Structured Integro-Differential models in Mathematical Biology

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Remarks on state-dependent delay

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State-dependent delays arise naturally in structured population models, but they create technical difficulties.
The aim of this talk (which isn't prepared yet) is most likely to review several aspects of state-dependent delay.

Aggregation models for protein polymerization & application to amyloid diseases

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Amyloid diseases are a group of diseases which involve the aggregation of misfolded proteins, called amyloid, which are specific for each disease (PrP for Prion, Abeta for Alzheimer's). Elucidating the intrinsic mechanisms of these chain reactions, most probably specific for each disease, is a major challenge of molecular biology. Up to now, only partial answers have been provided, due to the complexity of the considered processes, which may involve an infinite number of species and reactions (and thus, an infinite system of equations). Mathematical modelling, simulation and parameter estimation methods are thus required.

In this talk I will review existing results and explain our approach, which is based on combined ODE-PDE (and more recently stochastic) models. I will also develop some of our recent findings, both in a mathematical side and for specific applications.

Nonlinear cell population model structured by molecular content for the differentiation process

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In this talk, I will present a work in progress on cell differentiation models. The objective of this work is to combine gene expression models and structured cell population models. The general idea is that of the ``Waddington epigenetic landscape'', which basically says that cell fates are attractors of an underlying gene regulatory network. We are interested in this context how a cell population can achieve homeostasis.
I will first review important biological background. In particular, I will highlight the role of key regulatory proteins (transcription factors) for the activation of large scale gene expression programs and differentiation ``choice''. The recent evidence of stochasticity in gene expression in single cells is then an appealing explanation of apparent random fates of cells in \textit{in-vitro} cell culture differentiation experiments. I will also recall how biochemical signals are thought to regulate the population dynamics in different cell systems. %Recent experimental techniques have made possible to follow at the scale of indivual cells the level of expression of certain proteins during.
Then I will present the literature and recent results on stochastic gene expression models, for a single cell. I use the framework of piecewise deterministic Markov processes. The study of the probability density function leads to a Fokker-Planck-like equation that is a linear (mass-preserving) integro-differential equation. It is possible to include the division process in such framework (still under the Markovian hypothesis, though, that requires the cell cycle length to be exponentially distributed), and to obtain fairly general results for the long time behavior of such equations. Special cases lead to analytic solutions, suitable for a bifurcation study.
Finally, I will adress the issue of modelling the behavior of the whole population (rather than a single cell line). This leads to nonlinear structured cell population model, with nonlinear maturation rate. I will give specific cases where convergence towards non-trivial steady-states can be achieved. With the help of numerical solutions, I will compare different feedback strategies.
This work is performed during my stay as a ``post-doc'' in the MATCH laboratory, at the University of Heidelberg.

Inverse problem on a structured integro-differential model in population dynamics

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In this talk we consider a general growth-fragmentation model for a size-structured population of cells. In this model, the evolution of the population is driven by two process: a growth process by nutriment uptake for instance and a division or fragmentation process when a cell gives birth to two daughter cells. The experimental difficulty of following a cell from its birth to its division adress the following mathematical problem: how to estimate the division rate with knowledge of a sequence of measurements on the size repartition of the population? We give in this talk an attempt to answer this question.

Modelling stage-structured populations of crop pathogens: 1) under environmental change and 2) as part of a food web, using delay differential equations.

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Two examples of structured integro-differential models for populations of crop pathogens will be discussed. The first concerns a nematode species (the potato cyst nematode) whose stage durations are affected by temperature, such that higher temperatures will allow more generations per growing season. A model has therefore been developed to quantify how changes in climate will affect the impact of this pathogen on future potato crops. The second concerns a rice pest (the Brown Plant Hopper) which destroys large swathes of rice ('Hopper burn') in SE Asia. The Hopper is a host for various parasitoid species and also prey for spiders. Thus a model has been developed to investigate whether these parasitiod and predator species (which attack different stages of the Hopper life cycle) can be used to control Hopper populations and thus avoid the application of pesticides.

MULTISCALE MODEL ON OVARIAN FOLLICULAR DEVELOPMENT

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The development of ovarian follicles is a unique instance of a morphogenesis process still occurring during adult life and resulting from the interactions between somatic and germ cells. In mammals, the initiation of follicular development from the pool of resting follicles is characterized by an increase in the oocyte size concomitant with the surrounding somatic cells proliferating to build an avascular tissue called granulosa. I present a stochastic individual-based model describing the first stages of follicular development, where the cell population is structured with respect to age (progression within the cell cycle) and space (radial distance from the oocyte). The model accounts for the molecular dialogue existing between the oocyte and granulosa cells. Three dynamically interacting scales are considered in the model: (i) a microscopic, local scale corresponding to an individual cell embedded in its immediate environment, (ii) a mesoscopic, semi-local scale corresponding to anatomical or functional areas of follicles and (iii) a macroscopic, global scale corresponding to the morphology of the follicle.

