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ACTIVITY
REPORT

Project-Team

MAMBA

Modelling and Analysis for Medical and Biological Applications

IN COLLABORATION WITH: Laboratoire Jacques-Louis
Lions (LJLL)

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life
Sciences

The Inria logo is a stylized, cursive script in red, positioned in the bottom right corner of the page.

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Project-Team MAMBA

Creation of the Project-Team: 2015 April 01

Keywords

Computer sciences and digital sciences

- A3. – Data and knowledge
 - A3.1. – Data
 - A3.1.1. – Modeling, representation
 - A3.4. – Machine learning and statistics
 - A3.4.6. – Neural networks
 - A3.4.7. – Kernel methods
- A6. – Modeling, simulation and control
 - A6.1. – Methods in mathematical modeling
 - A6.1.1. – Continuous Modeling (PDE, ODE)
 - A6.1.2. – Stochastic Modeling
 - A6.1.3. – Discrete Modeling (multi-agent, people centered)
 - A6.1.4. – Multiscale modeling
 - A6.1.5. – Multiphysics modeling
 - A6.2. – Scientific computing, Numerical Analysis & Optimization
 - A6.2.1. – Numerical analysis of PDE and ODE
 - A6.2.2. – Numerical probability
 - A6.2.3. – Probabilistic methods
 - A6.2.4. – Statistical methods
 - A6.2.6. – Optimization
 - A6.3. – Computation-data interaction
 - A6.3.1. – Inverse problems
 - A6.3.2. – Data assimilation
 - A6.4. – Automatic control
 - A6.4.1. – Deterministic control
 - A6.4.4. – Stability and Stabilization
 - A6.4.6. – Optimal control

Other research topics and application domains

- B1. – Life sciences
 - B1.1. – Biology
 - B1.1.2. – Molecular and cellular biology
 - B1.1.5. – Immunology

- B1.1.6. – Evolutionary biology
- B1.1.7. – Bioinformatics
- B1.1.8. – Mathematical biology
- B1.2. – Neuroscience and cognitive science
- B2. – Health
- B2.2. – Physiology and diseases
- B2.2.3. – Cancer
- B2.2.4. – Infectious diseases, Virology
- B2.2.6. – Neurodegenerative diseases
- B2.3. – Epidemiology
- B2.4. – Therapies
- B2.4.1. – Pharmacokinetics and dynamics
- B2.4.2. – Drug resistance
- B2.6.3. – Biological Imaging
- B9.6.4. – Management science

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2 Overall objectives

The MAMBA (Modelling and Analysis in Medical and Biological Applications) team is the continuation of the BANG (Biophysics, Numerical Analysis and Geophysics) team, which itself was a continuation of the former project-team M3N. Historically, the BANG team, headed by Benoît Perthame during 11 years (2003-2013), has developed models, simulations and numerical algorithms for problems involving dynamics of Partial Differential Equations (PDEs).

The dynamics of complex physical or biophysical phenomena involves many agents, e.g. proteins or cells. The latter can be seen as active agents. Mathematically, agents can be represented either explicitly as individuals with their dynamics modelled e.g. through branching trees and piecewise deterministic Markov processes (PDMP), or as deterministic or stochastic differential equations, or under certain conditions be grouped or locally averaged, in which case their dynamics is mimicked by Ordinary or Partial Differential Equations (ODEs/PDEs).

Biology and medicine presently face the difficulty to make sense of the data newly available by means of recent signal acquisition methods and to take appropriate actions through possible treatment pathways. Modeling through agent-based or continuous models is a unique way to explain (model) experimental or clinical observations and then compute, control and predict the consequences of the mechanisms under study. These are the overall goals of Mamba.

3 Research program

3.1 Introduction

Data and image analysis, statistical, ODEs, PDEs, and agent-based approaches are used either individually or in combination, with a strong focus on PDE analysis and agent-based approaches. Mamba was created in January 2014. It aims at developing models, simulations, numerical and control algorithms to solve questions from life sciences involving dynamics of phenomena encountered in biological systems such as protein intra-cellular spatio-temporal dynamics, cell motion, early embryonic development, multicellular growth, wound healing and liver regeneration, cancer evolution, healthy and tumor growth control by pharmaceuticals, protein polymerization occurring in neurodegenerative disorders, control of dengue epidemics, etc.

Another guideline of our project is to remain close to the most recent questions of experimental biology or medicine. In this context, we develop many close and fruitful collaborations with biologists and physicians.

We focus mainly on the creation, investigation and transfer of new mathematical models, methods of analysis and control, and numerical algorithms, but in selected cases software development as that of CellSys and TiQuant by D. Drasdo and S. Hoehme is performed. More frequently, the team develops “proof of concept” numerical codes in order to test the adequacy of our models to experimental biology.

We have organized the presentation of our research program in three methodological axes (Subsections 3.2, 3.3 and 3.4) and two application axes (Subsections 4.2 and 4.4). Evolving along their own logic in close interaction with the methodological axes, the application axes are considered as application-driven research axes in themselves. The methodological research axes are the following.

Axis 1 is devoted to work in physiologically-based design, analysis and control of population dynamics. It encompasses populations of bacteria, of yeasts, of cancer cells, of neurons, of aggregating proteins, etc. whose dynamics are represented by partial differential equations (PDEs), structured in evolving physiological traits, such as age, size, size-increment, time elapsed since last firing (neurons).

Axis 2 is devoted to reaction equations and motion equations of agents in living systems. It aims at describing biological phenomena such as tumor growth, chemotaxis and wound healing.

Axis 3 tackles questions of model and parameter identification, combining stochastic and deterministic approaches and inverse problem methods in nonlocal and multi-scale models.

3.2 Methodological axis 1: Analysis and control for population dynamics

Population dynamics is a field with varied and wide applications, many of them being in the core of MAMBA interests - cancer, bacterial growth, protein aggregation. Their theoretical study also brings a qualitative understanding on the interplay between individual growth, propagation and reproduction in such populations. In the past decades, many results were obtained in the BANG team on the asymptotic and qualitative behavior of such structured population equations, see e.g. [152, 76, 108, 89]. Other Inria teams interested by this domain are Mycenae, Numed and Dracula, with which we are in close contacts. Among the leaders of the domain abroad, we can cite among others our colleagues Graeme Wake (New Zealand), Glenn Webb (USA), Jacek Banasiak (South Africa), Odo Diekmann (Netherlands), with whom we are also in regular contact. Most remarkably and recently, connections have also been made with probabilists working on Piecewise Deterministic Markov Processes (F. Malrieu at the university of Rennes, Jean Bertoin at the ETH in Zurich, Vincent Bansaye at Ecole Polytechnique, Julien Berestycki at Cambridge, Amaury Lambert at College de France, M. Hoffmann at Paris Dauphine, Alex Watson in UCL, London and J. Bertoin in Zurich), leading to a better understanding of the links between both types of results – see also the Methodological axis 3.

We divide this research axis, which relies on the study of structured population equations, according to four different applications, bringing their own mathematical questions, e.g., stability, control, or blow-up.

Time asymptotics for nucleation, growth and division equations

Following the many results obtained in the BANG team on the asymptotic and qualitative behavior of structured population equation, we put our effort on the investigation of limit cases, where the trend to a steady state or to a steady exponential growth described by the first eigenvector fails to happen. In [83], the case of equal mitosis (division into two equally-sized offspring) with linear growth rate was studied, and strangely enough, it appeared that the general relative entropy method could also be adapted to such a non-dissipative case. Many discussions and common workshops with probabilists, especially through the ANR project PIECE coordinated by F. Malrieu, have led both communities to work closer.

We also enriched the models by taking into account a nucleation term, modeling the spontaneous formation of large polymers out of monomers [163]. We investigated the interplay between four processes: nucleation, polymerization, depolymerization and fragmentation.

New perspectives are now to consider not only one species but several interacting ones, which may exhibit complex interplays which may lead to damped oscillations or to infinite growth; these are in collaboration with C. Schmeiser and within the Vienna associated team MaMoCeMa (J. Delacour's Ph.D) and with K. Fellner from Graz (M. Mezache's Ph.D).

Cell population dynamics and its control

One of the important incentives for such model design, source of many theoretical works, is the challenging question of drug-induced drug resistance in cancer cell populations, described in more detail below in the Applicative axis 1, Cancer. The adaptive dynamics setting used consists of phenotype-structured integro-differential [or reaction-diffusion, when phenotype instability is added under the form of a Laplacian] equations describing the dynamic behavior of different cell populations interacting in a Lotka-Volterra-like manner that represents common growth limitation due to scarcity of expansion space and nutrients. The phenotype structure allows us to analyse the evolution in phenotypic traits of the populations under study and its asymptotics for two populations [142], [139, 138, 140]. Space may be added as a complementary structure variable provided that something is known of the (Cartesian) geometry of the population [141], which is seldom the case. A recent review of mathematical methods aiming at improving cancer treatments has been published in Physics of Life Reviews [136].

Modelling Mendelian and non-Mendelian inheritances in density-dependent population dynamics

Classical strategies for controlling mosquitoes responsible of vector-borne disease are based on mechanical methods, such as elimination of oviposition sites; and chemical methods, such as

insecticide spraying. Long term usage of the latter generates resistance [86, 123], transmitted to progeny according to Mendelian inheritance (in which each parent contributes randomly one of two possible alleles for a trait). New control strategies involve biological methods such as genetic control, which may either reduces mosquito population in a specific area or decreases the mosquito vector competence [65, 133, 175]. Among the latter, infection of wild populations by the bacterium *Wolbachia* appears promising (see also Applicative axis 2 below). Being maternally-transmitted, the latter obeys non-Mendelian inheritance law. Motivated by the effects of the (possibly unwanted) interaction of these two types of treatment, we initiated the study of modelling of Mendelian and non-Mendelian inheritances in density-dependent population dynamics. First results are shown in [151].

Control and macroscopic limits of collective dynamics

The term *self-organization* is used to describe the emergence of complex organizational patterns from simple interaction rules in collective dynamics systems. Such systems are valuable tools to model various biological systems or opinion dynamics, whether it be the collective movement of animal groups, the organization of cells in an organism or the evolution of opinions in a large crowd. A special case of self-organization is given by *consensus*, i.e. the situation in which all agents' state variables converge. Another phenomenon is that of *clustering*, when the group is split into clusters that each converge to a different state. A natural question in this framework is that of control: can the system be guided to a desired predetermined configuration? In the case when self-organization is not achieved naturally by the system, can it be driven to it? On the contrary, in the case where consensus and clustering are situations to be avoided (for example in crowd dynamics), can we design control strategies to keep the system away from clustering?

Another natural question is that of the large population limit. When the number of agents tends to infinity, the previous system of equations becomes unmanageable, a problem well-known as the curse of dimensionality. A common answer to this issue consists of studying the macroscopic limit of the system. It is then crucial to understand whether the limit system retains the properties of the microscopic one.

Models of neural network

Mean field limits have been proposed by biophysicists in order to describe neural networks based on physiological models. The various resulting equations are called integrate-and-fire, time elapsed models, voltage-conductance models. Their specific nonlinearities and the blow-up phenomena make their originality which has led to develop specific mathematical analysis [156], followed by [149, 132, 157, 88]. This field also yields a beautiful illustration for the capacity of the team to combine and compare stochastic and PDE modelling (see Methodological axis 3), in [93].

Models of interacting particle systems

The organisation of biological tissues during development is accompanied by the formation of sharp borders between distinct cell populations. The maintenance of this cell segregation is key in adult tissue homeostatis, and its disruption can lead tumor cells to spread and form metastasis. This segregation is challenged during tissue growth and morphogenesis due to the high mobility of many cells that can lead to intermingling. Therefore, understanding the mechanisms involved in the generation and maintain of cell segregation is of tremendous importance in tissue morphogenesis, homeostasis, and in the development of various invasive diseases such as tumors. In this research axis, we aim to provide a mathematical framework which enables to quantitatively link the segregation and border sharpening ability of the tissue to these cell-cell interaction phenomena of interest [75]. As agent-based models do not enable precise mathematical analysis of their solutions due to the lack of theoretical results, we turn towards continuous -macroscopic- models and aim to provide a rigorous link between the different models [75].

Models of population dynamics structured in phenotype The collaboration of Jean Clairambault with Emmanuel Trélat and Camille Pouchol (from September last year assistant professor at MAP5 Paris-Descartes, University of Paris), together now with Nastassia Pouradier Duteil, has been continued and presently leads us to a possible quantitative biological identification of the structuring phenotypes of the model developed in [162], through a beginning collaboration with an Indian systems biologist (Mohit Kumar Jolly, IIS Bangalore). Our motivation in this collaboration is to couple a physiologically based system of 6 ODEs developed by our Indian

collaborator with our phenotype-structured cell population dynamics model [97, 99].

In the framework of the HTE project EcoAML 2016-2020, Thanh Nam Nguyen, Jean Clairambault, Delphine Salort and Benoît Perthame, in collaboration with Thierry Jaffredo at IBPS-SU, have designed a phenotype-structured integrodifferential model of interactions between haematopoietic stem cells (healthy or leukaemic) and their supporting stromal cells [146]. In this model, without diffusion, to our relative astonishment, our postdoctoral fellow T.N. Nguyen predicts in particular that under special circumstances, a coexistence between healthy and leukaemic stem cell subpopulations is possible. The explanation of such possible theoretical coexistence still remains to be explained.

