

BOOK OF ABSTRACTS

Scientific and Organizing Committee

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and Computer Science





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Jacek Banasiak

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Delayed stability switches and canard solution in mathematical biology

Classical Tikhonov theorem allows for approximation of singularly perturbed systems of differential equations by solutions on a limit manifold provided It is hyperbolic and isolated. When there are multiple and intersecting limit manifolds, one expects the solutions of the original problem to follow their attracting branches. However, in many cases the original solution follows the repelling branch of the limit manifold. Such solutions are related to famous canard solutions. In this talk we shall present a theory of such solutions for planar monotone systems such arise in analysis of predator-prey models.

Agnieszka Bartłomiejczyk

GDAŃSK UNIVERSITY OF TECHNOLOGY e-mail: agnes@mif.pg.gda.pl Joint work with: A. Bartłomiejczyk, M. Bodnar, M.J. Piotrowska

Mathematical analysis of a generalised p53-Mdm2 protein gene expression model

We study the asymptotic behaviour of the solutions of the p53-Mdm2 model proposed by Monk in 2003 [1]. The p53 gene is crucial for cellular inhibition of the angiogenesis process, while Mdm2 is a negative regulator of the p53 tumour-suppressor. We investigate the stability of the positive steady state and perform some numerical experiments. We formulate the conditions which guarantee the occurrence of the Hopf bifurcation and we prove its stability.

1. N.A. Monk, Oscillatory expression of Hes1, p53, and NF-eB driven by transcriptional time delays, *Curr. Biol.* **13**(2003) 1409–1413.

Piotr Biler

MATHEMATICAL INSTITUTE, UNIVERSITY OF WROCLAW e-mail: Piotr.Biler@math.uni.wroc.pl Joint work with: *G. Karch, J. Zienkiewicz*

Singularity formation in chemotaxis models

Two-dimensional Keller–Segel models for the chemotaxis with are considered. Criteria for blowup of solutions are derived. Similarly, a criterion for blowup of solutions in terms of the radial initial concentrations is shown for radially symmetric solutions of chemotaxis in several dimensions.

Adam Bobrowski

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An averaging principle for fast diffusions in domains separated by semi-permeable membranes.

The talk is devoted to an averaging principle saying that fast diffusions on domains separated by semi-permeable domains may be approximated by certain Markov chains. More specifically, if diffusion's speed in each domain increases while the flux through the boundaries remains constant, in the limit, all points in each domain are lumped together to form a single state, and the limit process is a Markov chain with the state-space composed of these lumped states. The jump intensities in the chain are in direct proportion to the boundary sizes, and to the diffusion and permeability coefficients, and in inverse proportion to the sizes of the domains. We note that the principle just described is akin to the famous Freidlin–Wentzell averaging principle, though it is motivated by biological rather than physical models.

Predecessors of our principle have already been studied. A. Bobrowski and K. Morawska, in an attempt to reconcile two models of so-called neurotransmitters: a macroscopic one of Aristizabal and Glavinovič, and a microscopic one of Bielecki and Kalita, have shown that fast diffusions in three domains, corresponding to the so-called large, small, and immediately available pools, may be approximated by a Markov chain with three states. In fact, they proved merely a one-dimensional variant of this limit theorem, in which three 3-dimensional pools are replaced by three adjacent intervals. This result has later been generalized to the case of fast diffusions on arbitrary finite graphs by A. Bobrowski; in both cases the limit theorems are stated as convergence theorems for semigroups in Banach spaces of continuous functions. Later, A. Gregosiewicz has proved a related result in a space of integrable functions.

In this talk, we come back to the general, *d*-dimensional setting, and focus on analysis in L^p spaces $(p \ge 1)$. We discuss the main result in L^2 first, using convergence theorems for quadratic forms, and then extend the analysis to other L^p by extrapolation and interpolation techniques.

Marek Bodnar

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Influence of distributed delays on the dynamic of a simple gene expression model

In the Hes1 gene expression system the protein (in fact dimmers of the protein) bounds to the promoter of its own DNA blocking transcription of its mRNA. As a result of such negative feedback loop an oscillatory behaviour is observed experimentally. The classical model that describes this system consists of two ordinary differential equations with discrete time delay in the term that reflects transcription. However, transcription take place in the nucleus while translation in the cytoplasm. This means that delay present in the system is in fact larger than transcription time. Moreover, it is somehow distributed around some mean value. During the pretension the model of the Hes1 gene expression system is presented. The similarities and differences between the model with discrete and distributed delay is discussed. It turns out that in the case of distributed delay the steady state is more stable than in the case of discrete delay. Jan Burczak INSTITUTE OF MATHEMATICS, POLISH ACADEMY OF SCIENCES e-mail: jb@impan.pl Joint work with: Rafael Granero-Belinchón

Smoothness of 1D fractional Keller-Segel system with critical and supercritical diffusion