Size-structured populations with distributed states at birth.

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Age-structured models have been employed successfully in population dynamics for a long time and are considerably well understood. In contrast to such models where every individual is born at the same age 0, size-structured models allow to take into account different, distributed birth sizes. «Size» here can be a quite general concept, for example mass, energy content or pathogen load in a disease model. This introduces a birth operator that takes values in an infinite-dimensional Banach space and complicates greatly the mathematical analysis. In this survey, we will describe some examples of models that we recently investigated in a series of joint papers with Jozsef Farkas (University of Stirling, United Kingdom). The emphasis will be on questions such as asymptotic growth for linear models and the existence and stability of steady states for nonlinear models.

Structured population model of clonal selection in acute leukemias

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Self-renewal is a constitutive property of stem cells. Testing the cancer stem cell hypothesis requires investigation of the impact of self-renewal on cancer expansion. To understand better this impact, we propose a mathematical model describing dynamics of a continuum of cell clones structured by the self-renewal potential. The model is an extension of the nite multicompartment models of interactions between normal and cancer cells in acute leukemias. It takes a form of a system of integro-dierential equations with a nonlinear and nonlocal coupling, which describes regulatory feedback loops in cell proliferation and dierentiation process. We show that such coupling leads to mass concentration in points corresponding to maximum of the self-renewal potential and the model solutions tend asymptotically to a linear combination of Dirac measures. Furthermore, using a Lyapunov function constructed for a finite dimensional counterpart of the model, we prove that the total mass of the solution converges to a globally stable equilibrium. Mathematical analysis suggests which mechanisms of clonal selection predict clonality observed in the course of disease.

A Singularly Perturbed HIV Model with Treatment and Antigenic Variation

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We study a within-host HIV differential equation model that considers both mutation and treatment with enzyme inhibitors. This model generalizes a number of other models that have been extensively used to describe the HIV dynamics.
Since the free virus dynamics occurs on a much faster time-scale than cell dynamics, the model has two intrinsic time
scales and should be viewed as a singularly perturbed system. Using Tikhonov's theorem we prove that the model can be approximated by a lower dimensional nonlinear model. Furthermore, we show that this reduced system is globally asymptotically stable by using Lyapunov's stability theory. This is joint work with N. Bobko (IMPA).

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

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

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Abstract
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 (that nevertheless may be experimentally identified and controlled in cell cultures, according to the drug and to the cell line at stake) of resistance structuring cancer cell populations. The models we propose rely on continuous adaptive dynamics of cell populations, and are amenable to predict 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 or not) 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 induction of emergent resistant cell clones due to mutations under drug pressure are 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 (model-guided) 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.

Integro-Differential Models in Epidemiology

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I shall discuss the use of integro-differential and related models in epidemiology, specifically to account for non-exponential waiting times in various infection states. The standard ODE formulation of the SEIR epidemic model assumes that latent and infectious periods are exponentially distributed, but these are poor descriptions of the true biological distributions. The question then becomes to understand the impact of non-exponential distributions on the dynamics of a model and on the predictions made using the model. We show that model-based estimation of the basic reproductive number (R_0) is particularly susceptible to distributional assumptions and that this can have important public health consequences. We shall also discuss implications for the endemic equilibrium and its stability.

Investigation of a Nucleated-Polymerization Model applied to Polyglutamine Aggregation