The idea of cooperation between cell subpopulations in a tumour is also studied using phenotype-structured models of cell populations by Frank Ernesto Alvarez Borges, PhD student of Stéphane Mischler (Paris-Dauphine University), Mariano Rodríguez Ricard (University of Havana, Cuba) and Jean Clairambault, in collaboration with José Antonio Carrillo (Oxford). A feature of these models, in as much as conflicting continuous phenotypes (e.g., adhesivity vs. motility, or fecundity vs. viability, or fecundity vs. motility¹) are supposed to structure a unique cell population, is that they can also represent the emergence of multicellularity in such a cell population, when two subpopulations of the same population, i.e., endowed with the same genome and represented w.r.t. relevant heterogeneity in the cell population by such conflicting phenotypes, are determined by two different choices of the 2-d phenotype. This has been this year the object of a submitted article associating Frank Ernesto Alvarez Borges, José Antonio Carrillo (Oxford) and Jean Clairambault [8], and this collaboration will be continued. In a simplified representation when the two phenotypes are just extreme values of a 1-d continuous phenotype (e.g., 0 for total adhesivity and no motility, 1 for no adhesivity and complete motility) this situation may be related to the previously described case, developed in [146], in which two extreme values of a convex function linked to proliferation are occupied by the two extreme phenotype values (0 and 1), leading to the coexistence of two cell subpopulations.

The principle of structuring cell population heterogeneities by a hidden phenotype has also been applied, in collaboration with Camille Pouchol (Université Paris Cité) and Zineb Kaid, PhD student at Tlemcen University, to study the interactions between a tumour cell population and a population of immune cells, NK-lymphocytes and CD8+ T-lymphocytes. The tumour cell population heterogeneity is defined by a continuous malignancy phenotype related to its potential of de-differentiation or transdifferentiation, whereas the heterogeneity within the immune cell population is coded by a continuous anti-tumor aggressiveness phenotype, which is drastically decreased by tumour cells in the process of immunotolerance, resulting in so-called “exhausted T-cells”. This process is fought by so-called Immune Checkpoint Inhibitors, a new class of drugs used in cancer immunotherapy, with some limited, nevertheless remarkable, success in clinical oncology, in particular in the treatment of melanoma. We have studied these tumour-immune interactions in the perspective of representing and later optimising the impact of such immunotherapies, a ongoing work which is reported in a preprint [53].

Collaborations

- Nucleation, growth and fragmentation equations: Klemens Fellner, university of Graz, Austria; Piotr Gwiązda, Polish Academy of Sciences, Poland; Christian Schmeiser, university of Vienna, through the associated team MaMoCeMa.
- Cell population dynamics and its control: Tommaso Lorenzi, former Mamba postdoc, now at the University of St. Andrews, Scotland, maintains a vivid collaboration with the Mamba team. He is in particular an external member of the HTE program MoGIImaging (see also Applicative axis 1). Emmanuel Trélat, Sorbonne Université professor, member of LJLL and of the CAGE Inria team, is the closest Mamba collaborator for optimal control. Benedetto Piccoli, Professor at Rutgers University (Camden, New Jersey), is collaborating on the analysis and control of collective dynamics. Nathalie Ayi, Sorbonne University, is participating in the development of graph-limit methods.

¹as proposed by John Maynard Keynes and Eős Száthmary in their book “The major transitions in evolution” (OUP 1995) as a condition of the emergence of multicellularity under environmental pressure

- Mendelian inheritance and resistance in density-dependent population dynamics: Pastor Pérez-Estigarribia, Christian Schaerer, Universidad Nacional de Asunción, Paraguay.
- Neural networks: Delphine Salort, Professor Sorbonne Université, Laboratory for computations and quantification in biology, and Patricia Reynaud, University of Nice, Maria Cáceres, University of Granada.
- Models of interacting particle systems: Pierre Degond, Imperial College London; Julien Barré, APMO, Orléans; Ewelina Zatorska, University College London; Sara Merino from the university of Vienna (through the associated team MaMoCeMa).

3.3 Methodological axis 2: Reaction and motion equations for living systems

The Mamba team had initiated and is a leader on the works developed in this research axis. It is a part of a consortium of several mathematicians in France through the ANR Blanc project *Kibord*, which involves in particular members from others INRIA team (DRACULA, COMMEDIA). Finally, we mention that from Sept. 2017 on, Mamba benefited from the ERC Advanced Grant ADORA (Asymptotic approach to spatial and dynamical organizations) of Benoît Perthame.

We divide this research axis, which relies on the study of partial differential equations for space and time organisation of biological populations, according to various applications using the same type of mathematical formalisms and methodologies: asymptotic analysis, weak solutions, numerical algorithms.

Aggregation equation

In the mathematical study of collective behavior, an important class of models is given by the aggregation equation. In the presence of a non-smooth interaction potential, solutions of such systems may blow up in finite time. To overcome this difficulty, we have defined weak measure-valued solutions in the sense of duality and its equivalence with gradient flows and entropy solutions in one dimension [129]. The extension to higher dimensions has been studied in [91]. An interesting consequence of this approach is the possibility to use the traditional finite volume approach to design numerical schemes able to capture the good behavior of such weak measure-valued solutions [122, 130].

Identification of the mechanisms of single cell motion

In this research axis, we aim to study the mechanisms of single cell adhesion-based and adhesion free motion. This work is done in the frame of the recently created associated team MaMoCeMa (see Section 9) with the WPI, Vienna. In a first direction [170] with N. Sfakianakis (Heidelberg University), we extended the live-cell motility Filament Based Lamellipodium Model to incorporate the forces exerted on the lamellipodium of the cells due to cell-cell collision and cadherin induced cell-cell adhesion. We took into account the nature of these forces via physical and biological constraints and modelling assumptions. We investigated the effect these new components had in the migration and morphology of the cells through particular experiments. We exhibit moreover the similarities between our simulated cells and HeLa cancer cells.

In a second work done in collaboration with the group of biologist at IST (led by Michael Sixt Austria), we developed and analyzed a two-dimensional mathematical model for cells migrating without adhesion capabilities [131]. Cells are represented by their cortex, which is modelled as an elastic curve, subject to an internal pressure force. Net polymerization or depolymerization in the cortex is modelled via local addition or removal of material, driving a cortical flow. The model takes the form of a fully nonlinear degenerate parabolic system. An existence analysis is carried out by adapting ideas from the theory of gradient flows. Numerical simulations show that these simple rules can account for the behavior observed in experiments, suggesting a possible mechanical mechanism for adhesion-independent motility.

Free boundary problems for tumor growth

Fluid dynamic equations are now commonly used to describe tumor growth with two main classes of models: those which describe tumor growth through the dynamics of the density of tumoral cells subjected to a mechanical stress; those describing the tumor through the dynamics of its

geometrical domain thanks to a Hele-Shaw-type free boundary model. The first link between these two classes of models has been rigorously obtained thanks to an incompressible limit in [155] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [134].

Since more realistic systems are used in the analysis of medical images, we have extended these studies to include active motion of cells in [154], viscosity in [159] and proved regularity results in [144]. The limiting Hele-Shaw free boundary model has been used to describe mathematically the invasion capacity of a tumour by looking for travelling wave solutions, in [158], see also Methodological axis 3. It is a fundamental but difficult issue to explain rigorously the emergence of instabilities in the direction transversal to the wave propagation. For a simplified model, a complete explanation is obtained in [135].

Coupling of diffusion and growth

The growth of an organism is triggered by signaling molecules called morphogens that diffuse in the organism during its development. Meanwhile, the diffusion of the morphogens is itself affected by the changes in shape and size of the organism. In other words, there is a complete coupling between the diffusion of the morphogens and the evolution of the shapes. We are working on the elaboration of a mathematical framework for diffusion equations on time-evolving manifolds, both theoretically and in collaboration with developmental biologists, for the special case of the diffusion of Gurken during the oogenesis of *Drosophila*.

Migration of cells in extracellular matrix

A single cell based model has been developed that reproduces a large set of experimental observations of cells migrating in extracellular matrix based on physical mechanisms with minimal internal cell dynamics. This includes individually migrating cells in micro-channels of different size, and their collective dynamics in case of many cells, as well as the impact of cell division and growth. The model explicitly mimics the extracellular matrix as the cells as deformable objects with explicit filopodia.

Collaborations

- Shanghai Jiao Tong University, joint publications with Min Tang on bacterial models for chemotaxis and free boundary problems for tumor growth.
- Imperial College London, joint works with José Antonio Carrillo on aggregation equation.
- University of Maryland at College Park, UCLA, Univ. of Chicago, Univ. Autónoma de Madrid, Univ. of St. Andrews (Scotland), Politecnico di Torino and Politecnico di Milano, joint works on mathematics of tumor growth models.
- Joint work with Francesco Rossi (Università di Padova, Italy) and Benedetto Piccoli (Rutgers University, Camden, New Jersey, USA) on Developmental PDEs.
- Cooperation with Shugo Yasuda (University of Hyogo, Kobe, Japan) and Vincent Calvez (EPI Dracula) on the subject of bacterial motion.
- Cooperation with Nathalie Ferrand (INSERM), Michèle Sabbah (INSERM) and Guillaume Vidal (Centre de Recherche Paul Pascal, Bordeaux) on cell aggregation by chemotaxis.
- Nicolas Vauchelet, Université Paris 13

3.4 Methodological axis 3: Model and parameter identification combining stochastic and deterministic approaches in nonlocal and multi-scale models

Direct parameter identification is a great challenge particularly in living systems in which part of parameters at a certain level are under control of processes at smaller scales. Mamba developed and addressed model and parameter identification methods and strategies in a number of mathematical and computational model applications including growth and fragmentation processes emerging in

bacterial growth and protein misfolding, in liver regeneration [113], TRAIL treatment of HeLa cells [77], growth of multicellular spheroids [128], blood detoxification after drug-induced liver damage [169, 119].

This naturally leads to increasingly combine methods from various fields: image analysis, statistics, probability, numerical analysis, PDEs, ODEs, agent-based modeling methods, involving inverse methods as well as direct model and model parameter identification in biological and biomedical applications. Model types comprise agent-based simulations for which Mamba is among the leading international groups, and Pharmacokinetic (PK) simulations that have recently combined in integrated models (PhD theses Géraldine Cellière, Noémie Boissier). The challenges related with the methodological variability has led to very fruitful collaborations with internationally renowned specialists of these fields, e.g. for bacterial growth and protein misfolding with Marc Hoffmann (Paris Dauphine) and Patricia Reynaud-Bouret (University of Nice) in statistics, with Philippe Moireau (Inria M3DISIM) in inverse problems and data assimilation, and with numerous experimentalists.

Estimation methods for growing and dividing populations

In this domain, all originated in two papers in collaboration with J.P. Zubelli in 2007 [153, 103], whose central idea was to use the asymptotic steady distribution of the individuals to estimate the division rate. A series of papers improved and extended these first results while keeping the deterministic viewpoint, lastly [83]. The last developments now tackle the still more involved problem of estimating not only the division rate but also the fragmentation kernel (i.e., how the sizes of the offspring are related to the size of the dividing individual) [105]. In parallel, in a long-run collaboration with statisticians, we studied the Piecewise Deterministic Markov Process (PDMP) underlying the equation, and estimated the division rate directly on sample observations of the process, thus making a bridge between the PDE and the PDMP approach in [110], a work which inspired also very recently other groups in statistics and probability [78, 125] and was the basis for Adélaïde Olivier's Ph.D thesis [148, 127] and of more recent work [147][111] (see also axis 5).

Data assimilation and stochastic modeling for protein aggregation

Estimating reaction rates and size distributions of protein polymers is an important step for understanding the mechanisms of protein misfolding and aggregation (see also axis 5). In [67], we settled a framework problem when the experimental measurements consist in the time-dynamics of a moment of the population.

To model the intrinsic variability among experimental curves in aggregation kinetics - an important and poorly understood phenomenon - Sarah Eugène's Ph.D, co-supervised by P. Robert [116], was devoted to the stochastic modeling and analysis of protein aggregation, compared both with the deterministic approach traditionally developed in Mamba [163] and with experiments.

Parameter identification in multi-level and multi-scale models of liver

Several projects are pursued on multiscale, multilevel modeling of liver regeneration and its consequences with integration of an increasingly amount of data. So far the most promising strategy working was for every additional data set, first testing whether the model would be able to simulate it without any modifications, and to modify the model if necessary by inclusion of further biological mechanisms or information. A key unsolved problem is that biological data seem often not perfectly reproducible, and measurements at different times may differ from each other. This can result from slightly different experimental settings or conditions, or different measurement methods. While for testing of qualitative mechanisms this is usually sufficient, the quantitative difference is sometimes of the order of the effect which makes a quantitative modeling very challenging. For ammonia detoxification during fibrosis, extensive simulations have been performed varying multiple clinically relevant parameters. The basis model needed to integrate multiple data sets and could only be modelled if modifications in tissue microarchitecture, adaptations of intracellular enzyme activities, and possible aging effects were taken into account (ongoing project close to finalization).

Collaborations

- Marc Hoffmann, Université Paris-Dauphine, for the statistical approach to growth and division processes, Miguel Escobedo, Bilbao and Magali Tournus, Marseille, for the deterministic approach.

- Philippe Moireau, Inria M3DISIM, for the inverse problem and data assimilation aspects [73], [66]

4 Application domains

4.1 Introduction

The team has three main application-driven research axes. Applicative axis 1 focuses on cancer, an application on which almost all team members work, with various approaches. A main focus of the team is to study cancer as a Darwinian evolutionary phenomenon in phenotype-structured cell populations. Optimal control methods take into account the two main pitfalls of clinical cancer therapeutics, namely unwanted toxic side effects in healthy cell populations and drug resistance in cancer cell populations. Other studies concern telomere shortening, and multi-scale models. Applicative axis 2 is devoted to growth, evolution and regeneration in populations and tissues. It involves protein aggregation and fragmentation models for neurodegenerative diseases (prion, Alzheimer), organ modeling, mainly of the liver, its damages induced by toxic molecules, and its regeneration after toxic insult. Applicative axis 3 is new and encompasses works related to epidemiology, both for infectious and vector-borne diseases.