There is a strong evidence, both theoretical and experimental, that feeding strategies based on isotropic α -stable Lévy processes (generated by $(-\Delta)^{\frac{\alpha}{2}}u$) are both closer to optimal than Brownian motion (generated by $-\Delta u$) and indeed used by certain organisms, especially in low-prey-density conditions. Hence it is justified to consider the *fractional* (parabolicelliptic) Keller-Segel equations:

$$u_t + (-\Delta)^{\frac{\alpha}{2}} u = -\chi \operatorname{div} (u \nabla v),$$

$$-\Delta v = u - \langle u \rangle.$$
(1)

Let us focus on the case of one space dimension D = 1. Then problem (1) has global-in-time, regular solutions for $\alpha > 1$ as well as $\alpha = 1$ with small data. Blowups occur for $\alpha < 1$ – see [1], [5] and [2]. Consequently, the case $\alpha = 1$ seemed critical: thus in [1] the authors conjecture a blowup for large data.

It my talk I will show that in fact the opposite claim holds and that, having added to $(1)_1$ logistic damping ru(1-u), the solutions are smooth also in the supercritical regime $\alpha > max(1-r/\chi, 0)$. This is joint work with Rafael Granero-Belinchon (Davis), see [3,4].

- 1. Bournaveas, N., Calvez. V., The one-dimensional Keller-Segel model with fractional diffusion of cells, Nonlinearity, 23(4):923, 2010.
- 2. Burczak, J., Granero-Belinchón, R., Boundedness of large-time solutions to a chemotaxis model with nonlocal and semilinear flux, to appear in Topological Methods in Nonlinear Analysis, for a preliminary version, see arxiv preprint arXiv:1409.8102 [math.AP].
- 3. Burczak, J., Granero-Belinchón, R., *Keller-Segel meets Burgers on* S¹, submitted, for a preliminary version, see arxiv preprint arXiv:1504.00955 [math.AP].
- 4. Burczak, J., Granero-Belinchón, R., *Global solutions for a supercritical drift-diffusion equation*, submitted, for a preliminary version, see arxiv preprint arXiv:1507.00694 [math.AP].
- Escudero., C., The fractional Keller-Segel model, Nonlinearity, 19(12), 2006, 2909 2918.

Vincenzo Capasso

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Regional control for a class of spatially structured epidemics: Think globally, act locally

A review will be presented of recent research carried out by the speaker on optimal control problems related to spatially structured epidemics mediated by environmental pollution.

A relevant problem, related to the possible eradication of the epidemic, is the so called zero stabilization. In a series of papers, necessary conditions, and sufficient conditions of stabilizability have been obtained. It has been proved that it is possible to diminish exponentially the epidemic process, in the whole habitat, just by reducing the concentration of the pollutant in a nonempty and sufficiently large subset of the spatial domain. The stabilizability with a feedback control of harvesting type is related to the magnitude of the principal eigenvalue of a certain operator. Finally the problem of finding the optimal position (by translation) of the support of the feedback stabilizing control will be discussed in order to minimize both the infected population and the pollutant at a certain finite time.

Vincenzo Capasso

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Deterministic approximation of stochastic multiparticle systems

Scope of this lecture is an introduction to the possible approximation of a system of stochastic differential equations modelling a population of individuals subject to mutual interaction and random dispersal; possible applications are related to the collective behaviour of individuals in swarms, herds, etc. Conditions are presented under which the stochastic system, in the limit of a large number of individuals, may be described in terms of nonlinear deterministic reaction-diffusion system, according to the paradigm of "propagation of chaos". This kind of approach, already well established in the general framework of Statistical Physics, has gained increasing attention since it also provides a framework for the modelling, analysis, and simulation of agent based models in Biology, Economics and Finance.

Jean Clairambault

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An evolutionary perspective on cancer, with applications to anticancer drug resistance modelling

I will present an evolutionary viewpoint on cancer, seen as the 2 time scales of (largetime) evolution in the genomes and of (short-time) evolution in the epigenetic landscape of a constituted genome. These widely metaphoric views, based on works by Lineweaver, Davies and Vincent (cancer as anatomically localised backward evolution in multicellular organisms) and by Sui Huang and collaborators (revisited Waddington epigenetic landscape), respectively, may serve as guidelines to propose a global conception of cancer, including towards possible innovating therapeutic strategies.

The question of drug-induced drug resistance in cancer will be considered in this framework, and a modelling setting, relying on phenotype-structured reaction-diffusion-advection equations, will be presented and interpreted biologically, speculating on the evolutionary mechanisms represented by the terms in the equations. Possible therapeutic consequences will be discussed.

This talk will be an enriched and re-interpreted version of a previous one on modelling drug resistance in cancer, that I gave at the Micro-Macro conference in Będlewo in June 2015. It presently aims to offer a rational and integrative - in the sense of systems biology - perspective on cancer, with mathematical tools to predict and possibly control its evolution by combinations of drugs and of other means, and without focusing on such and such intracellular druggable signalling pathway.