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Aggregation of polyglutamine (PolyQ)-containing proteins is responsible for several neurodegenerative disorders including Alzheimer's, Mad Cow and Huntington's diseases. PolyQ41 are peptides containing a repetition of 41 glutamine residues per monomer, which is a sufficient length to induce aggregation in vitro and in transfected cells. Due to its simplicity, PolyQ provides an excellent model to investigate nucleated polymerization. We can assume that neither fragmentation nor coalescence occur in a significant manner, which leads to a model that only includes nucleation (spontaneous reaction of i0 monomers into a nucleus) and polymerization (addition of one monomer to a given polymer).
To describe such nucleation and polymerization processes, deterministic models consist of huge systems of ordinary differential equations. The coefficients defining these equations are unknown, and thus we have an inverse problem. In this talk, we will first present a numerical scheme for the forward problem, necessary to solve the inverse problem, approximating the system of ordinary differential equations for a given set of parameters. The difficulty lays in the size difference between a single monomer and an aggregate which might be several orders of magnitude. For large polymers, the system of ODEs can be well approximated by a PDE, however for small polymer sizes this is by no means accurate. We will therefore present a mixed model where we solve the ODE up to a certain polymer size and use the PDE with boundary conditions derived from the ODE solution thereafter.
In the second part of this talk, we will focus on the actual aim of this project, the inverse problem and parameter estimation, using experimental data obtained from our collaborators (H.Rezaei et al., INRA). We will discuss possible statistical models for the error in the data collection process on the basis of residual plots between a set of experimental curves and the corresponding simulated ones with best fit parameters. By choosing the statistical model correctly, we are able to determine, amongst others, confidence intervals and standard errors for the estimated parameter sets. This will give us an indication about the size of the model parameters and thus a mean to quantify the quality of the inverse problem solution.

Adaptive evolution of a reversible phenotype in cancer cell populations, mediated by stochastic and drug-induced epimutations: individual-based and continuum representations

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Recent experiments on NSCLC-derived (PC9) cell lines revealed a sub-population of cells that, in response to anti-cancer drugs, were able to acquire transient drug-resistance [Sharma et al., Cell 141, (2010)]. Interestingly, this reversible drug-tolerant state was shown to be the result of epigenetic modifications, rather than genetic mutations. Motivated by these results, we formulate two mathematical models of phenotype variation in a cancer cell population in order to understand the mechanisms responsible for the reversible, drug-resistant phenotype observed in NSCLC-derived (PC9) cell lines. We assume that both stochastic variation in cell phenotype due to cellular noise and stress-induced adaption are functioning in parallel without genetic mutations. Both our individual-based model and structured PDE model, recover the evolution of the PC9 cells into the drug-tolerant cells in the presence of a cytotoxic drug therapy. They also capture the dynamics of drug-re-sensitisation, which were observed after drug-washout.

Structured equations for adaptation and evolution in cancer cell populations

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The emergence of resistance to anti-cancer therapies can be considered as a process of Darwinian micro-evolution in tumour cell populations. In fact, cancer cells with heterogeneous levels of proliferation and resistance can be seen as competing for space and resources (i.e. oxygen, glucose or other nutrients), under the selective pressure exerted by therapeutic actions. In this respect, partial differential equations for structured populations provide a promising research framework. They can be used as in-silico laboratories, where different hypothetical scenarios can be tested, in order to uncover mechanisms that underlie emergent features of tumour aggregates and support the design of more effective anti-cancer protocols. In this framework, we focus here on the evolution of phenotype-structured populations of cancer cells exposed to dynamic selective pressures, and adaptation in cancer cell populations structured by phenotypic traits and space variables.

Asymptotic optimization of linear growth-fragmentation processes

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I will present recent advances in the optimization of linear, finite dimensional models of growth-fragmentation processes. Consider a linear differential inclusion which preserves positivity. When the matrices are uniformly irreducible and bounded, there exists a unique Lyapunov exponent which characterizes the infinite horizon optimal growth of the linear system. Moreover this exponent is related to the critical viscosity solution of a Hamilton-Jacobi-Bellman equation. Existence of such a critical viscoisty solution is known as Fathi's weak-KAM theorem in Lagrangian dynamics. The corresponding Aubry set informs us about the optimal trajectories of the linear differential inclusion. The talk will be illustrated with numerical simulations of three dimensional systems.
This is a joint work with Pierre Gabriel (University of Versailles, France) and Stéphane Gaubert (Inria, Saclay, France).

A mathematical model of cell dynamics when cells are considered as punctual

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I will present a very simple model to describe cell trajectories when cells are considered as punctual and off external stimuli. Our assumption is that cell motion is due to fluctuations in protrusion activity. The results provided by this simple model will be compared with data in dimension one.

What triggers the bacterial division ?

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Models describing the growth of cell populations have been developed based on assumptions on the stochastic mechanisms underlying growth and division at the single cell level. In particular, two different models have been widely used for decades, assuming that cell division probability depends respectively on cell age (the renewal equation) or cell size (the size-structured or growth-fragmentation equation) - or both.
We confront these models with data on E. coli single cells growth, and develop a new estimation methodology, based on nonparametric functional testing within the PDE models, in order to test the hypothesis of an age-dependent versus size-dependent division rate. We conclude that in E. Coli, the division is controlled by a size-sensing rather than timing mechanism.
This is a joint work with M. Hoffmann, L. Robert and N. Krell.

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