4.2 Applicative axis 1: Focus on cancer

The MAMBA team designs and analyses mathematical models of tumor growth and therapy, at the cell population level, using agent-based or partial differential equations, with special interest in methodologies for therapeutic optimization using combined anticancer drug treatments. Rather than, or not only, modeling the effect of drugs on molecular targets, we represent these effects by their functional consequences on the fate of healthy and cancer cell populations: proliferation (velocity of the cell division cycle, decreasing it, e.g., by antagonizing growth factor receptors), apoptosis, cell death or senescence. Our goal in doing this is to circumvent the two main issues of anticancer therapy in the clinic, namely unwanted toxic side effects in populations of healthy cells and emergence of drug-induced drug resistance in cancer cell populations. This point of view leads us to take into account phenomena of transient and reversible resistance, observed in many cancer cell populations, by designing and analyzing models of cell populations structured in continuous phenotypes, relevant for the description of the behavior of cell populations exposed to drugs: either degree of resistance to a given drug, or potential of resistance to drug-induced stress, proliferation potential, and plasticity. Such modeling options naturally lead us to take into account in a continuous way (i.e., by continuous-valued phenotype or relevant gene expression) the wide phenotypic heterogeneity of cancer cell populations. They also lead us to adopt the point of view of adaptive dynamics according to which characteristic traits of cell populations evolve with tumor environmental pressure (drugs, cytokines or metabolic conditions, mechanical stress and spatial conditions), in particular from drug sensitivity to resistance. This position is original on the international scene of teams dealing with drug resistance in cancer. Recently, we have also extended our approach to the study of Tumour-Immune System interac

Modeling Acute Myeloid Leukemia (AML) and its control by anticancer drugs by PDEs and Delay Differential equations

In collaboration with Catherine Bonnet (Inria DISCO, Saclay) and François Delhommeau (St Antoine hospital in Paris), together with DISCO PhD students José Luis Avila Alonso and Walid Djema, this theme has led to common published proceedings of conferences: IFAC, ACC, CDC, MTNS [68, 70, 71, 82, 102, 69]. These works study the stability of the haematopoietic system and its possible restabilization by combinations of anticancer drugs with functional targets on cell populations: proliferation, apoptosis, differentiation.

Adaptive dynamics setting to model and circumvent evolution towards drug resistance in cancer by optimal control

We tackle the problem to represent and inhibit - using optimal control algorithms, in collaboration with Emmanuel Trélat, proposed Inria team CAGE - drug-induced drug resistance in cancer cell

populations. This theme, presently at the core of our works on cancer modeling with a evolutionary perspective on tumor heterogeneity, is documented in a series of articles [94, 95, 138, 139, 141]. Taking into account the two main pitfalls of cancer therapy, unwanted side effects on healthy cells and evolution towards resistance in cancer cells, it has attracted to our team the interest of several teams of biologists, with whom we have undertaken common collaborative works, funded by laureate answers to national calls (see ITMO Cancer HTE call).

This theme is also at the origin of methodological developments (see Research axis 1). In collaboration with Shensi Shen from Institut Gustave Roussy and Francois Vallette from Université de Nantes, we aim to develop simple non-spatial models to understand the mechanisms of drug resistance acquisition -and loss- in melanoma and glioblastoma. The models are systematically compared with in vitro and in vivo data generated by our collaborators and treated via image processing techniques developed in the team.

Senescence modeling by telomere shortening

In many animals, aging tissues accumulate senescent cells, a process which is beneficial to protect from cancer in the young organism. In collaboration with Teresa Teixeira and Zhou Xu from IBCP, we proposed a mathematical model based on the molecular mechanisms of telomere replication and shortening and fitted it on individual lineages of senescent *Saccharomyces cerevisiae* cells, in order to decipher the causes of heterogeneity in replicative senescence [84].

Biomechanically mediated growth control of cancer cells other cell types

Model simulations indicate that the response of growing cell populations on mechanical stress follows a simple universal functional relationship and is predictable over different cell lines and growth conditions despite the response curves look largely different. We developed a hybrid model strategy in which cells were represented by coarse-grained individual units calibrated in a high resolution cell model and parameterized each model cell by measurable biophysical and cell-biological parameters. Cell cycle progression in our model is controlled by volumetric strain, the latter being derived from a bio-mechanical relation between applied pressure and cell compressibility. After parameter calibration from experiments with mouse colon carcinoma cells growing against the resistance of an elastic alginate capsule, the model adequately predicts the growth curve in i) soft and rigid capsules, ii) in different experimental conditions where the mechanical stress is generated by osmosis via a high molecular weight dextran solution, and iii) for other cell types with different growth kinetics. Our model simulation results suggest that the growth response of cell population upon externally applied mechanical stress is the same, as it can be quantitatively predicted using the same growth progression function [137]. This model has now been extended to compare the efficiency of different culturing methods, monolayer growth, multicellular spheroids growth and growth within elastic capsules. The methodology of culturing is relevant in terms of cell yield and cell homogeneity.

Bio-mechanical models of tissue growth

The degenerate Cahn-Hilliard equation is a standard model to describe living tissues. It takes into account cell populations undergoing short-range attraction and long-range repulsion effects. In this framework, we consider the usual Cahn-Hilliard equation with a singular single-well potential and degenerate mobility. These degeneracy and singularity induce numerous difficulties, in particular for its numerical simulation. To overcome these issues, we propose in [hal-02274417] a relaxation system formed of two second order equations which can be solved with standard packages. This system is endowed with an energy and an entropy structure compatible with the limiting equation. Here, we study the theoretical properties of this system; global existence and convergence of the relaxed system to the degenerate Cahn-Hilliard equation. We also study the long-time asymptotics which interest relies on the numerous possible steady states with given mass.

Free boundary multiphase models of tumor growth

Multiphase mechanical models are now commonly used to describe living tissues including tumour growth. The specific model we study here consists of two equations of mixed parabolic and hyperbolic type which extend the standard compressible porous media equation, including cross-reaction terms. We study the incompressible limit, when the pressure becomes stiff, which generates a free boundary problem. We establish the complementarity relation and also a segregation result. Several major mathematical difficulties arise in the two species case which are addressed in [87]. Firstly, the system structure makes comparison principles fail. Secondly, segregation and internal layers limit

the regularity available on some quantities to BV. Thirdly, the Aronson-Bénilan estimates cannot be established in our context. We are lead, as it is classical, to add correction terms. This procedure requires technical manipulations based on BV estimates only valid in one space dimension. Another novelty is to establish an L^1 version in place of the standard upper bound.

Philosophy of cancer

The quite natural idea that cancer is a disease of the control of coherent multicellularity, expressed when cohesion of tissues and coherence of (unknown, except maybe for the case of a centralised circadian clock) synchronising signals fail to ensure it, by a regression towards unicellularity, stopping in this “reverse evolution path” at a coarse, incoherent multicellularity state ² continues to be developed and popularised by Jean Clairambault in seminars and workshops, and published in review articles [97, 99] and conference proceedings [96]. This view, and the investigation of the immune system in the design of such coherence of all multicellular organisms ³ is naturally inscribed in a *philosophy of cancer* perspective, and from a mathematical viewpoint, to multicellularity genes - and links between them and unicellularity genes - seen as a *hyperstructure* ⁴ above structures consisting of the genes of unicellularity, i.e., those that make a single cell a coherent living system, such hyperstructure being failed in cancer; this view is presently under development with colleagues from universities of the Paris region, together with Nils Baas at NTNU, Trondheim, Norway). This perspective, that makes use of category theory as a structuring point of view to apprehend multicellularity and cancer, is also meant to endow us with an innovative methodology to apply *topological data analysis (TDA)* to investigate cancer genome data.

Modelling of TMZ induced drug resistance

Temozolomide (TMZ) is a standard chemotherapy treatment in patients with glioblastoma. Resistance to this drug is correlated to the presence of a specific enzyme, which activity in cancer cells creates a drug-induced cell death resistant phenotype. Understanding the transition of cancer cells to a resistant phenotype is still a topic of research where multiple hypothesis have been studied: From an adaptive process to an inherent resistance to treatment. It has been recently shown that if TMZ treatment does not significantly induce cell death in glioblastoma, it still generates a response in terms of the spatial arrangement of cell aggregates. Moreover, the coupling of TMZ with irradiation has been shown to generate a better response in patients compared with using irradiation alone. Therefore, understanding the mechanisms of glioblastoma reaction to TMZ treatment could open new therapeutic avenues. In the frame of the post-doctorate of Gissell Estrada Rodriguez, we developed a 2D mathematical model in [63], suggesting a new possible mechanism for TMZ induced rearrangement of cancer cells (see section new results).

Modelling of the Epithelial-Mesenchymal Transition (EMT)

Understanding cell-fate decisions remains a major research challenge in developmental biology. In particular, the forward and backward epithelial-mesenchymal cellular transitions (EMT-MET) play a crucial role in embryonal development, tissue repair and cancer metastasis. The epithelial cell phenotype (E) is characterized by strong cell-to-cell adhesion, while the mesenchymal phenotype (M) is characterized by a strong cellular motility. Recent research has shown that there even exists a third hybrid phenotype (E/M) with mixed characteristics, that enables collective cell migration. EMT and MET play a crucial role in cancer metastasis, for instance when cancer cells from a primary tumor gain the ability to migrate through the bloodstream or lymph system to distant organs and then recover their adhesion to form secondary tumors. Thus, understanding the dynamics of MET and EMT is crucial for decoding metastasis and for designing effective therapeutics.

Collaborations

- AML modelling: Catherine Bonnet, DISCO Inria team, Saclay, and François Delhommeau, INSERM St Antoine (also collaborator in the INSERM HTE laureate project EcoAML, see

²Metazoa 1.0, as theorised by PCW Davies and CH Lineweaver in their article “Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors”, *Physical Biology* 2011, that popularised the so-called atavistic hypothesis of cancer

³this latter point partly, nevertheless nicely, developed in Thomas Pradeu’s book “The limits of the self”, OUP 2012

⁴See on this point, e.g., Nils Baas: “On the philosophy of higher structures”, *Int. J. General Systems* 2019

below).

- INSERM HTE laureate project MoGIIImaging, headed by E. Moyal (Toulouse): François Vallette, CRCNA and INSERM Nantes
- INSERM HTE laureate project EcoAML, headed by François Delhommeau, INSERM St Antoine: François Delhommeau, Thierry Jaffredo (IBPS), Delphine Salort (LCQB-IBPS)
- Adaptive dynamics to model drug resistance and optimal control to circumvent it:
Alexandre Escargueil, Michèle Sabbah (1 PhD thesis in common), St Antoine Hospital, Paris
Emmanuel Trélat (1 PhD thesis in common) at Inria team CAGE and Laboratoire Jacques-Louis Lions at Sorbonne Université.
Frédéric Thomas at CREEC, Montpellier.
Tommaso Lorenzi (Univ. of St Andrews).
- Telomere shortening: Teresa Teixeira and Zhou Xu (IBCP, Paris).
- Biomechanical control of cancer cells: Pierre Nassoy, Bioimaging and Optofluidics Group, LP2N – UMR 5298. IOGS, CNRS & University of Bordeaux; TreeFrog Pharmaceuticals, 30 Avenue Gustave Eiffel Bâtiment A, 33600 Pessac
- EMT: Camille Pouchol (Université de Paris), Mohit Kumar Jolly (Indian Institute of Science, Bengalore)

4.3 Applicative axis 2: Growth, evolution and regeneration in populations and tissues

The applications in this category span very different subjects from amyloid diseases, wound healing, liver regeneration and toxicity, up to bacterial growth and development of organisms. As the applications, the methods span a wide range. Those concerning identification of models and parameters with regard to data have partially been outlined in axis 3. Focus in this axis is on the model contribution to the biologically and/or medically relevant insights and aspects.

Liver-related modelling is partially performed within the INRIA team MIMESIS (Strasbourg) with the focus on real-time, patient-specific biomechanical liver models to guide surgery and surgeons. Internationally, spatial temporal liver related models are developed in Fraunhofer MEVIS (Bremen), by T. Ricken (TU Dortmund), and P. Segers group (Leuven).

Different from these, Mamba has a strong focus on spatial-temporal modeling on the histological scale, integration of molecular processes in each individual cell, and single-cell (agent) based models [112]. Works by Schliess [169, 119] have been highlighted in editorials.

Mathematical modeling of protein aggregation is a relatively recent domain, only a few other groups have emerged yet; among them we can cite the Inria team Dracula, with whom we are in close contact, and e.g., the work by Jean-Michel Coron (Sorbonne Université) and Monique Chyba (Hawaii, USA) in control, and Suzanne Sindi (USA) for the modeling of the yeast prion. We have interactions with all these groups and organized a workshop in June 2017, gathering both the biophysics and applied mathematics communities.

Amyloid disease

Application to protein aggregation in amyloid diseases is a long-standing interest of Mamba, dating back to 2010 [90], and developed through the collaboration with n rHuman Rezaei's team at Inra. More recently, with Wei-Feng Xue in Canterbury, we investigated the intrinsic variability among identical experiments of nucleation [106, 117], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [116].

In collaboration with Tom Banks first [74, 73] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [67], we proposed new models and mechanisms.

Wound healing: adipose tissues

After injury, if regeneration can be observed in hydra, planaria and some vertebrates, regeneration is rare in mammals and particularly in humans. In this research axis, we investigated the mechanisms by which biological tissues recover after injury. We explored this question on adipose tissue, using the mathematical framework recently developed in [161]. Our assumption is that simple mechanical cues between the Extra-Cellular Matrix (ECM) and differentiated cells can explain adipose tissue morphogenesis and that regeneration requires after injury the same mechanisms. We validated this hypothesis by means of a two-dimensional Individual Based Model (IBM) of interacting adipocytes and ECM fiber elements [160]. The model successfully generated regeneration or scar formation as functions of few key parameters, and seemed to indicate that the fate of injury outcome could be mainly due to ECM rigidity.

Following these encouraging results, the team is currently taking a step further in the model validation and confrontation to experimental data. The first direction concerns the development of a 3D framework to validate the mechanisms observed in 2D, in the frame of the PhD of P. Chassonery, co-directed by D. Peurichard and L. Casteilla (RESTORE, Toulouse).