Jean Clairambault

JACQUES-LOUIS LIONS LABORATORY, INRIA MAMBA TEAM & UPMC, PARIS, FRANCE e-mail: jean.clairambault@inria.fr

Drug resistance in cancer: perspectives in therapeutic control

Drug-induced drug resistance, the question we are tackling from a theoretical 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 modelling framework of adaptive dynamics I will present is more likely to correspond biologically 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.

The built-in targets for theoretical therapeutic control present in our models are not supposed to represent well-defined molecular effects of the drugs in use, but rather functional effects, i.e., related to cell death (cytotoxic drugs), or to proliferation in the sense of slowing down the cell division cycle without killing cells (cytostatic drugs). We propose that cell life-threatening drugs (cytotoxics) induce by far more resistance in the highly plastic cancer cell populations than drugs that only limit their growth (cytostatics), and that a rational combination of the two classes of drugs may be optimised to propose therapeutic control strategies to avoid the emergence of drug resistance in tumours.

The models used are nonlocal Lotka-Volterra-like integro-differential equations, controlled by continuous inputs to be optimised. Some theorems will be mentioned, and simulations will illustrate the biological and medical situations under description.

Antoni Leon Dawidowicz

FACULTY OF MATHEMATICS AND COMPUTER SCIENCE, JAGIELLONIAN UNIVERSITY e-mail: Antoni.Leon.Dawidowicz@im.uj.edu.pl Joint work with: D. Jabłczyk

Delayed differential equation with non-constant delay in biology. Modified step method.

Differential equations with delayed argument have numerous applications in biology, like e.g. in immunology, whether of epidemiology. These equation has the form

$$\frac{dx}{dt} = f(x(t), x(t-\tau))$$

where the set X of values of function x may be also multidimensional. We shall present the applications of more general equations i. e. equations of the form

$$\frac{dx}{dt} = f(x_t)$$

where $x_t: (-r, 0] \to X$ is defined by the formula

$$x_t(s) = x(t+s).$$

In our presentation we shall present the example of such equations in mathematical biology. For the equations of such type classical step method is not useful. The modification of this method will be presented.

Piotr Drygaś

RZESZÓW UNIVERSITY e-mail: drygaspi@ur.edu.pl

Effective properties of fiber biomaterials

According to Muskhelishvili's approach, two-dimensional elastic problems for media with non-overlapping inclusions are reduced to boundary value problems for analytic functions in multiply connected domains. Using a method of functional equations developed by Mityushev we reduce such a problem for a circular multiply connected domain to functional-differential equations. We present new analytical results for the effective planar elastic moduli of composites containing circular inclusions. We assume that the interface between the matrix and inclusions is either perfectly bonded. The obtained formulae can be used to model fiber biomaterials, for instance, to model carbon nano-composites which improve the functions of biomaterials. It is important that they are integrated by the organism without causing foreign body reaction.

Grzegorz Dudziuk

ICM, UNIVERSITY OF WARSAW e-mail: dudziuk@icm.edu.pl

A cellular heat shock response model and simulations

We present a model of cell response to a temperature stress. The model describes production of heat shock proteins in response to elevated levels of temperature-misfolded proteins. The misfolded proteins are refolded in the presence of the heat shock proteins. In our model, description of this phenomena and underlying cellular kinetics is achieved via a system of ordinary differential equations. Models of this kind were already investigated (e.g. Szymańska and Żylicz 2009; Rybiński et al. 2013; Sheff et al. 2015). Now, we continue exploration of the model.

- 1. Szymańska, Z., Zylicz, M., "Mathematical Modeling of Heat Shock Protein Synthesis in Response to Temperature Change", J. Theor. Biol., 259:562–569, 2009;
- 2. Rybiński, M., Szymańska, Z., Lasota, S., Gambin, A., "Modelling the efficacy of hyperthermia treatment", J R Soc Interface, 10:20130527, 2013;
- Scheff, J.D., Stallings, J.D., Reifman J., Rakesh V., "Mathematical Modeling of the Heat-Shock Response in HeLa Cells", Biophys J. 109(2):182–93, 2015.

