protein type show that MT organizations such as asters, parallel bundles, and vortices,

persist. These patterns are similar to those that are found in in vitro experiments. In simulations where two opposing motor protein types are present, MTs can organize into anti-parallel bundles, similar to MT patterns that are observed in the mitotic spindle during cell division.

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Joint work with: *R. Rudnicki*

A nonlinear age-structured model of semelparous species

A species is called semelparous if its specimen reproduces only once in the lifetime, and usually dies afterwards. We consider such a semelparous population that individuals may give birth only at a given age. Discrete-time models of semelparous population have been intensively studied recently, because they have unexpected asymptotic properties, such as the extinction of all but one year classes. It is an interesting question if a continuous time age-structured model may exhibit similar properties. We present a non-linear McKendrick-type age-structured model given by a linear partial differential equation with a nonlinear boundary condition. Properties of measure-valued periodic solutions of the system are investigated. We observe that there exists a unique nonnegative stationary distribution which is often unstable. We investigate also the behavior of classical solutions that converge to periodic degenerated Dirac measure solutions, which means that the population asymptotically consists of individuals at the same age. Such a phenomenon is observed in nature in some insects populations.

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Modeling tumor growth and anti-angiogenic drugs efficacy: from multiscale to mixed-effect models

The dynamics associated with treating cancer with anti-angiogenic drugs are complex and must be understood in order to maximize the benefits of such a therapy. Mathematical modeling can be used as a strategy to quantify the dynamics of the interactions between tumor growth, vasculature generation and anti-angiogenic

treatment. Multiscale approaches offer powerful tools to model multiple biological interactions in time and space. However, the number of parameters and the time to simulate often restrict the applications of these models for real data analysis. Here, we present both a multiscale and a reduced model of vascular tumor growth that we apply to the analysis of longitudinal tumor size data in mice bearing colorectal tumors and treated with sunitinib, a potent anti-angiogenic compound. The reduced model is a mixed-effect non-linear ODE model. Mixed-effect parameter estimation aids in quantifying the typical dynamics within a population as well as those that contribute to individual dynamics. The developed model accurately predicts tumor growth dynamics in mice and allows us to study the multifaceted effects of anti-angiogenic treatment.

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Joint work with: *N. Komarova*

Treatment of chronic lymphocytic leukemia (CLL) with new targeted inhibitors

Chronic lymphocytic leukemia (CLL) is a malignancy of B cells and is the most common leukemia in adults. Patients have typically been treated with a combination of chemo and immuno-therapies. These have resulted in relatively good responses except in high risk patients in which p53 has been inactivated. Recently, new, targeted treatment approaches have been developed which have so far shown great promise in the clinic. One such drug is the Bruton tyrosine kinase (BTK) inhibitor ibrutinib. Upon treatment initiation, a lymphocytosis phase is observed during which the number of CLL cells can show a pronounced rise in the blood. The number of cells eventually reaches a peak and declines during therapy. It is thought that the lymphocytosis phase represents the redistribution of cells from tissue where the majority of the disease burden lies (lymph nodes, spleen, bone marrow) into the blood. One question is whether upon treatment the majority of the tissue CLL cells redistributes to blood, or whether only a small fraction of the tumor cells redistributes while a large fraction of tissue cells dies. We used mathematical models, applied to clinical data, in order to kinetically characterize the treatment responses to ibrutinib, and to investigate this question. In addition, the measurements of all crucial CLL parameters allowed us to build evolutionary mathematical models in order to study the emergence of ibrutinib-resistant cells. An important aim of this work is the development of a predictive computational

framework that can give personalized predictions for patients about the long-term outcome of ibrutinib therapy.

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Predator–prey model with diffusion and indirect prey-taxis

In a join work with Jose Ignacio Tello we analyze predator-prey models in which the movement of predator searching for prey is the superposition of random dispersal and taxis directed towards gradient of concentration of some chemical released by prey (e.g. feromon), model II, or released from damaged or injured prey due to predation (e.g. blood), model I. Parabolic chemotaxis equations for predator and chemoattractant are coupled with logistic o.d.e. describing the dynamics of prey population. Global-in-time solutions are proved and stability of homogeneous steady states is shown by linearization. For space dimension $N \leq 2$ the basin of attraction of such a steady state is characterized by means of nonlinear analysis. In contrast to model II, model I possesses, at least in the case N=1, spatially inhomogeneous steady states.

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A bovine babesiois model with dispersion

Bovine Babesiosis (BB) is a tick borne parasitic disease with worldwide over 1.3 billion bovines at potential risk of being infected. An important factor in the spread of the disease is the dispersion or migration of cattle as well as ticks. In this talk, we study the effect of this factor. We introduce a number P - a "proliferation index", which plays the same role as the basic reproduction number $R0$ with respect to the stability/instability of the disease-free equilibrium, and observe that P decreases as the dispersion coefficients increase. We prove, mathematically, that if $P > 1$ then the tick fever will remain endemic. We also consider the case where the birth rate of ticks undergoes seasonal oscillations. Based on data from Colombia,

South Africa, and Brazil, we use the model to determine the effectiveness of several intervention schemes to control the progression of BB.

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Joint work with: *K. Clark, C. Fan, A. Nkwanta*

A mathematical model of Nutrients-Phytoplankton-Oysters in a bay ecosystem

In this talk, we will introduce a simple mathematical model that describes the interactions of nutrients, phytoplankton and oysters in a bay ecosystem. Using the model, we will derive verifiable conditions for the persistence and extinction of phytoplankton and oysters in the bay system. In addition, we will use sensitivity analysis and simulations to illustrate how human activities such as increased oyster harvesting and environmental factors such as increased nutrients inflow and increased oyster filtration can generate phytoplankton bloom with corresponding oscillations in the oyster biomass and nutrients level in the bay ecosystem.

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Joint work with: *R. Rudnicki*

Phenotypic evolution in sexual populations

In order to describe evolution of sexual populations, we study constant lifetime phenotypic traits of individuals and build a stochastic process as an individual-based model including mating/inheritance, intra-specific competition and mortality at trait-dependent rates. When the number of individuals tends to infinity, we state a law of large numbers: suitably rescaled stochastic processes tend in Skorokhod space to a nonlinear measure-valued evolution equation. In the case of hermaphroditic populations with random mating the limiting equation contains a bilinear mating-inheritance operator; a particular case is the Tjon-Wu equation, which appears as a description of the energy distribution of colliding gas particles. Under suitable conditions, we prove the asymptotic stability result: the

distribution of the phenotypic traits in the population converges to a stationary distribution as time tends to infinity. As a by-product, we obtain Lasota-Traple theorem concerning asymptotic stability of the Tjon-Wu equation. In case of two-sex populations, we obtain a system of two nonlinear transport equations and prove similar asymptotic stability result: under some conditions trait distributions of males and females tend to a stationary distribution as time goes to infinity. The stationary distribution is identical for males and females, provided the phenotypic trait is non-sex-linked.