Influence of cell mechanics in embryonic bile duct lument formation: insight from quantitative modeling

In vitro construction of hepatic tissue for regenerative therapy consists in recapitulating mechanisms of embryonic development. However, implementing those mechanisms in a spatially and temporally coordinated way remains difficult. Specifically, the construction of bile ducts and in particular the controlled formation of luminal structures formed by cholangiocytes is a challenge. The team works on a high resolution individual-based computational model which can help in unravelling the mechanisms of initial bile duct lumen formation. Guided by the quantification of morphological features and expression of genes in developing bile ducts from embryonic mouse liver, hypotheses for the mechanisms of biliary lumen formation were generated and tested with the model. Our simulations with a hybrid simulation technology as developed in ref. [137] suggest that successful bile duct lumen formation primarily requires the simultaneous contribution of several mechanisms discussed in the literature.

Mathematical modelling of axolotl regeneration

Tissue response after injury/amputation induces one or two alternatives: scar formation versus regeneration (complete recovery of tissue shape and functions). In most mammals, regeneration is considered largely impaired for the benefit of a fibrotic scar after injury automatically associated with dysfunctions, but complete regeneration has been largely described and investigated in animal models such as zebra fish, salamander, or axolotl. Despite several processes regulating regeneration have been identified at different scales -from diffusing molecules and cellular gene expression patterns up to tissue mechanics-, how these mechanisms individually or collectively play a role in the regulation of regenerative processes remains poorly understood. In order to give insights into the mechanisms of tissue regeneration, Valeria Caliaro started an Inria PhD project in october 2019, in collaboration with Osvaldo Chara, internationally recognized group leader of SysBio in Argentina. This project focuses on the role of cell proliferation in space and time along the two first phases of regeneration after injury: (i) initiation of a regeneration response, (ii) tissue patterning during regenerate growth. The first part of the project aims at building an agent-based model featuring few key mechanisms regulating cell proliferation after injury. By introducing heuristic rules which rely on Prof O. Chara expertise, we propose a 2D-ABM using methodologies borrowed from socio-dynamics and collective behavior studies (based on many interacting agent systems). While the focus is made on proliferation-based mechanisms, other mechanisms responsible for collective behavior such as volume exclusion, diffusion or aggregation are taken into account. The resulting model will provide a synthetic tissue model which will serve to investigate regeneration in cellular systems, focusing on cell proliferation properties. The second part of the PhD will be devoted to the derivation of continuous models from the agent-based formalism. This will provide a large scale 'synthetic tissue' model to explore the role of large scale effects in general tissue models.

Quantitative cell-based model predicts mechanical stress response of growing tumor spheroids

Model simulations indicate that the response of growing cell populations on mechanical stress

follows the same functional relationship and is predictable over different cell lines and growth conditions despite experimental response curves look largely different. We developed a hybrid model strategy in which cells are represented by coarse-grained individual units calibrated with a high resolution cell model and parameterized by measurable biophysical and cell-biological parameters. Cell cycle progression in our model is controlled by volumetric strain, the latter being derived from a bio-mechanical relation between applied pressure and cell compressibility. After parameter calibration from experiments with mouse colon carcinoma cells growing against the resistance of an elastic alginate capsule, the model adequately predicts the growth curve in i) soft and rigid capsules, ii) in different experimental conditions where the mechanical stress is generated by osmosis via a high molecular weight dextran solution, and iii) for other cell types with different growth kinetics from the growth kinetics in absence of external stress. Our model simulation results suggest a generic, even quantitatively same, growth response of cell populations upon externally applied mechanical stress, as it can be quantitatively predicted using the same growth progression function ⁽⁵⁾.

Bacterial population growth

We exploited all the methods developed to estimate the division rate of a population (see axis 3) to address a seminal question of biology: is it a size-sensing or a timing mechanism which triggers bacterial growth? In [165], we showed that a sizer model is robust and fits the data well. Several studies from other groups came at the same time, showing a renewed interest on a question dated back to Jacques Monod's PhD thesis (1941). Of special interest is the "adder" model, for which we are currently developing new estimation methods [111].

A quantitative high resolution computational mechanics cell model for growing and regenerating tissues

Mathematical models are increasingly designed to guide experiments in biology, biotechnology, as well as to assist in medical decision making. They are in particular important to understand emergent collective cell behavior. For this purpose, the models, despite still abstractions of reality, need to be quantitative in all aspects relevant for the question of interest. Considered as a showcase example the regeneration of liver after drug-induced depletion of hepatocytes, in which the surviving and dividing hepatocytes must squeeze in between the blood vessels of a network to refill the emerged lesions. Here, the cells' response to mechanical stress might significantly impact the regeneration process. We present a 3D high-resolution cell-based model integrating information from measurements in order to obtain a refined and quantitative understanding of the impact of cell-biomechanical effects on the closure of drug-induced lesions in liver. Our model represents each cell individually and is constructed by a discrete, physically scalable network of viscoelastic elements, capable of mimicking realistic cell deformation and supplying information at subcellular scales. The cells have the capability to migrate, grow, and divide, and the nature and parameters of their mechanical elements can be inferred from comparisons with optical stretcher experiments. Due to triangulation of the cell surface, interactions of cells with arbitrarily shaped (triangulated) structures such as blood vessels can be captured naturally. Comparing our simulations with those of so-called center-based models, in which cells have a largely rigid shape and forces are exerted between cell centers, we find that the migration forces a cell needs to exert on its environment to close a tissue lesion, is much smaller than predicted by center-based models. To stress generality of the approach, the liver simulations were complemented by monolayer and multicellular spheroid growth simulations. In summary, our model can give quantitative insight in many tissue organization processes, permits hypothesis testing *in silico*, and guide experiments in situations in which cell mechanics is considered important [137].

Liver regeneration and disease: towards a full virtual liver model at histological scale

In our work towards a full virtual liver model at histological level, a number of steps were performed. The models under points (1)-(4) focus on either a single or a few liver lobules. A liver lobule is the smallest repetitive functional and anatomical building block of liver, while (5) addresses a much larger organisational building block of the liver, a liver lobe that consists of thousands to hundreds

⁵liedekerke:hal-01956017

of thousands of lobules depending on the species. A second strand (6), (7) addresses image analysis, which in most cases forms the entrance to modeling as it provides the data necessary to generate model hypotheses and to parameterize a model.

(1) Cell types: In a former work by Hoehme et. al. ([126]) a model of liver regeneration after drug-induced damage was established considering hepatocytes and blood vessels. This model has now been expanded to include all relevant cell types, including hepatocytes, blood vessels, hepatic stellate cells, Kupffer cells, invading macrophages and other immune cells. Thereby it is now possible to study perturbations in the temporal scenario of damage and regeneration after signaling events or cells types are knocked down individually or collectively. This model is currently compared to respective perturbation experiments. In addition, alternative mechanisms at the level of molecularly intermediated cell-cell communication discussed in the vast medical and biological literature have been implemented and are systematically assessed for their biological consequence at the tissue level. This permits an in-silico testing of alternative hypotheses contributing to a more efficient identification of informative future experiments.

(2) Liver disease: Degenerative liver diseases such as liver fibrosis and cirrhosis develop out of a disturbed balance of degenerative and regenerative processes. The model under (1) has thereby been extended by the formation of extracellular matrix, mimicked as fiber networks, to capture the disease process leading to liver fibrosis. In that process characteristic streets form that modify the mechanics, perfusion behavior and detoxification capacity of the liver. The model is now used to simulate disease pathways emerging from different administration schemes of drugs that are knowing to long-term lead to hepatocellular cancer.

(3) Consequence of liver fibrosis: Whole-slide scans from fibrotic liver in a mouse model has been analysed at different time points after emergence of the disease with regard to the degree of excess matrix to mimic the possible consequences of fibrotic inclusions on perfusion and function of liver within a multiscale model that considers ammonia detoxification in each individual hepatocyte as well as blood flow and transport processes in the liver lobule. This model has now be confronted on multimodal data in healthy liver, liver after a toxic dose of a drug, and fibrosis. The requirement to explain simultaneously all data sets in the same model imposes significant challenges for which solutions are currently explored.

(4) Bile flux: Bile flux has been for decades believed to be controlled by convection at the level of liver lobules as well as at the level of the entire organ. By a methodology based on correlative imaging for quantitative intravital flux analysis no directed advection was detectable in bile canaliculi at the resolution limit. Instead, after active transport across hepatocyte membranes bile salts within the liver lobules are transported in the canaliculi by a diffusion-dominated process. Only in the interlobular ducts i.e., at super-lobular level, diffusion is augmented by advection. In silico simulations of bile transport in real 3D bile network microarchitectures can quantitatively explain the data assuming diffusive transport as sole mechanism.

(5) Liver regeneration after partial hepatectomy (partial organ removal): Partial hepatectomy is an adequate therapy in case of diseases or events that destructed only part of the liver. A typical case is a primary tumor or a metastasis affecting only a single liver lobe. Within an biophysical agent-based model capturing many aspects of the cell mechanics we studied regrowth of liver after partial organ removal in mouse calibrated with multivariate experimental data. Our model predicts characteristic proliferation pattern that change from small animals (as mouse) to large animals (as pig).

(6) Bile duct ligation: Bile duct ligation (BDL) is an experimental procedure that mimics obstructive cholestatic disease. One of the early consequences of BDL in rodents is the appearance of so-called bile infarcts that correspond to Charcot-Gombault necrosis in human cholestasis. The mechanisms causing bile infarcts and their pathophysiological relevance are unclear. Therefore, intravital two photon-based imaging of BDL mice was performed with fluorescent bile salts (BS) and non-BS organic anion analogues. Key findings were followed up by matrix-assisted laser desorption ionization imaging, clinical chemistry, immunostaining, and gene expression analyses. Our group performed analysis of intravital imaging. The key finding is that bile microinfarcts occur in the acute phase after BDL in a limited number of dispersed hepatocytes followed by larger infarcts involving neighboring hepatocytes, and they allow leakage of bile from the BS-overloaded biliary tract into blood, thereby protecting the liver from BS toxicity; in the chronic phase after BDL,

reduced sinusoidal BS uptake is a dominant protective factor, and the kidney contributes to the elimination of BS until cholemic nephropathy sets in[120].

(7) Periportalisation during liver fibrosis formation: Within a liver lobule, the function of hepatocytes is zonated i.e., certain functions are only executed by either hepatocytes close to the center (pericentral region) or hepatocytes in the periphery of the lobule (periportal region). Little is known about how liver fibrosis influences lobular zonation. To address this question, three mouse models of liver fibrosis were used, CC14 administration repeated for 2, 6 and 12 months to induce pericentral damage, as well as bile duct ligation (21 days) and a particular *mdr2*-mouse model to study periportal fibrosis. Analyses were performed by RNA-sequencing, immunostaining of zonated proteins and image analysis. Image analysis was performed by our group. The key result was that liver fibrosis leads to strong alterations of lobular zonation, where the pericentral region adopts periportal features. Beside adverse consequences, periportalization supports adaptation to repeated doses of hepatotoxic compounds[121].

Toxicity extrapolation from in vitro to in vivo

In vivo toxicity prediction from in vitro data is a major objective in toxicology as it permits bypassing animal experiments, and as the predictive power of animal experiments for human is limited. Objective was the prediction of paracetamol (acetaminophen)-induced hepatotoxicity from in vitro experiments. For this purpose, numerous iterations between in vitro experiments, in vivo experiments and simulations were performed for mouse. Using a recent thesis (G eraldine Celli ere’s PhD thesis [92]) as a start point, two candidate mechanisms could be identified both explaining the in vivo data after calibration of the in silico model with in vitro toxicity data.

Relating imaging on microscopic scales with imaging on macroscopic scales: From Diffusion-Weighted MRI Calibrated With Histological Data: an Example From Lung Cancer

Diffusion-weighted magnetic resonance imaging (DWI) is a key non-invasive imaging technique for cancer diagnosis and tumor treatment assessment, reflecting Brownian movement of water molecules in tissues. Since densely packed cells restrict molecule mobility, tumor tissues produce usually higher signal (less attenuated signal) on isotropic maps compared with normal tissues. However, no general quantitative relation between DWI data and the cell density has been established. In order to link low-resolution clinical cross-sectional data with high resolution histological information, we developed an image processing and analysis chain, which was used to study the correlation between the diffusion coefficient (D value) estimated from DWI and tumor cellularity from serial histological slides of a resected non-small cell lung cancer tumor. Color deconvolution followed by cell nuclei segmentation was performed on digitized histological images to determine local and cell-type specific 2d (two-dimensional) densities. From these, the 3d cell density was inferred by a model-based sampling technique, which is necessary for the calculation of local and global 3d tumor cell count. Next, DWI sequence information was overlaid with high resolution CT data and the resected histology using prominent anatomical hallmarks for co-registration of histology tissue blocks and non-invasive imaging modalities’ data. The integration of cell numbers information and DWI data derived from different tumor areas revealed a clear negative correlation between cell density and D value. Importantly, spatial tumor cell density can be calculated based on DWI data. In summary, our results demonstrate that tumor cell count and heterogeneity can be predicted from DWI data, which may open new opportunities for personalized diagnosis and therapy optimization [176]. The work of that paper has been further advanced to adapt the procedures for clinical use (in preparation).

Collaborations

- Protein aggregation in amyloid diseases: Human Rezae’s team at Inra Jouy-en-Josas (France) and W-F Xue’s team in at university of Kent (Great Britain); Tom Banks at the North Carolina State University (USA) and Philippe Moireau (M3DISIM)
- Bacterial growth and division: Lydia Robert, Sorbonne Universit  (France)
- Liver research & toxicology: JG. Hengstler group (IfADo, Dortmund, Germany); R. Gebhardt

(Univ. Leipzig); U. Klingmueller (DKFZ, Heidelberg); Irène Vignon-Clementel (INRIA, COMMEDIA)

- Growth in capsules and biomechanics: Pierre Nassoy, Institut d'Optique Graduate School, Talence, France; Josef Kaes, Peter Debye Institute for Soft Matter Physics, Physics, Univ. Leipzig, Germany.
- Wound healing: (Adipose tissue regeneration) team of L. Casteilla (StromaLab, Toulouse). (Axolotl regeneration) team of O. Chara, SysBio group, Argentina.
- Diffusion of morphogen: Center for Computational and Integrative Biology, Rutgers University (Camden, New Jersey), joint work with Professor Nir Yakoby's Drosophila Laboratory
- Linking micro and macro-image information: Oliver Sedlacek, Univ. and DKFZ Heidelberg, Kai Breuhahn, Univ. Heidelberg.