Dominique Duncan

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Diffusion Component Analysis in Post-Traumatic Epilepsy

Epileptogenesis is common after traumatic brain injury (TBI), and because much is known about the physical history of post-traumatic epilepsy (PTE), it represents a near-ideal human model in which to study the process of developing seizures. The latency period between the injury and the development of seizures is usually short, with a median latency of one year, making it practical to study epileptogenesis with reasonable follow up periods. Using scalp EEG recordings for 29 patients as well as depth EEG recordings for 6 of those patients, the goal of our analysis is to find a way to quantitatively detect seizure onset post trauma. A novel approach based on the diffusion map framework, which is considered to be one of the leading manifold learning methods, is proposed. Diffusion mapping provides dimensionality reduction of the data as well as pattern recognition that can be used to distinguish different states of the patient, such as seizures and non-seizure spikes in the EEG. A new algorithm, which is an adaptation of diffusion maps, is developed to construct coordinates that generate efficient geometric representations of the complex structures in the data. This method is also adapted to the data to enable the extraction of the underlying brain activity. Some new, interesting and promising results showing how this algorithm is used to detect spikes in the EEG data as well as other changes over time will be presented. This nonlinear and local network approach has been used to determine if the early occurrences of specific electrical features of epileptogenesis, such as interictal epileptiform activity and morphologic changes in spikes and seizures, during the initial week after TBI predicts the development of PTE.

Dmitri Finkelshtein

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Travelling waves and long-time behaviour in a doubly nonlocal Fisher-KPP equation

We consider a Fisher–KPP-type equation, where both diffusion and nonlinear parts are nonlocal, with anisotropic probability kernels. Under minimal conditions on the coefficients, we prove existence, uniqueness, and uniform space-time boundedness of a positive solution. We investigate existence, uniqueness, and asymptotic behavior of monotone traveling waves for the equation. We also describe the existence and main properties of the front of propagation. Foryś Urszula INSTITUTE OF APPLIED MATHEMATICS AND MECHANICS, UNIVERSITY OF WARSAW e-mail: urszula@mimuw.edu.pl Joint work with: *E. Attia, M. Bodnar*

Angiogenesis model with Erlang distributed delays

We consider the model of angiogenesis process proposed by Bodnar and Foryś (2009) with time delays included into the vessels formation and tumour growth processes. Some results are stated for general distributions, while main results concerning stability are formulated for delays distributed according to the Erlang distribution.

Viktor Gerasimenko

INSTITUTE OF MATHEMATICS NAS OF UKRAINE e-mail: gerasym@imath.kiev.ua Joint work with: V.I. Gerasimenko

On kinetic evolution of condensed states of soft active matter

We develop a new approach to the description of the collective behavior of large entity systems of mathematical biology within the framework of the evolution of observables. This representation of the kinetic evolution seems in fact the direct mathematically fully consistent formulation modeling collective behavior of biological systems, since the notion of state is more subtle and implicit characteristic of living entities.

One of the advantages of the developed approach is the opportunity to construct kinetic equations in scaling limits, involving initial correlations, in particular, that can characterize the condensed states of soft active matter. We note also that a such approach is also related to the problem of a rigorous derivation of the non-Markovian kinetic-type equations from underlaying many-cell dynamics which make it possible to describe the memory effects of the kinetic evolution of cells.

Using suggested approach, we established the mean field asymptotic behavior of the hierarchy of evolution equations for marginal observables of a large system of interacting stochastic processes of the collisional kinetic theory modeling the microscopic evolution of soft active matter. The constructed scaling limit of a nonperturbative solution of this hierarchy is governed by the set of recurrence evolution equations, namely, by the dual Vlasov hierarchy for interacting stochastic processes.

Furthermore, we established that for initial states specified by means of a one-particle distribution function and correlation functions the evolution of additive-type marginal observables is equivalent to a solution of the Vlasov-type kinetic equation with initial correlations, and the mean field asymptotic behavior of nonadditive-type marginal observables is equivalent to the sequence of explicitly defined correlation functions which describe the propagation of initial correlations of soft active matter.

- 1. Gerasimenko V.I. and Fedchun Yu.Yu. On kinetic models for the evolution of many-entity systems in mathematical biology. J. Coupled Syst. Multiscale Dyn., 2013, 1 (2), 273–279.
- Gerasimenko V.I. and Fedchun Yu.Yu. On semigroups of large particle systems and their scaling asymptotic behavior. In: Semigroups of Operators – Theory and Applications. Series: Springer Proceedings in Mathematics and Statistics, Springer, 2015, 113, 165–182.

Damian Jabłczyk

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Delayed differential equation with non-constant delay in Biology. Modified step method.

Differential equations with delayed argument have numerous applications in biology, like e.g. in immunology, whether of epidemiology. These equation has the form

$$\frac{dx}{dt} = f(x(t), x(t-\tau))$$

where the set X of values of function x may be also multidimensional. We shall present the applications of more general equations i. e. equations of the form

$$\frac{dx}{dt} = f(x_t)$$

where $x_t: (-r, 0] \to X$ is defined by the formula

$$x_t(s) = x(t+s).$$

In our presentation we shall present the example of such equations in mathematical biology. For the equations of such type classical step method is not useful. The modification of this method will be presented.

