Preface to Session 70 " Mathematical models and methods to investigate heterogeneity in cell and cell population biology "

Loic Barbarroux, Jean Clairambault, Nick Cogan, Jan Elias, Shalla Hanson, Marek Kimmel, Tommaso Lorenzi

Preface to Session 70 "Mathematical models and methods to investigate heterogeneity in cell and cell population biology"

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Abstract. This session investigates hot topics related to mathematical representations of cell and cell population dynamics in biology and medicine, in particular, but not only, with applications to cancer. Methods in mathematical modelling and analysis, and in statistical inference using single-cell and cell population data, should contribute to focus this session on heterogeneity in cell populations. Among other methods are proposed: a) Intracellular protein dynamics and gene regulatory networks using ordinary/partial/delay differential equations (ODEs, PDEs, DDEs); b) Representation of cell population dynamics using agent-based models (ABMs) and/or PDEs; c) Hybrid models and multiscale models to integrate single-cell dynamics into cell population behaviour; d) Structured cell population dynamics and asymptotic evolution w.r.t. relevant traits; e) Heterogeneity in cancer cell populations: origin, evolution, phylogeny and methods of reconstruction; f) Drug resistance as an evolutionary phenotype: predicting and overcoming it in therapeutics; g) Theoretical therapeutic optimisation of combined drug treatments in cancer cell populations and in populations of other organisms, such as bacteria.

Keywords: Cell population dynamics, Ordinary/partial/delay differential equations, Physiologically structured models, Spatio-temporal dynamics, Agent-based models, Cell fate decision, Reaction-diffusion equations, Genotype/phenotype evolution, Probabilistic models, Single cell/cell population models, Drug tolerance, Persisters, Cancer, Immune response, Biofilms, Treatment optimisation
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Speakers:
Loïc Barbarroux, Jean Clairambault, Nick Cogan, Ján Eliaš, Shalla Hanson, Marek Kimmel and Tommaso Lorenzi.

Loïc Barbarroux presents a multi-scale model of the CD8 immune response that reproduces the dynamics for both the primary response and the secondary responses. The intracellular model is a delay differential equation model describing the competition between the proteins Ki-67, which promotes cellular division, and Bcl-2, which promotes cell survival. Cellular heterogeneity in the modeled population plays a key role in the phenomena occurring at the cellular population scale since the fate of each cell, and its interactions with other cells depend on its intracellular content, represented by its Ki-67/Bcl-2 maturation state. These two maturities are then included in a maturity-structured transport equation which describes the population scale.

Jean Clairambault presents results on optimisation of combined anticancer treatments using a model of adaptive dynamics consisting of PDEs structured in a phenotypic trait representing drug resistance - the structure variable carrying the heterogeneity that is focused here - in cancer cell populations. Furthermore in this presentation are sketched general principles for establishing innovating strategies to understand and fight cancer in an evolutionary framework, with respect to both long-term genotype (mutations) and short-term phenotype (epimutations) evolution.

Nick Cogan analyses resistance to antibiotics in bacterial populations that, among other tolerance mechanisms, use phenotypic, i.e., plastic, adaptation. Even though these so-called persisters display complex strategies that as yet are not completely understood, it is possible to represent such tolerance dynamics by systems of partial, and subsequently ordinary, differential equations, on which methods of optimal control by externally added terms impinging on the bacterial growth rate, representing delivery of antibiotics, are proposed to eradicate the bacterial population.

Ján Eliaš considers intracellular dynamics of the p53 protein which allows for DNA repair or eliminates cells from becoming malignant - the two properties attributing to tumour suppressing function of p53. According to recent

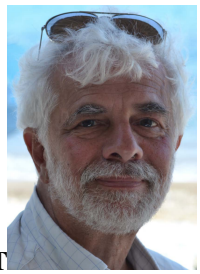
[1] See JC's short CV at the end of this preface

experiments, spatio-temporal dynamics of p53 can be considered as a marker of the chosen cell fate in response to DNA damage. In this presentation he proposes a spatio-temporal reaction-diffusion model for activation and regulation of p53 and we suggest further applications of this and similar models in anticancer treatment.

Shalla Hanson reviews published biological data from which several opposing theories describing the initiation of the T-cell response to pathogens have been developed, discusses principal population-level implications of these theories, and examines the consistency of several recently published mathematical models with the data presented. The presentation also summarizes key results from a delay differential equation model of T-cell differentiation which seeks to unify the opposing but not so disparate theories.

Marek Kimmel presents a brief study of conditions for fixation of a cancer driver mutation if selective pressures change during individual's lifetime. A branching process model is used to represent the pre-selection stage, which leads to creation of highly heterogeneous subclones of transformed cells. A Moran model with selection is used to represent the second phase, which leads to development of a primary tumor. Simple calculations allow determining feasibility of the mechanism proposed.

Tommaso Lorenzi, starting from published in-vitro observations on the emergence of so-called tolerant persisters in a cancer cell population submitted to high doses of anticancer drugs, proposes two different models, one agent-based, and the other relying on a phenotype-structured partial differential model, to account for the biological phenomena. Both models are relevant to represent the observed dynamics of tolerance, in particular its total reversibility when the drug is withdrawn. Different scenarios are examined in the models and further biological experiments are suggested.



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Research topics: mathematical models for biology and medicine
- Evolution of phenotypes in cancer cell populations towards drug resistance
- The cell division cycle and its physiological and pharmacological control in cell populations
- Physiologically structured partial differential equation models for cell population dynamics
- Molecular pharmacokinetics-pharmacodynamics (PK-PD) of anticancer drugs
- Pharmacotherapeutic optimisation in oncology w.r.t. toxic side effects and drug resistance