4.4 Applicative axis 3: Modelling and control in mathematical epidemiology

This axis is new and encompasses different works related to epidemiology, both for infectious and vector-borne diseases. The team was working since several years on the modeling, analysis and control of the propagation of vector-borne diseases such as dengue fever. Ordinary or partial differential equations of reaction-diffusion are used, and various (optimal or not) control strategies. In parallel and with the acknowledged opportunity of the onset and spreading of the Covid-19 pandemic, we expanded our interest to issues related to infectious diseases, using similar evolution systems.

Biological control of arboviroses

Sterile Insect Technique (SIT) [114] is a biological control method relying on massive releases of sterile male insects into the wild. The latter compete with wild males to mate with the females, and induce no offspring to the latter, thus reducing the next generation's population. This can result in a progressive reduction, or even disappearance, of the target population.

A related technique is based on the infection by *Wolbachia* [124]. This symbiotic bacterium is maternally transmitted from infected females to their offspring, but induces *cytoplasmic incompatibility* [172, 85]: mating between infected males and uninfected females gives no offspring. Releases of *Wolbachia* infected males alone is thus comparable to classical SIT.

On the other hand, releasing both infected males and females in sufficient quantity may result in infection of the wild population. This gives rise to an interesting new control principle, as *Wolbachia* has been shown to severely reduce the insect vectorial ability to transmit dengue, zika or chikungunya, indirectly by lifespan and fertility reduction, and directly by reducing the ability of the viruses to proliferate within the organism [145].

We proposed new insights on the practical and theoretical issues raised by the implementation of the previous methods. Concerning the SIT, we obtained control synthesis results through impulsive periodic release of controlled amplitude [80], and through optimal control approach [81]. Concerning *Wolbachia* technique, we investigated general control principles [79] capable of spreading the infection.

We also considered the effects of hindrances to these strategies [150].

Moreover, while continuing our work on the problem of controlling the mosquito population by itself, we have extended our studies to systems that consider the dynamics of the arboviroses in both the human and mosquito populations. This should allow us to confirm the pertinence of our previous and future works concerning the control of the mosquito population, but also motivate new criteria that take directly into account the dynamics of the epidemics in the human population.

Mathematical epidemiology of infectious diseases

The current outbreak of Covid-19 resulted in the appearance of many novel experiences at individual and collective, biological and social, national and international levels, making this pandemic a full epistemological experience as well. Motivated by the great number of questions raised by this global event, some members of the team devoted part of their time to exploring more

or less closely related scientific issues. One should notice however that this evolution constitutes indeed the continuation of a movement already initiated previously, and only accelerated by the current events.

The issues raised by the effective implementation of the social distancing measures largely implemented on the Earth's surface during the whole year 2020, have been the focus of intense reflection. We contributed to this debate by studying optimal control policies aiming at reducing the total number of infected people during the whole epidemic outbreak, the so-called epidemic final size. In another research line, we established the equation fulfilled by the epidemic final size for a fully general SEIR model in a heterogenous population characterized by some trait in a discrete or continuous subset, and studied the uniqueness of its solution. This allowed to extend the use and meaningfulness of the classical concept of next-generation operator introduced by O. Diekmann et al. in 1990 [101]. Last, in cooperation with the Inria team NeCS (Inria Grenoble-Rhône-Alpes), we studied in a control theory perspective the effects of the testing policies in the dynamics and in the control of the epidemic.

Collaborations

- Biological control of arboviroses: Nicolas Vauchelet (Université Paris 13); Yannick Privat (Université de Strasbourg); Carlota Rebelo (Univ. Lisboa), D. Villela, C. Struchiner (Fiocruz, Brazil); Jorge Zubelli (IMPA, Brazil); Alain Rapaport (INRA-Montpellier), Y. Dumont (CIRAD-Montpellier); Ch. Schaerer, P. Pérez-Estigarribia (UNA, Paraguay), O. Vasilieva (Universidad del Valle, Cali, Colombia), D. Cardona-Salgado (Universidad Autónoma de Occidente, Cali, Colombia); Hervé Bossin (ILM, Papeete); René Gato and Misladys Rodriguez (Inst. Pedro Kouri, La Havane)
- Mathematical epidemiology of infectious diseases: Nicolas Vauchelet (Université Paris 13); Michel Duprez (Inria Nancy - Grand Est); Yannick Privat (Université de Strasbourg); Carlos Canudas de Wit (Inria Grenoble - Rhône-Alpes and CNRS); Alain Kibangu (Université Grenoble-Alpes).

5 Social and environmental responsibility

5.1 Footprint of research activities

All members of the team decided to carefully review his or her trip policy (especially by air), in order to reduce carbon footprint.

6 Highlights of the year

6.1 Awards

Luis Almeida, Marie Doumic and Benoit Perthame organized (together with Vincent Calvez and Patricia Reynaud-Bouret) the one trimester program at IHP on Mathematical modeling of organization in living matter. from January to April 2022.

6.2 Research stays

From October to December 2022, Jules Guilberteau went to the Cancer Systems Biology Laboratory, at the Indian Institute of Science of Bangalore (India), in order to concretize a collaboration with Mohit Kumar Jolly and Paras Jain. The research stay was entirely funded by the Raman-Charpak fellowship, an Indo-French bilateral Fellowship programme, which was awarded to Jules to develop further the collaboration between the team of Indian systems biologists and our team of French mathematicians. The main purpose was to develop PDE models for the Epithelial-Mesenchymal Transition (EMT), a cell differentiation phenomenon which plays a crucial role in cancer development. The previous ODE models developed by M. Kumar Jolly and his team focused on a single cell undergoing EMT, while PDE aim to model the behaviour of a cell colony. Our models include an

advection term, based on previous ODE models, a selection term and an integral term representing respectively cell division and epimutations. The use of PDEs for EMT is in its early stages, and allow to consider several phenomena which occur at the same time and involve the whole colony, via non-local terms. We have been able to model some typical behaviours, such as hysteresis, at the scale of a cell colony, and to reproduce (at least qualitatively) some experimental observations that remained out of reach with the previous models.

6.3 Institutional life

In the year 2022, the activity of our team, MAMBA, was impacted by the serious dysfunctions and heavy atmosphere in the institute.

- The failure of the deployment of a new financial and human resource information system (Eksae) impacted and still impacts negatively all administrative colleagues with whom researchers interact. It forces them to duplicate their works, when not making them unable to perform even simple tasks. It also directly impacts researchers, who cannot oversee their budget in any reliable way, and occasionally have to delay simple purchases as a consequence of a reprioritization of overburdened administrative forces.
- The continuously diminishing emphasis on research in the presentation of Inria and the growing fuzziness around the status of researchers and the role and position of the institute attack the meaning of work and our collective values. We are extremely concerned over the neglect by our management of research for itself, showing preference for short term, short lived activities, judged by their “impact”, whatever this may mean.
- The extremely degraded relationship between the Inria Commission d’Évaluation and the current Inria direction is unbearable. It causes a general distrust in the direction’s intentions and in the outcome of future hiring and promoting process. We deeply deplore the current situation. We thank and congratulate the Commission d’Évaluation for its tireless and continued efforts in ensuring fair and bias-free evaluation of the hiring and promotion committees, and for its outstanding information to the researchers.

7 New software and platforms

7.1 New software

7.1.1 TiQuant

Name: Tissue Quantifier

Keywords: Systems Biology, Bioinformatics, Biology, Physiology

Functional Description: Systems biology and medicine on histological scales require quantification of images from histological image modalities such as confocal laser scanning or bright field microscopy. The latter can be used to calibrate the initial state of a mathematical model, and to evaluate its explanatory value, which hitherto has been little recognized. We generated a software for image analysis of histological material and demonstrated its use in analysing liver confocal micrografts, called TiQuant (Tissue Quantifier). The software is part of an analysis chain detailing protocols of imaging, image processing and analysis in liver tissue, permitting 3D reconstructions of liver lobules down to a resolution of less than a micrometer.

Authors: Dirk Drasdo, Stefan Hoehme, Adrian Friebel

Contact: Dirk Drasdo

7.1.2 TiSim

Name: Tissue Simulator

Keywords: Systems Biology, Bioinformatics, Biology, Physiology

Scientific Description: TiSim (Tissue Simulator) is a versatile and efficient simulation environment for tissue models. TiSim is a software for agent-based models of multicellular systems. It permits model development with center-based models and deformable cell models, it contains modules for monolayer and multicellular spheroid simulations as well as for simulations of liver lobules. Besides agent-based simulations, the flow of blood and the transport of molecules can be modelled in the extracellular space, intracellular processes such as signal transduction and metabolism can be simulated, for example over an interface permitting integration of SBML-formulated ODE models. TiSim is written in modern C++ , keeping central model constituents in modules to be able to reuse them as building blocks for new models. For user interaction, the GUI Framework Qt is used in combination with OpenGL for visualisation. The simulation code is in the process of being published. The modeling strategy and approaches slowly reach systems medicine and toxicology. The diffusion of software is a fundamental component as it provides the models that are complex and difficult to implement (implementing a liver lobule model from scratch takes about 2-2.5yrs) in form of a software to the developer and users who like to build upon them. This increases significantly the speed of implementing new models. Moreover, standardization is indispensable as it permits coupling different software tools that may have implemented models at different scales / levels.

Functional Description: TiSim is a software that permits agent-based simulations of multicellular systems. - center-based lattice-free agent-based model - modular - C++, Qt, OpenGL, GUI, batch mode - permits multiscale simulations by integration of molecular pathways (for signaling, metabolisms, drug) into each individual cell - applications so far: monolayer growth, multicellular spheroids - Boolean networks (development time = coding time (60 MMs) + model development time (264 MMs)) - in follow-up version 1: - liver lobule regeneration - SBML interface - in follow-up version 2: - deformable cell model (by triangulation of cell surface) - deformable rod models - extracellular matrix - vascular flow and transport TiSim can be directly fed by processed image data from TiQuant.

Contact: Dirk Drasdo

Participants: Andreas Buttenschoen, Dirk Drasdo, Eugenio Lella, Géraldine Cellière, Johannes Neitsch, Margaretha Palm, Nick Jagiella, Noémie Boissier, Paul Van Liedekerke, Stefan Hoehme, Tim Johann

Partner: IZBI, Université de Leipzig

8 New results

8.1 Direct and inverse Problems in Structured-population equations

The many results obtained during the last years have oriented us towards new research directions in the wide field of structured population equations: nonlinear renewal equations applied to neurosciences; the study of the direct and inverse problem in the newly-proposed "adder model" [173]; oscillatory behaviors of such equations; the study of models for heterogeneous aggregation, *i.e.* where the aggregates are formed out of several monomeric species.

8.1.1 Multitime renewal equation in the neuroscience

Participants: Benoît Perthame, Delphine Salort, Nicolás Torres.

The multitime renewal equation extends the classical elapsed time equation in order to describe neurons by the elapsed time since the last and the penultimate discharge, [25]. In this extension, we obtain a more complex system of integro-differential equations. For this new system, we prove convergence with exponential rate to stationary state by means of Doeblin's theory in the case of weak non-linearities using an appropriate functional setting. Numerical simulations allows to show how different firing rates can give different types of behaviors and to contrast them with theoretical results of both the classical and extended models.

8.1.2 Individual and population approaches for calibrating division rates in population dynamics: Application to the bacterial cell cycle

Participants: Marie Doumic, Marc Hoffmann.

Modelling, analysing and inferring triggering mechanisms in population reproduction is fundamental in many biological applications. It is also an active and growing research domain in mathematical biology. In the book chapter [47], we review the main results developed over the last decade for the estimation of the division rate in growing and dividing populations in a steady environment. These methods combine tools borrowed from PDE's and stochastic processes, with a certain view that emerges from mathematical statistics. A focus on the application to the bacterial cell division cycle provides a concrete presentation, and may help the reader to identify major new challenges in the field.

8.1.3 Heterogeneous aggregation: application to autophagy

Participants: Julia Delacour, Marie Doumic, Christian Schmeiser.

To date, there exists very few studies of heterogeneous aggregation, *i.e.* aggregates formation out of several monomeric species. Last year, we proposed a bimonomeric model of Becker-Döring type, capable of explaining damped oscillations observed in prion fibrils aggregates [107]; however, in this study, we kept the standard formalism where a given aggregate is characterised by its size, *i.e.* by the number of monomers it contains, irrespective of the monomeric species.

In a different and still more complex direction, there is the case where each aggregate is formed out of two or more monomeric species, arranged in a particular way. This is typically the case of the aggregation of ubiquitinated cargo by oligomers of the protein p62. This is an important preparatory step in cellular autophagy, which has been Julia Delacour's Ph.D subject, defended in December 2020 [100], and co-supervised by M. Doumic and C. Schmeiser of the associated team MaMoCeMa. The dynamics of protein aggregation has been studied by mathematical modelling for several decades, but most models consider the aggregation of only one type of protein, which gives rise to models belonging to the class of nucleation-coagulation-fragmentation equations. Contrary to these studies, Julia Delacour's Ph.D thesis studied aggregates composed of two different types of particles with varying mixing ratios, which drastically increases the complexity of the problem. This phenomenon appears in autophagy, a natural mechanism of the cell which degrades unnecessary material.

Aggregation of ubiquitinated cargo by oligomers of the protein p62 is an important preparatory step in cellular autophagy. In a first study [14], a mathematical model for the dynamics of these heterogeneous aggregates in the form of a system of ordinary differential equations is derived and analyzed. Three different parameter regimes are identified, where either aggregates are unstable, or their size saturates at a finite value, or their size grows indefinitely as long as free particles are abundant. The boundaries of these regimes as well as the finite size in the second case can be computed explicitly. The growth in the third case (quadratic in time) can also be made explicit by formal asymptotic methods. The qualitative results are illustrated by numerical simulations. A comparison with recent experimental results permits a partial parametrization of the model.