Winfried Just

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Emergence of global firing patterns in neuronal networks with random connectivities

An assumption of random connectivities can be used to study expected dynamical properties of neuronal networks for which only some parameters of the connectivity, but not the entire wiring diagrams are known. We study the behavior of a class of such models near the critical connectivity where the most complex dynamics are expected. When the critical threshold is crossed, the local interactions of randomly connected individual neurons will self-organize into fairly simple global firing patterns. This presentation will illustrate how methods of random graph theory and dynamics combine to derive this kind of prediction. Most notably, our fairly basic questions about neuronal networks naturally lead to problems that appear to require development of new methods for the study of random structures.

Nobuyuki Kenmochi

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Mathematical model of biomass development

A mathematical model for biofilm development in a fluid is considered. The model consists of the Stokes equation with nonlocal convection, the nutrient transport equation with gradient constraint and the biofilm evolution equation with degeneracy and singularity. Our approach is based on the recent results of quasi-variational inequalities. Major difficulty arises in the mathematical treatment of the Stokes equation formulated on the unknown-dependent region. In this talk an appropriate approximation to the original system is proposed and an existence result is given.

Piotr Knosalla

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Some one dimensional aerotaxis model

A colony of bacteria lives in a capillary filled with oxygen dissolved in water. The metabolism of the bacteria depends on the concentration of oxygen, which plays the role of both attractant (at moderate concentrations) and repellent (at high and low concentrations). Aerotaxis is the movement of bacteria toward the optimal concentration of oxygen for their growth. The model consists of two parabolic equations considered on [0,1] with an appropriate boundary conditions. During the talk both stationary and evolutionary problems will be analyzed.

Yuri Kogan

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Analysis of a mathematical model of the canonical Wnt signalling pathway

Wnt signalling pathway controls cell proliferation and differentiation, in particular, in the adult stem cells. Its deregulation is implicated in cancer and other diseases. Understanding its details and learning how to manipulate it, both in wild-type and mutated cells, could help the development of new approaches in disease treatment. I will present results of the mathematical and computational modelling of the initial part of the pathway, from the extracellular ligands down to beta-catenin accumulation, including the effect of inhibitors. The results include model parameter estimation and validation by independent experimental data. The simulations of the model suggest insights regarding the ability to control the pathway function using external signals, even in the case of downstream mutations. These insights are also supported by the theoretical analysis. Taken together, our results suggest a practical approach to the estimation of the expected effect of inhibitors of Wnt signalling, alone and in combination, paving the way for the development of novel molecular therapies.

Mikhail Kolev

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On a mathematical model of tumor - immune system interactions

I will present a mathematical model describing the competition between tumor and immune system of an organism. Results of some numerical experiments will be shown.

Tadeusz Kosztołowicz

INSTITUTE OF PHYSICS, JAN KOCHANOWSKI UNIVERSITY IN KIELCE e-mail: tadeusz.kosztolowicz@ujk.edu.pl Joint work with: Katarzyna D. Lewandowska

Anomalous diffusion in a membrane system

We consider subdiffusion and slow subdiffusion in a system with a thin membrane. The anomalous diffusion parameters may be different in both parts of the system separated by the membrane. The equation describing anomalous diffuion contains time derivative of fractional order which is nonlocal in the time domain. Using the random walk model with discrete time and space variables the probabilities describing a particle's random walk are found. From the obtained probabilities we derive boundary conditions at the membrane. The boundary conditions, which contain Riemann-Liouville fractional time derivative, are rather unexpected and show that the 'memory effect' is created by the membrane. The model presented in this contribution is of a general nature and can be used to model anomalous diffusion in various biological systems.

- 1. T. Kosztołowicz, 'Random walk model of subdiffusion in a system with a thin membrane', Phys. Rev. E 91, 022102 (2015).
- 2. T. Kosztołowicz, 'Subdiffusive random walk in a membrane system. The generalized methods of images approach', J. Stat. Mech. P10021 (2015).

Jurij Kozicki UMCS e-mail: jkozi@hektor.umcs.lublin.pl

Nonlocality in a spatial ecological model

An infinite system of point entities in \mathbb{R}^d which reproduce themselves and die, also due to competition, is studied. The states of the system are probability measures on the corresponding configuration space. Their dynamics are described by solving the Fokker-Planck equation in a scale of spaces. The mesoscopic description is based on a nonlocal kinetic equation derived from that describing the evolution of states. The main aim of the talk is to analyze spatial properties of the solutions of the latter.

Jacek Kubiak CNRS e-mail: jacek.kubiak@univ-rennes1.fr Joint work with: *M. Dembowski, M. Lachowicz, M. Kloc, J. Malejczyk*

New model of M-phase entry with CDC6-dependent inhibition of CDK1 upon its activation

The cell cycle is composed of four main phases: G1, S, G2 and M. We are interested in M-phase regulation. During this phase of the cell cycle the cell undergoes division. Among crucial enzymes involved in the cell division CDK1 (Cyclin-Dependent Kinase 1) plays a crucial role. We found recently that CDK1 is regulated upon its activation during the entry into the M-phase by CDC6 protein. We show that CDC6-dependent mechanism inhibits CDK1 during the process of its activation. It may seem paradoxical that inhibition is involved in the process of CDK1 activation. However, this paradox has a deep biological significance. In fact it seems that a slow and highly regulated in time CDK1 activation is necessary for the normal M-phase entry and the cell division. Obviously, mathematical models describing the process of the M-phase entry so far did not include the inhibitory role of CDC6. We propose a novel mathematical model explaining the role of CDC6 in CDK1 activation and the relationship between other, so far known regulators of the process like phosphatase CDC25 and kinase Wee1.