In a more theoretical article [14], in collaboration with P. Smzolyan from the university of Vienna, the qualitative behavior of the model is analyzed, certain aspects of the previously conjectured asymptotics being proven rigorously. In particular, the stability of the zero state, where the model has a smoothness deficit is analyzed by a combination of regularizing transformations and blow-up techniques. On the other hand, in a different parameter regime, the existence of polynomially growing solutions is shown by Poincaré compactification, combined with a singular perturbation analysis .

8.1.4 Insights into protein filament division

Participants: Marie Doumic, Miguel Escobedo, Magali Tournus, Wei-Feng Xue.

The dynamics by which polymeric protein filaments divide can be described by the universal mathematical equations of 'pure fragmentation'. The rates of fragmentation reactions reflect the stability of the protein filaments towards breakage, which is of importance in biology and biomedicine for instance in governing the creation of amyloid seeds and the propagation of prions. In the numerical study [174], we devised from mathematical theory inversion formulae - analysed in their own right in previous studies [105] - to recover the division rates and division kernel information from time dependent experimental measurements of filament size distribution. The numerical approach to systematically analyze the behaviour of pure fragmentation trajectories was also developed. We illustrate how these formulae can be used, provide some insights on their robustness, and show how they inform the design of experiments to measure fibril fragmentation dynamics. These advances are made possible by our central theoretical result on how the length distribution profile of the solution to the pure fragmentation equation aligns with a steady distribution profile for large times.

Thanks to the thorough numerical investigation carried out in [174], we realized the limitation of the previous approaches. Whereas analysing the long-time dynamics allowed us to infer in a very efficient way the division rate characteristics, this does not provide enough information to infer the fragmentation *kernel*, *i.e.* the distribution of offspring sizes out of the breakage of a polymer. We thus developed a totally different approach in [104], where we considered *short-time* instead of *large-time* behaviour, which revealed strikingly informative. We first provided a new representation of the solution to the fragmentation equation as a power series in the Banach space of Radon measures endowed with the total variation norm. This representation is used to justify how the fragmentation kernel, which is one of the two key parameters of the fragmentation equation, can be recovered from short-time experimental measurements of the particle size distributions when the initial condition is a delta function. A new stability result for this equation is also provided using a Wasserstein-type norm. We exploit this stability to prove the robustness of our reconstruction formula with respect to noise and initial data.

8.1.5 Telomere-shortening and senescence in yeast cells

Participants: Marie Doumic, Anais Rat, Teresa Teixeira, Zhou Xu.

Background Telomerase-negative cells have limited proliferation potential. In these cells, telomeres shorten until they reach a critical length and induce a permanently arrested state. This process called replicative senescence is associated with genomic instability and participates in tissue and organismal ageing. Experimental data using single-cell approaches in the budding yeast model organism show that telomerase-negative cells often experience abnormally long cell cycles, which can be followed by cell cycles of normal duration, before reaching the terminal senescent state. These series of non-terminal cell cycle arrests contribute to the heterogeneity of senescence, as we already established in previous studies [84], and likely magnify its genomic instability. Due to their apparent stochastic nature, investigating the dynamics and the molecular origins of these arrests

has been difficult. In particular, whether the non-terminal arrests series stem from a mechanism similar to the one that triggers terminal senescence is not known.

In [143], we provide a mathematical description of sequences of non-terminal arrests to understand how they appear. We take advantage of an experimental data set of cell cycle duration measurements performed in individual telomerase-negative yeast cells that keep track of the number of generations since telomerase inactivation. Using numerical simulations, we show that the occurrence of non-terminal arrests is a generation-dependent process that can be explained by the shortest telomere reaching a probabilistic threshold length. While the onset of senescence is also triggered by telomere shortening, we highlight differences in the laws that describe the number of consecutive arrests in non-terminal arrests compared to senescence arrests, suggesting distinct underlying mechanisms and cellular states.

Anais Rat's Ph.D builds upon these studies in order to analyse and simulate a full model for telomere-shortening induced senescence, capable of capturing population as well as lineage experiments.

8.1.6 Long-time behaviour of an advection-selection equation

Participants: Jules Guilberteau, Camille Pouchol, Nastassia Pouradier Duteil.

In the context of J. Guilberteau's PhD thesis and in collaboration with C. Pouchol (MAP5, Paris-Descartes), we studied the long-time behaviour of the advection-selection equation

$$\partial_t n(t, x) - \nabla \cdot (f(x)n(t, x)) - (r(x) - \rho(t))n(t, x), \quad \rho(t) = \int_{\mathbb{R}^d} n(t, x) dx \quad t \geq 0, x \in \mathbb{R}^d,$$

with an initial condition $n(0, \cdot) = n^0$. Our work is available in the pre-publication [50]. In the field of adaptive dynamics, this equation typically describes the evolution of a phenotype-structured population over time. In this case, $x \mapsto n(t, x)$ represents the density of the population characterised by a phenotypic trait x , the advection term ' $\nabla \cdot (f(x)n(t, x))$ ' a cell differentiation phenomenon driving the individuals toward specific regions, and the selection term ' $(r(x) - \rho(t))n(t, x)$ ' the growth of the population, which is of logistic type through the total population size $\rho(t) = \int_{\mathbb{R}^d} n(t, x) dx$.

The phenomena of advection and growth have antagonistic effects. Indeed, it is well-known that the advection term drives the solution to the asymptotically stable equilibria of the corresponding ODE, whereas the growth term pushes it towards the regions where the growth function is maximised. In the one-dimensional case $x \in \mathbb{R}$, we proved that the solution to this equation can either converge to a weighted Dirac mass or to a function in L^1 . Depending on the parameters n^0 , f and r , we determine which of these two regimes of convergence occurs, and we specify the weight and the point where the Dirac mass is supported, or the expression of the L^1 -function which is reached.

8.1.7 Phenotype divergence in a phenotype-structured reaction-advection-diffusion model

Participants: Frank Ernesto Alvarez Borges, José Antonio Carrillo, Jean Clairambault.

Plasticity, and 'bet hedging' in cancer have been modelled, in the framework of Frank Ernesto Alvarez Borges's PhD thesis at Paris-Dauphine University, and in collaboration with José Antonio Carrillo (Oxford) by a phenotype-structured reaction-advection-diffusion equation [8] in which the structure variables are viability, fecundity - with a trade-off condition between them - and plasticity, this last variable tuning in a nondecreasing mode a Laplacian that represents nongenetic instability of the other two phenotype variables. The asymptotics of the model, which has been inspired by the Bouin-Calvez cane toad equation, yields phenotypic divergence between viability and fecundity

traits, while the plasticity trait asymptotically decreases. The main equation, where $z(x, y, \theta)$ with x =viability, y =fecundity, θ =plasticity, runs as:

$$\partial_t n \nabla \cdot \{Vn - A(\theta)\nabla n\} (r(z) - d(z)\rho(t))n,$$

where

$$(Vn - A(\theta)\nabla n) \cdot \mathbf{n} = 0 \quad \forall z \in \partial D$$

and

$$n(0, z) = n_0(z) \quad \forall z \in D \cap \Omega \times [0, 1], \text{ with } \Omega : \{C(x, y) \leq K\},$$

defining a trade-off between traits x and y .

This model, applied with the aim to investigate the emergence of dimorphism in trait-monomorphic cell populations, is intended to represent both ‘bet hedging’ in cancer populations exposed to cellular stress, and emergence of multicellularity in evolution/development, in the perspective of the atavistic theory of cancer. This reaction-advection-diffusion setting explores the frequent and reversible phenomenon of *epimutations* (due in particular to the reversible graft of methyl and acetyl radicals on DNA and histones, changing the expression of genes without altering the DNA by any mutation in the sequence of bases) in very plastic cancer cell populations - and also, in the early stages of animal development from a zygote to a multicellular individual, when evolving cell populations are also plastic, i.e., frequently capable of differentiations, de-differentiations and transdifferentiations, all reversible phenomena - in isogenic cell populations, i.e., without mutations.

8.1.8 Interacting cell populations: Tumour-immune interactions

Participants: Jean Clairambault, Zineb Kaid, Camille Pouchol.

In the framework of Zineb Kaid’s PhD thesis at Tlemcen University, directed there by Abdelkader Lakmeche, University Djillali Liabes, Sidi Belabbes, Algeria, and in collaboration with Camille Pouchol, Université Paris-Cité, we have studied a phenotype-structured model of tumour-immune interactions, of the nonlocal Lotka-Volterra type.

The heterogeneous tumour cell population density $n(t, x)$ is structured according to a *tumour malignancy* continuous phenotype x , here identified to ‘stemness’. Focusing for the sake of this presentation on adaptive immunity, the effector cells, at contact with tumour cells, T-cell population density $\ell(t, y)$ and the naive cells, present in lymphoid organs, T-cell population density $p(t, y)$, unique source term of the effector T-cell population $\ell(t, y)$, are structured according to an *anti-tumour efficacy* phenotype y . The action of Antigen Presenting Cells (APCs), which instruct naive T-cells with the tumour aggressiveness phenotype x is represented below by the weighted integral $\chi(t, y)$. The model runs as follows:

$$\begin{cases} \frac{\partial n}{\partial t}(t, x) [R(x, \rho(t)) - \mu(x)\varphi(t, x)] n(t, x) \\ \frac{\partial \ell}{\partial t}(t, y) p(t, y) - \left(\frac{\nu(y)\rho(t)}{1 + h \cdot ICI(t)} - k_1\right) \ell(t, y), \\ \frac{\partial p}{\partial t}(t, y) \alpha \chi(t, y) p(t, y) - k_2 p^2(t, y). \end{cases}$$

with total tumour cell mass at time t

$$\rho(t) = \int_0^1 n(t, x) dx,$$

and

$$\varphi(t, x) = \int_0^1 \psi(x, y) \ell(t, y) dy, \quad \chi(t, y) = \int_0^1 \omega(x, y) n(t, x) dx, \quad \omega(x, y) = \frac{1}{s} e^{-|x-y|/s}, \quad \psi(x, y) = \frac{1}{s_1} e^{-|x-y|/s_1}.$$

The first question concerns the large time behaviour of the system, depending in particular on functions $\mu(x)$ (sensitivity of tumour cells to the action of T-cells) and $\nu(y)$ (sensitivity of T-cells to PD-ligands), without treatment. We have also studied its behaviour with added constant control *ICI* (Immune Checkpoint Inhibitors), aiming in particular at representing reversal from escape to extinction or equilibrium (between the tumour and immune cell population, i.e., containment of the tumour) in the cancer cell population. Some analytical results on phenotype concentration in x have been reached, visible in [53].

8.2 Stochastic Models of Biological Systems

8.2.1 Stochastic models for spike-timing dependent plasticity

Participants: Philippe Robert, Gaëtan Vignoud.

In neuroscience, learning and memory are usually associated to long-term changes of neuronal connectivity. In this context, *synaptic plasticity* refers to the set of mechanisms driving the dynamics of neuronal connections, called *synapses* and represented by a scalar value, the *synaptic weight*. Spike-Timing Dependent Plasticity (STDP) is a biologically-based model representing the time evolution of the synaptic weight as a functional of the past spiking activity of adjacent neurons.

If numerous models of neuronal cells have been proposed in the mathematical literature, few of them include a variable for the time-varying strength of the connection. A new, general, mathematical framework is introduced to study synaptic plasticity associated to different STDP rules. The system composed of two neurons connected by a single synapse is investigated and a stochastic process describing its dynamical behavior is presented and analyzed. The notion of *plasticity kernel* is introduced as a key component of plastic neural networks models, generalizing a notion used for pair-based models. We show that a large number of STDP rules from neuroscience and physics can be represented by this formalism. Several aspects of these models are discussed and compared to canonical models of computational neuroscience. An important sub-class of plasticity kernels with a Markovian formulation is also defined and investigated. In these models, the time evolution of cellular processes such as the neuronal membrane potential and the concentrations of chemical components created/suppressed by spiking activity has the Markov property.

In neuroscience, *synaptic plasticity* refers to the set of mechanisms driving the dynamics of neuronal connections, called *synapses* and represented by a scalar value, the *synaptic weight*. A Spike-Timing Dependent Plasticity (STDP) rule is a biologically-based model representing the time evolution of the synaptic weight as a functional of the past spiking activity of adjacent neurons. A general mathematical framework has been introduced in [167].

We have developed and investigated a scaling approach of these models based on several biological assumptions. Experiments show that long-term synaptic plasticity evolves on a much slower timescale than the cellular mechanisms driving the activity of neuronal cells, like their spiking activity or the concentration of various chemical components created/suppressed by this spiking activity. For this reason, a scaled version of the stochastic model of [167] in [168] is introduced and a limit theorem, an averaging principle, is stated for a large class of plasticity kernels. A companion paper [166] is entirely devoted to the tightness properties used to prove these convergence results.

These averaging principles are used to study two important STDP models: *pair-based rules* and *calcium-based rules*. Our results are compared with the approximations of neuroscience STDP models. A class of discrete models of STDP rules is also investigated for the analytical tractability of its limiting dynamical system. See [26].

Hawkes Processes We have finished this project this year. Stationary non-linear Hawkes processes are revisited by formulating the Hawkes dependence as a Markovian property on the space of non-negative sequences. A characterization of the associated point process is obtained in terms of the solution of stochastic differential equations. When the influence of past jumps decreases exponentially over time, the Palm measure of the associated stationary point process is expressed

with the distribution of the stationary version of a one-dimensional Harris ergodic Markov chain. Finally a scaling result for some Hawkes processes exhibiting a blow-up phenomenon is derived. See [55].

8.3 Stochastic Chemical Networks

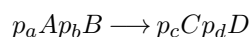
Participants: Lucie Laurence, Philippe Robert.

The general goal of this PhD work, started in September 2020, is of developing a scaling approach to analyze stochastic models of chemical networks.

A chemical network is defined with three components

- A set of chemical species \mathcal{S} ;
- A set of complexes, i.e. subsets of elements of chemical species with possible repeated entries;
- A graph connecting complexes.

As an example, if A, B, C, D are chemical species, $p_u, u \in \{a, b, c, d\}$, are integers and the relation



corresponds to an edge of the graph for the transformation of the complex $p_a A p_b B$ (p_a copies of A and p_b copies of B) into the complex $p_c C p_d D$. The associated dynamical system is a mass action kinetic, i.e. the rate at which such reaction occurs is given by

$$\prod_{i=0}^{p_a-1} (x_A - i) \prod_{i=0}^{p_b-1} (x_B - i)$$

if x_A, x_B is the number of copies of A and B .

Historically, Horn, Jackson and Feinberg developed in the 70's, in a deterministic framework associated to a polynomial differential system, several results based on the geometry of the graph. We can mention the famous deficiency zero theorem, that give sufficient conditions on the structure of the graph of the reaction network to have a stable equilibrium point. Most of the stochastic stability results are essentially based on these results.

The goal of this study is to find alternative ways to show results of stability and convergence in distribution. The general approach is to use some scaling arguments on the Markov process associated to the Chemical Reaction Network studied. Scaling in time and/or in space gets us some converging results, avoiding the usual search for a Lyapunov function. We also used averaging results in specific border cases.

This year we have analyzed topologies of chemical reaction networks: triangular networks: a CRN with three complexes and two chemical species for which we have a complete analysis of the stability properties as well as some scaling behavior. Secondly, we have studied circular networks with complexes of size two from the point of view of stability. We are currently investigating an unusual averaging principle in this setting. Finally, we are studying k -unary networks for which complexes are composed only of copies of one chemical species, despite its simple topology the scaling properties of these networks are not trivial at all.

8.4 Allocation of Resources in Prokaryotic Cells

Participants: Vincent Fromion, Philippe Robert, Jana Zaherddine.

The information flow from DNA genes to proteins is a fundamental process that is common to all living organisms. We analyze it in the context of a bacterial cell. The production of proteins is the most important process that takes place inside a bacterium consuming around 90% of its resources.

Bacterium adapts very quickly to changes in the environment. It succeeds in making a balance between supply allocating the resources available in the environment for its growth. All of this is achieved via regulatory mechanisms in the bacterium.

Basically the bacterium has two different regimes. The exponential phase during which resources are abundant, enabling the doubling of the cell on a fast pace. The Stationary phase during which resources are scarce, a regulatory mechanisms known by the "sequestration by the 6S RNA" comes into play. The 6S RNA is a macromolecule which is a regulator of transcription by preventing the polymerase from binding to the gene promoter.

Basically the bacterium has two different regimes. The exponential phase during which resources are abundant, enabling the doubling of the cell on a fast pace. The Stationary phase during which resources are scarce, a regulatory mechanisms known by the "sequestration by the 6S RNA" comes into play. The 6S RNA is a macromolecule which is a regulator of transcription by preventing the polymerase from binding to the gene promoter.

Our main objective is to estimate the efficiency of the 6S RNA regulatory mechanisms via the analysis of the time evolution of the concentration of free, sequestered and in transcription polymerases according to the growth rate. Due the disorganized medium, stochastic models are used for such analysis.

In [49], we have worked on a model for which we have the same constant number N of polymerases. We have studied an important *global* regulation mechanism of transcription of biological cells using specific macro-molecules, 6S RNAs. The functional property of 6S RNAs is of blocking the transcription of RNAs when the environment of the cell is not favorable. We investigate the efficiency of this mechanism with a scaling analysis of a stochastic model. The evolution equations of our model are driven by the law of mass action and the total number of polymerases is used as a scaling parameter. Two regimes are analyzed: exponential phase when the environment of the cell is favorable to its growth, and the stationary phase when resources are scarce. In both regimes, by defining properly occupation measures of the model, we prove an averaging principle for the associated multi-dimensional Markov process on a convenient timescale, as well as convergence results for "fast" variables of the system. An analytical expression of the asymptotic fraction of sequestered polymerases in stationary phase is in particular obtained. The consequences of these results are discussed.

We are currently investigating the regulation of translation for which there is also a kind of sequestration mechanism, although it is not as direct as for transcription. Another difficulty of this case is that, in addition to the various states of ribosomes (translating, free, in initiation or sequestered), the production of amino-acids has to be taken into account.

8.5 Analysis and control of populations of mosquitoes

8.5.1 Optimal replacement strategies, application to Wolbachia

Participants: Luis Almeida, Jesus Bellver Arnau, Yannick Privat, Nicolas Vauchelet.

We modelled and designed optimal release control strategy with the help of a least square problem. In a nutshell, one wants to minimize the number of uninfected mosquitoes at a given time horizon, under relevant biological constraints. We derived properties of optimal controls and studied a limit problem providing useful asymptotic properties of optimal controls [4, 30].

8.5.2 Migration effects on biological control of dengue vectors

Participants: Luis Almeida, Pierre-Alexandre Bliman, Yves Dumont, Thi Quynh Nga Nguyen, Nicolas Vauchelet.

Application of Sterile Insect Technique (SIT) in the field is not easy, and its success hinges upon several constraints, one of them being that the treated area must be sufficiently isolated to limit migration or re-invasion by mosquitoes from the outside.

We studied the effects of the migration of mosquitoes on the spread and sustainability of Wolbachia invasion. Recent works focused on the time dynamical systems or consider the spatial dynamics in an unbounded domain, typically the real line. Based on a previous work by M. Strugarek and N. Vauchelet, we considered in [40] the spatial dynamics in a bounded domain, with Robin boundary conditions taking into account migration term. Existence and stability of the equilibrium points have been considered.

We also studied the impact of males and (fertile) females migration on SIT [10]. We showed that a critical release rate for sterile males exists for every migration level, in the context of continuous or periodic releases. In particular, when (fertile) females migration is sufficiently low, then SIT can be conducted successfully using either open-loop control or closed-loop control (or a combination of both methods) when regular measurements of the wild population are completed. We also derived a threshold value for the females migration rate, when viruses are circulating, under which it is possible to lower the epidemiological risk in the treated area, according to the size of the human population.

8.5.3 Control of Mosquito populations using the Sterile Insect Technique

Participants: Luis Almeida, Jorge Estrada, Alexis Leculier, Grégoire Nadin, Thi Quynh Nga Nguyen, Yannick Privat, Nicolas Vauchelet.

The sterile insect technique consists in massive release of sterilized males in the aim to reduce the size of mosquitoes population or even eradicate it. In [5], we studied the optimal release strategies in order to maximize the efficiency of this technique. We considered simplified models that describe the dynamics of eggs, males, females and sterile males in order to optimize the release protocol. We determined in a precise way optimal strategies, which allows us to tackle numerically the underlying optimization problem in a very simple way. We also present some num In this work, we investigated the feasibility of using the sterile insect technique as a barrier against invasion of a mosquito-free zone (e.g. an urban area) by the mosquitoes coming from outside. In [31] and [6] we were able to show (both analytical and numerical results) that performing the sterile insect technique on a sufficiently large band we may stop invasion. In [64], for the bi-stable case, we were also able to extend this study to the feasibility of implementing a Rolling Carpet strategy to increase the size of the mosquito-free area thanks to performing sterile male releases on a band that is moved towards the mosquito infected area at an appropriate speed depending on its size and on the number of sterile mosquitoes released. These results were extended to the mono-stable case in [51]. In the latter the release zone extends to infinity on the mosquito-free side. In [38] we study the optimal profile of the barrier for a killing action in the bi-stable setting.

8.5.4 Sex-structured model of Wolbachia invasion to design sex-biased release strategies

Female mosquitoes infected with Wolbachia need to ingest human blood while male mosquitoes, either wild or Wolbachia-carrying, do not bite people. Moreover, Wolbachia-carrying females may transmit the virus to people during blood-feeding, even though with a far less probability than the wild ones. Therefore, massive releases of Wolbachia-carrying females may increase both the nuisance and the epidemiological risk among human residents. In [41], we proposed a sex-structured model of Wolbachia invasion that brings forward the possibility of developing male-biased release strategies of Wolbachia-carriers leading to Wolbachia invasion. Thanks to this model, we studied the minimal

amount of mosquitoes necessary to complete this task, according to the relative sex-ratio of the released mosquitoes and to the release schedule. We also paid attention to the estimate of the time needed to achieve the ultimate population replacement.

8.6 Modelling and control in epidemiology

8.6.1 Vector-borne disease outbreak control using instant vector releases

Participants: Luis Almeida, Jesus Bellver-Arnau, Yannick Privat, Carlota Rebelo.

In [37] we study optimal vector release strategies to control vector-borne diseases, such as dengue, Zika, chikungunya and malaria. We consider both the sterile insect technique (SIT) and Wolbachia (presently used mainly for mosquitoes). In each case, the time dynamics of the vector population is modeled by a system of ordinary differential equations in which the releases are represented by linear combinations of Dirac measures with positive coefficients determining their intensity. We introduce optimal control problems that we solve numerically. We discuss the results obtained, focusing in particular on the complexity and efficiency of optimal controls and comparing the strategies obtained.

8.6.2 Epidemic Dynamics with Reinfections

Participants: Pierre-Alexandre Bliman, Denis Efimov, Marcel Fang, Rosane Ushirobira.

We considered in [27] a general SEIRS model describing the dynamics of an infectious disease including latency, waning immunity and infection-induced mortality. Pretty much in the spirit of Becker-Döring system [107], we derived an infinite system of differential equations that provides an image of the same infection process, but counting also the reinfections. Existence and uniqueness of the corresponding Cauchy problem has been established in a suitable space of sequence valued functions, and the asymptotic behavior of the solutions is characterized, according to the value of the basic reproduction number. This allowed to determine several mean numbers of reinfections related to the population at endemic equilibrium. We then showed how using jointly measurement of the number of infected individuals and of the number of primo-infected provides observability and identifiability to a simple SIS model for which none of these two measures is sufficient to ensure on its own the same properties.

Observation and identification are important issues for the practical use of compartmental models of epidemic dynamics. They are usually evaluated based on the number of infected individuals (the prevalence) or the newly infected cases (the incidence). We are interested in a general question: may the measure of the number of primo-infected individuals and the prevalence improve state estimation? To study this issue, we analyzed in [29] a simple model of infection with waning immunity and, consequently, the possibility of reinfections. A class of nonlinear observers was built for this model, and tractable sufficient conditions on the gain matrices were established, ensuring asymptotic convergence of the state estimate towards its actual value.

8.6.3 Modelling of the population movements and epidemic spread

Participants: Pierre-Alexandre Bliman, Boureima Sangaré, Assane Savadogo.

Modelling the movements and mixing of populations in complex urban environments is an important issue to attempt to reproduce epidemic dynamics. To begin the exploration of this

question, we study in this methodological work the effects of various modelling options on the stability of the disease-free equilibrium of simple systems.

8.6.4 Modelling and analysis of social distancing policies

Participants: Pierre-Alexandre Bliman, Alberto d’Onofrio, Piero Manfredi.

In [9] we used ideas from Behavioural Epidemiology to represent the tiered social distancing policies adopted by many governments to mitigate the nasty consequences of COVID-19. Such policies have a number of well-established features i.e., they are short-term, adaptive (to the changing epidemiological conditions), and multi-criteria i.e., based on a multiplicity of indicators of the prevailing epidemiological activity. These features have been included in an SEIRS model by using a composite information index including multiple indicators of current and past epidemic activity mimicking those used by governments during the COVID-19 pandemic, such as transmission intensity, infection incidence and hospitals’ occupancy. In its turn, the dynamics of the information index is assumed to endogenously inform the governmental social distancing interventions. Simulations suggest a rich spectrum of possible results. These also include pitfalls and undesired results, such as a worsening of epidemic control, that can arise following such types of approaches to epidemic responses.

8.7 Focus on cancer

8.7.1 Effects of surface tension in living tissues

Participants: Charles Elbar, Marco Mason, Benoît Perthame, Alexandre Poulain, Jakub Skrzeczkowski.

We continued the research axis on mechanical models of living tissues based on the degenerate Cahn-Hilliard model. The general goal is to understand how different types of cells undergo phase separation effects, or in contrast, well mixing. To do so, it is fundamental to understand the surface tension effect.

Since living tissues are mostly incompressible, we derived the incompressible limit of a compressible model in [115], using energy methods and asymptotic analysis. A remarkable feature is the common structure of the degenerate Cahn-Hilliard models with the famous Keller-segel system for chemotaxis.

We were also interested in proving rigorously that such models can be derived from a mesoscopic description (Vlasov equation), [48]. The method, issued from the kinetic theory, is based on entropy estimates and averaging lemmas. This also makes the connection with more physical phenomena in fluids and plasmas.

8.7.2 Analysis and numerics for mechanical models of tumor growth

Several class of models have been devised to describe the macroscopic dynamics of living tissues (including growing tumors), depending on the mechanical behaviour of the tissue. The team has progressed on several aspects: analysis of models and asymptotic analysis towards free boundary problem, numerical methods compatible with energy properties.

This direction of research has been continued in [43]. Motivated by biological applications on tumour invasion through thin membranes, we study a porous-medium type equation where the density of the cell population evolves under Darcy’s law and assuming continuity of both the density and flux velocity on the thin membrane which separates two domains. The complexity due to the presence of such layer and the drastically different scales and mobility rates between the membrane and the adjacent tissues, lead to consider the limit problem where the thickness of the membrane approaches zero. We recover the effective interface problem, and in particular, we are interested in

the rigorous derivation of the transmission conditions on the limiting zero-thickness surface, already conjectured by Chaplain et al., which are compatible with nonlinear generalized Kedem-Katchalsky ones.