Henryk Leszczyński

UNIVERSITY OF GDAŃSK e-mail: hleszcz@mat.ug.edu.pl Joint work with: *M. Lachowicz*

Modelling swarms

We are going to present new mathematical structures that can model swarming behaviour. These structures lead to interesting mathematical problems of blow-up versus global existence.

Maciej Leszczyński

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A mathematical model for virotherapy: formulation and initial analysis

Oncolytic viruses are genetically altered replication-competent viruses which infect, and reproduce in, cancer cells but do not harm normal cells. The problem with delivering such viruses is that it requires a temporary suppression of the immune system which otherwise attacks the virus. In this talk, we will present a mathematical model for a combination therapy which includes injections of oncolytic viruses along with inhibition of TNF- α produced by macrophages. We will give a preliminary analysis of the stability properties of the system along with numerical illustrations of the dynamics for varying constant viral injections. This analysis will serve us as a background for an optimal control problem in which we will optimize the therapy performance.

Katarzyna Lewandowska

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Subdiffusion – reaction processes in a membrane system

We study subdiffusion – reaction processes in a system with partially absorbing or partially reflecting walls. We consider this problem in two ways. Firstly, we start off the analysis of the problem with a random walk model in a system with both discrete time and discrete space variables. Then the system with discrete variables is transformed into a system with both continuous time and continuous space variables. This method allow us to determine Green's functions without a necessity of solving a fractional differential subdiffusion – reaction equation with boundary conditions at the walls. Employing a simple phenomenological model, we also derive equations related to the reaction parameters used in the considered models. Secondly, we consider a fractional differential subdiffusion – reaction equations which allow us to solve them approximately in modelling carious lesion progress.

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- 2. T. Kosztołowicz, K.D. Lewandowska, Application of fractional differential equations in modelling the subdiffusion-reaction process, Math. Model. Nat. Phenom. 8, 44 (2013).
- 3. K.D. Lewandowska, T. Kosztołowicz, Application of diffusion reaction equations to model carious lesion progress, Physica A **391**, 2608 (2012).

Yoram Louzoun

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Diffusion rate determines transition between directed percolation and mean field induced collapse in birth death processes

Resource based spatially extended birth death processes are observed in multiple biological scenario, including among others: ecology (nutrients and growth), immunology (antigens and lymphocytes) and molecular biology (signaling molecules initiating signaling cascades). Such systems often exhibit an extinction-proliferation transition, where varying properties of the nutrients can lead to either extinction or survival of the reactants or some of the reactant populations. We show in a large variety of such system that when the stochasticity of the reactions, the presence of discrete reactants and their spatial distribution is incorporated into the analysis, a non-uniform reactant distribution emerges, even when all parameters are uniform in space. We then use tools from ODEs, percolation theory and self-organized criticality to show that in such systems that he overall survival of the reactant population is based on the size and shape of the reactant aggregates and their distribution in space, which are determined by the reactant diffusion rate. An interesting result is that for a large class of models, high reactant densities and coexistence between different types of reactants are limited to intermediate diffusion rates. We give multiple examples of such system, including the coexistence of similar species in ecological systems, the dynamics of host-parasite systems and .bacteria-phage interactions. We provide a generic explanation for this behavior. The set of models presented here provides a new insight on the population dynamics in chemical, biological and ecological systems.

Vladmir Mityushev

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Pattern formation and representative volume element

We discuss a new theory of the 2D representative volume element (RVE) made from a collection of non-overlapping disks on the plane. The number of disks and their locations can be arbitrary. Hence, any two-phase structure can be discussed since it can be approximated by an appropriate disks packing. The proposed theory is based on the decomposition of the effective property tensors which can be considered as an expansion on the "basic elements" which depend only on locations of the disks. These elements are expressed in terms of the Eisenstein series. The representative cell (RVE) is defined as the minimal size cell corresponding to the set of basic elements calculated for the considered structure. This approach has advantages in comparison with the traditional statistical theory of the RVE, frequently used but hardly computationally realized. An algorithm to determine the representative cell for a given structure is constructed and applications to pattern formation are discussed.

Andrzej Nowakowski

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ϵ – optimality conditions for existence of atherosclerosis

There are several mathematical models that describe the growth of a plaque in the artery. The most recent and most comprehensive model, in [2], [3], includes smooth muscle cells, \mathbf{T} cells and various cytokines satisfying a system of 17 PDEs. In [2] is determined by rigorous mathematical analysis, whether small steady state plaques exist and whether they are stable. The aim of the paper is to introduce to the system of 17 PDEs controls functions which will allow to steer the system to minimize some cost functional defining a plaque in artery in a given final time.

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- 2. A. Friedman, W. Hao, A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors, Bull. Math. Biol. (2014) 1–24.
- 3. W. Hao, A. Friedman, The LDL-HDL profile determines the risk of atherosclerosis: a mathematical model, PLoS ONE 9(3) (2014) e90497.

Zbigniew Peradzyński

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Nonlocal Travelling Waves of Calcium Concentration

According to L. Jaffe there is a number of cells where the calcium waves are supported by the substantial inflow of calcium trough the cell membrane from the intercellular space. The influx of calcium is controlled 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 (10-20 μ m). 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.

We propose a mathematical theory of such (Calcium Induced Calcium Influx) waves. The model is based on a system of reaction diffusion system for calcium and buffer proteins coupled with the mechanical equations for the traction forces produced by the cortex.

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

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Coalescing random jumps in continuum

A Markov-type infinite system evolution of point entities in \mathbb{R}^d is described. The elementary acts are repulsive jumps and coalescing jumps. The model is considered in both microscopic and mesoscopic scope. In the microscopic approach the states are measures on a configuration space. Their evolution is obtained using an equation for corresponding correlation functions. The mesoscopic description is obtained by a Vlasov-type scaling, which leads to a kinetic equation. The model can be considered as a simple one-population predatory model.

Monika J. Piotrowska

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Can CA approach help in planning a multi-dose radiotherapy?

Multi-fraction radiotherapy protocols (fractional dose and timing) currently used in the clinic are the product of human selection based on received wisdom, physicians' experience and intra-day patient timetabling. However, due to combinatorial considerations, the potential treatment protocol space for a given total dose or treatment length is enormous and beyond the capacity of traditional in-vitro methods to explore. In contrast, high fidelity numerical simulation of tumour development under pseudo-irradiation treatment is well suited to the challenge. Building on our previous single-dose numerical simulation model of EMT6/Ro spheroids, a multi-dose irradiation response module is developed and calibrated. With the developed model a constrained, non-linear, search for better performing candidate protocols is conducted within the vicinity of two benchmarks by genetic algorithm (GA) techniques. Candidate protocols were discovered which by the GA which conferred an average of 9.4%(max benefit 16.5%) and 7.1% (13.3%) improvement (reduction) on tumour cell count compared to the two benchmarks, respectively. Noticing that a convergent phenomenon of the top performing protocols was their temporal synchronicity, a further series of numerical experiments was conducted with periodic time-gap protocols (10 h to 23 h), leading to the discovery that the performance of the GA search candidates could be replicated by 17-18 h periodic candidates. The study thus provides powerful evidence towards the hypothesis that even simple inter-fraction timing manipulations may present a facile, and highly cost-effective means of improving clinical efficacy.

Camille Pouchol JACQUES-LOUIS LIONS LABORATORY, INRIA MAMBA TEAM & UPMC, PARIS, FRANCE e-mail: pouchol.camille@gmail.com Joint work with: J. Clairambault, A. Lorz E. Trélat

Some phenotype-structured integro-differential models, asymptotic analysis and optimal control

We consider integro-differential models for which the structuring variable is a continuous phenotype. Such models are known to lead to concentration of populations on one or several phenotypes.

The first model aims at investigating optimal therapeutical strategies combining cytotoxic and cytostatic drugs. The difficulty comes from the usual pitfalls of such treatments: resistance to the therapy must be avoided, and toxicity to healthy cells must be taken into account. Two populations of healthy and cancer cells, both structured by a phenotype representing resistance to the drugs, are thus considered. The optimal control problem consists of minimizing the number of tumorous cells after some fixed time T, with constraints on the number of healthy cells as well as their proportion with respect to the total number of cells. Together with simulations, we conjecture a best administration strategy for T large.

The second model is designed to study the mutualistic interaction between cancer cells and adipocytes in breast cancer. Biological evidence indeed suggests that the interaction results in a greater proliferation of cancer cells and a change of phenotype in both populations: cancer cells become more motile as they undergo the epithelial-to-mesenchymal transition, and adipocytes change size and other characteristics to become what is now commonly called Cancer Associated Adipocytes (CAAs). The cancer population is thus structured by a phenotype representing motility, the adipocyte population by a phenotype representing how much the cell has become a CAA. We analyze the model and prove that some asymptotic properties known for a single equation can be extended to a system. Elżbieta Ratajczyk

Łódź UNIVERSITY OF TECHNOLOGY e-mail: 192529@edu.p.lodz.pl Joint work with: *M. Leszczyński*

A mathematical model for virotherapy: formulation and initial analysis

Oncolytic viruses are genetically altered replication-competent viruses which infect, and reproduce in, cancer cells but do not harm normal cells. The problem with delivering such viruses is that it requires a temporary suppression of the immune system which otherwise attacks the virus. In this talk, we will present a mathematical model for a combination therapy which includes injections of oncolytic viruses along with inhibition of TNF- α produced by macrophages. We will give a preliminary analysis of the stability properties of the system along with numerical illustrations of the dynamics for varying constant viral injections. This analysis will serve us as a background for an optimal control problem in which we will optimize the therapy performance.

Massimiliano Rosini

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Macroscopic models for pedestrian flows with non-local point constraints

In this talk we present the recent results we achieved for one-dimensional conservation laws with variable unilateral point constraints on the flow. Evacuation of a crowd through an exit door is one of the main motivating applications behind these equations.

More precisely, we first consider the Cauchy problem for a scalar conservation law with a *non-local* point constraint proposed in [3]. In particular, as underlined in [4], we also show how the regularity of the constraint operator impacts the well-posedness of the problem. We then present the *ad hoc* simulations performed in [5] to qualitatively validate the model by proving its ability to reproduce typical phenomena at the bottlenecks, such as the faster-is-slower effect and the Braess' paradox.

The final part of the talk deals with the Cauchy problem for the 2×2 system of conservation laws introduced in [1,7] with a point constraint, see [3,6].

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- 3. B. Andreianov, C. Donadello and M. D. Rosini, A second order model for vehicular traffics with local point constraints on the flow. *submitted*.
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- 7. H. M. Zhang, A non-equilibrium traffic model devoid of gas-like behavior. *Transporta*tion Res., Part B **36** (2002) 275–290.

Ryszard Rudnicki

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Asymptotic properties of some phenotypic evolution models

We present an individual based model of phenotypic evolution which includes random and assortative mating process of individuals. By increasing the number of individuals to infinity we obtain a nonlinear transport equation, which describes the evolution of distribution densities of phenotypic trait. In the case of random mating we show that this equation has one-dimensional attractor. In the case of assortative mating we expect convergence of the phenotype profile to multimodal limit distributions. This result suggests that assortative mating can lead to polymorphic population and adaptive speciation.

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Cristiana Silva

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The effect of migration on tuberculosis epidemic

We propose a new tuberculosis (TB) mathematical model, with 25 state-space variables where 15 are evolution disease states (EDSs), which takes into account the flux of populations between a country of origin (A) and a community (G) plus the rest of the population (C) of a host country (P). Contrary to some beliefs, related to the fact that agglomerations of individuals increase proportionally to the disease spread, analysis of the model shows that the existence of communities are simultaneously benefic for the TB control from a global and regional viewpoint. We prove the existence of an optimal ratio for the distribution of individuals in C versus G, which minimizes the reproduction number R_0 . A sensitivity analysis is derived and we show that the TB transmission rate β does not act linearly on R_0 , as it is common in compartment models where system feedback or group interactions do not occur. Further, we find the most important parameters for the increase of each EDS. The model and techniques proposed are applied to a case-study with concrete parameters, which model the situation of Angola (A) and Portugal (P), in order to show its relevance and meaningfulness.

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Calcium homeostasis model

We examine mathematical properties of 5-dimensional nonlinear ODE and DDE systems describing calcium homeostasis in the rat introduced by D. Granjon, O. Bonny, and A. Edwards, in order to investigate the mechanisms that lead to hypercalciuria. The crucial quantity the authors' aim to predict is the concentration of ionised calcium (Ca^{2+}) in the plasma (the liquid part of the blood). The equations determine total amounts of PTH inside parathyroid glands, PTH in plasma, concentration of calcitriol in plasma, concentration of ionised calcium (Ca^{2+}) in plasma, and total amount of calcium in rapidly exchangeable pool in bones. We analyse the stability of the stationary solution either from theoretical, or from computational point of view.

Paulina Szymańska

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Energy costs of information transmission in small regulatory circuits

Every biological system transmit information about the state of its elements. In order to do so, it needs energy that gets dissipated during the process. We analyse a simple regulatory system of an input and a delayed output and we measure information transmitted between them at a given energy constraint. We ask for the topology of the circuit (i.e., the rates of transition between the states) that optimizes the information transmitted.

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Diagolalization of ternary diffusion systems

It is known that all biological gas exchange processes involve more than two gas species. We analyse ternary diffusion couples with mass-balance and no-flux conditions. Two methods of diagonalization will be presented. Our approach explains why such systems are strongly nonlocal.

Dariusz Wrzosek

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Interspecies competition and chemotaxis

We consider the model of competition of Lotka-Volterra type in which the competitors are distributed in space and may migrate according to random dispersal and some chemotaxis mechanism. The case when one of the competing species is capable to avoid encounters with the other and the problem of spatial segregation are studied.