Collective motion of cells plays an important role and the case of self-propelled particles confined between two parallel plates has attracted a lot of attention. In [118], we considered cells moving with a constant speed while their direction changes by rotational diffusion. The probability distribution of such micro-organisms in confined environment is singular because particles accumulate at the boundaries. This leads us to distinguish between the probability distribution densities in the bulk and in the boundaries. They satisfy a degenerate Fokker-Planck system and we propose boundary conditions that take into account the switching between free-moving and boundary-contacting particles. Relative entropy property, a priori estimates and the convergence to an unique steady state are established. The steady states of both the PDE and individual based stochastic models are compared numerically.

8.7.3 Adaptive dynamics setting to model and circumvent evolution towards drug resistance in cancer by optimal control

The research topic “Evolution and cancer”, designed in the framework of adaptive dynamics to represent and overcome acquired drug resistance in cancer, initiated in [142, 141] and later continued in [95, 140], has been summarised in [62], presented in more detail in [99], and has been the object of the PhD thesis work of Camille Pouchol, see above “Cell population dynamics and its control”. In collaboration with F. Vallette’s INSERM team in Nantes, it gave rise to the publication of the article [164]. It is now oriented, thanks to work underway by Frank Ernesto Alvarez Borges, Jean Clairambault, and Stéphane Mischler, in particular towards the mathematical representation of *bet hedging* in cancer, namely a supposed optimal strategy consisting for cancer cell populations under life-threatening cell stress in diversifying their phenotypes according to several resistance mechanisms, such as overexpression of ABC transporters (P-glycoprotein and many others), of DNA repair enzymes or of intracellular detoxication processes. According to different deadly insults the cancer cell population is exposed to, some phenotypes may be selected, any such successful subpopulation being able to store the cell population genome (or subclones of it if the cell population is already genetically heterogeneous) and make it amenable to survival and renewed replication.

8.7.4 Mathematical modeling of Tumour-Immune System interaction

Participants: Luis Almeida, Chloe Audebert, Emma Leschiera, Tommaso Lorenzi.

In the setting of Emma Leschiera’s thesis [35], we studied the interaction between the tumor and the immune system. In particular, a first paper concerning the role of Intra-tumor heterogeneity (ITH) was recently accepted for publication in J. Theor. Biol. [22]. Several experimental papers that inspired this work, have shown that ITH has a strong impact on the efficacy of the immune response against solid tumors. In this work we considered that ITH can be measured both through the number of sub-populations of cancer cells expressing different antigens and through the percentage of immunogenic cells in a tumor. We proposed and implemented a spatially explicit stochastic individual-based model of the interaction dynamics between tumor cells and CD8+ T cells, which makes it possible to evaluate the contribution of these two aspects of ITH on anti-tumor immune response and which are able to retrieve several immunosurveillance scenarios (both successful and unsuccessful) identified in the experimental works.

In [39] we also developed an individual-based model for the coevolutionary dynamics between T-cells and tumor cells. We also formally derive the deterministic continuum limit of this individual-based model, which comprises a non-local partial differential equation for the phenotype distribution of tumor cells coupled with an integro-differential equation for the phenotype distribution of T-cells.

We obtain results of the individual-based model, and show that there is a good agreement between them and analytical and numerical results of the continuum model.

In [3] we model T-cell infiltration in solid tumours and to retrieve the notion of immunoscore which is a widely used tool to evaluate the chances of success of immunotherapy and an important information to guide the choice of a particular treatment or combination of treatments.

8.7.5 A new mechanotransduction mechanism could explain glioblastoma response to chemotherapeutic treatment

Participants: Luis Almeida, Gissell Estrada-Rodriguez, Diane Peurichard, Xinran Ruan.

In the frame of the HTE project MoGIIImaging and the post-doctorate of Gissell Estrada Rodriguez, we developed a 2D mathematical model to study and analyse the evolution of a population of glioblastoma cells that are exposed to TMZ [63]. Based on the experimental data generated by our partner team led by F. Valette (Inserm Nantes), we proposed a Keller-Segel type model where tumour aggregate formation is obtained as the result of nutrient-limited cell proliferation coupled with chemotaxis-based cell movement. The introduction of a chemotherapeutic treatment is supposed to induce mechanical changes at the cell level, with cells undergoing a transition from rigid bodies to semi-elastic entities. We analysed the influence of these individual mechanical changes on the properties of the aggregates obtained at the population level by introducing a nonlinear volume-filling chemotactic system of partial differential equations. The elastic properties of the cells were taken into account through the so-called squeezing probability, which allowed us to change the packing capacity of the aggregates, depending on the concentration of the treatment in the extracellular microenvironment. By confronting the model results to experimental data, we showed that the changes observed in cellular structures under a non-cytotoxic drug could be due to this mechanotransduction phenomenon. This study suggests a new mechanism which, if experimentally validated, opens interesting therapeutic avenues.

Following these works, we studied how the volume-filling Keller-Segel model (VFKS) could be obtained as the diffusion limit of a kinetic ‘velocity jump’ model, giving insights into how the individual mechanisms at the cell level can lead to volume-filling effects at the population level. In the framework of Xinran Ruan post-doctorat, we were able to successfully derive the VFKS model from a kinetic ‘run-and-tumble’ model, and showed that density effects had to be included both in the transport term and in the turning operator [52]. We developed an asymptotic preserving numerical method to show numerically the convergence of the kinetic model to the PDE system.

8.7.6 Plasticity in cancer cell populations and philosophy of cancer

From a biological point of view, adaptive dynamics and its asymptotics rely on the so-called *plasticity* of cancer cell populations, i.e., their ability to easily change their phenotypes, thanks to their poor differentiation, to adapt to a changing environment, in particular to develop resistance to cancer treatments. This point of view has been reviewed, from a biological, mathematical and ‘philosophy of cancer’ point of view in [171, 98]. In these articles, and in the invited conference paper [96], is particularly developed the idea according to which cancer is characterized, not so much as a default of control on cell proliferation, but at least equally as a default of control on cell differentiations. This idea is not new (in particular it has been put forward in Marta Bertolaso’s book of 2016 “Philosophy of cancer”, Springer Publ.), nevertheless it could lead to modeling developments that should complement the classical models based on sheer proliferation of cell populations, and possibly open the way to new therapeutic tracks, provided that can be found actual means of control and reestablishment of physiological cell differentiation, that so far exist for very few cancer diseases (e.g., for acute promyelocytic leukemia).

Of note, philosophy of cancer is thus a point of convergence between mathematics, biology and social and human sciences, that may help biologists and mathematicians to bring new insight to understanding this old disease.

8.8 Macroscopic limit and asymptotic behavior of collective dynamics

8.8.1 Graph limit

Participants: Nathalie Ayi, Nastassia Pouradier Duteil.

We have developed a model for collective dynamics with weights, in which each agent is described not only by its position, but also by a positive “weight of influence”. The weights allow us to model a social hierarchy within the group, where the most influential agents (the ones with the largest weights) have a larger impact on the behavior of the group. Moreover, the weights of influence are susceptible to evolve in time, which models the changing social hierarchy.

As often in models of collective dynamics, we focused on the question of its continuum limit when the number of agents tends to infinity. However, for this particular model, the classical mean-field limit can fail when the weight dynamics do not preserve indistinguishability of the particles: indeed, the essence of the mean-field approach is to describe the population by its density, hence requiring all particles to be indistinguishable. This led us to another approach: the graph limit method.

In 2014, Medvedev used techniques from the recent theory of graph limit to derive rigorously the continuum limit of dynamical models on deterministic graphs. In our paper [72], we extended this idea to our collective dynamics model with time-varying weights, adopting the graph point of view. The central point of this approach consists of describing the infinite population by two functions $x(s)$ and $m(s)$ over the space of continuous indices s . The discrete system of ODEs is then shown to converge as N goes to infinity to a system of two non-local diffusive equations in the space of continuous indices. We showed that this approach is more general than the mean-field one, and the Graph Limit can be derived for a much greater variety of models. We established the existence and uniqueness of solutions to the models, and provided a rigorous mathematical justification for taking the graph limit in a general context.

8.8.2 Large-scale dynamics of self-propelled particles moving through obstacles

Participants: Pedro Aceves-Sanchez, Pierre Degond, Eric Keaveny, Angelika Manhart, Sara Merino, Diane Peurichard.

In [60], we modeled and studied the patterns created through the interaction of collectively moving self-propelled particles (SPPs) and elastically tethered obstacles. Simulations of an individual-based model reveal at least three distinct large-scale patterns: travelling bands, trails and moving clusters. This motivated the derivation of a macroscopic partial differential equations model for the interactions between the self-propelled particles and the obstacles, for which we assumed large tether stiffness. The result is a coupled system of non-linear, non-local partial differential equations. By performing a linear stability analysis, we showed that patterning was expected if the interactions are strong enough and allowed for the predictions of pattern size from model parameters. The macroscopic equations revealed that the obstacle interactions induce short-ranged SPP aggregation, irrespective of whether obstacles and SPPs are attractive or repulsive. Following these works, in [13] we performed an in-depth investigation of pattern formation of the discrete and continuum models in two dimensions: we provided phase-diagrams and determined the key mechanisms for bifurcations to happen using linear stability analysis. As a result, we discovered that the agent-agent repulsion, the agent-obstacle repulsion and the obstacle’s spring stiffness are the key forces in the appearance of patterns, while alignment forces between the particles play a secondary role. The second major novelty of [13] lies in the development of an innovative methodology to compare discrete and continuum models that we proposed to perform an in-depth analysis of the agreement between the discrete and continuum models.

8.8.3 Early morphogenesis of rod-shaped bacteria

Participants: Marie Doumic, Sophie Hecht, Marc Hoffmann, Diane Peurichard.

To model the morphogenesis of rod-shaped bacterial micro-colony, several individual-based models have been proposed in the biophysical literature. When studying the shape of micro-colonies, most models present interaction forces such as attraction or filial link. In the article [109], we propose a model where the bacteria interact only through non-overlapping constraints. We consider the asymmetry of the bacteria, and its influence on the friction with the substrate. Besides, we consider asymmetry in the mass distribution of the bacteria along their length, and the division follows the so-called "adder model" (see Section 8.1.1). These new modelling assumptions allow us to retrieve mechanical behaviours of micro-colony growth without the need of interaction such as attraction. We compare our model to various sets of experiments, discuss our results, and propose several quantifiers to compare model to data in a systematic way. We now aim at deriving a space-and-size structured population equation as the macroscopic limit of a simplified version of this model.

8.8.4 A new model for the emergence of blood capillary networks

Participants: Pedro Aceves-Sanchez, Benjamin Aymard, Louis Casteilla, Pierre Degond, Patrick Kennel, Anne Lorisgnol, Diane Peurichard.

In [60], we propose a new model for the emergence of blood capillary networks. We assimilate the tissue and extra cellular matrix as a porous medium, using Darcy's law for describing both blood and interstitial fluid flows. Oxygen obeys a convection-diffusion-reaction equation describing advection by the blood, diffusion and consumption by the tissue. Discrete agents named capillary elements and modelling groups of endothelial cells are created or deleted according to different rules involving the oxygen concentration gradient, the blood velocity, the sheer stress or the capillary element density. Once created, a capillary element locally enhances the hydraulic conductivity matrix, contributing to a local increase of the blood velocity and oxygen flow. No connectivity between the capillary elements is imposed. The coupling between blood, oxygen flow and capillary elements provides a positive feedback mechanism which triggers the emergence of a network of channels of high hydraulic conductivity which we identify as new blood capillaries. We provide two different, biologically relevant geometrical settings and numerically analyze the influence of each of the capillary creation mechanism in detail. All mechanisms seem to concur towards a harmonious network but the most important ones are those involving oxygen gradient and sheer stress. This work offers a new paradigm for capillary network creation by placing the flow of blood at the central place in the process. The model proposed in [61] provides a proof of concept of this approach and elaborates a road map by which the model can be gradually improved towards a fully fledged simulator of blood capillary network formation. Such simulator would have huge potential for biological or clinical applications in cancer, wound healing, tissue engineering and regeneration.

9 Bilateral contracts and grants with industry

9.1 Bilateral grants with industry

Participants: Gaëtan Vignoud, Philippe Robert.

Contract Safran Electronics, Defense and Sorbonne Universite (G. Vignoud) Computer-Vision and Deep Learning applied to Safran Electronics Defense objectives. Survey of multiple-instance learning and few-shot learning algorithms applied to DRI (detection, recognition, identification).

Contract with TreeFrog Pharmaceuticals Simulation of growth efficiency and cell yield in multiple in vitro experimental settings to better understand the impact of the chosen culturing method and to guide potential improvements of the outcome.

10 Partnerships and cooperations

Participants: Luis Almeida, Pierre-Alexandre Bliman, Marie Doumic, Benoit Perthame, Diane Peurichard, Nastassia Pouradier-Duteil.

10.1 International initiatives

10.1.1 Inria associate team not involved in an IIL or an international program

MoCoVec

Title: Modelling and Biological Control of Vector-Borne Diseases: the case of Malaria and Dengue

Duration: 2020 -> 2024

Coordinator: Cláudia Pio Ferreira (claudia.pio@unesp.br)

Partners:

- Universidade Estadual Paulista Guaratingueta (Brésil)

Inria contact: Pierre-Alexandre Bliman

Summary: Taking into account all the infectious disease spread worldwide, vector-borne diseases account for over 17%. For a huge part of them, no efficient vaccine is available, and control efforts must be done on the vector population. Focusing on dengue and malaria, two diseases transmitted by vector mosquito and which cause high morbidity and mortality around the world, this project aims to model disease transmission, its spread and control, in a context of climatic and environmental change. For this, the main drives of disease transmission will be addressed to understand which factors modulate the spatio-temporal patterns observed, especially in Brazil. Combining techniques of data analysis with mathematical models and control theory, the plan is to work on data analysis to define potential biotic and abiotic factors that drives malaria and dengue disease dynamics; to study and model the effects of seasonality on the spread of the diseases; to understand spatial aspects of the transmission through the setup of models capable to account for nonlocal and heterogeneous aspect; and to analyse alternative approaches of mosquito control, especially the biological control methods based on sterile mosquitoes or on infection by bacterium that reduces the vectorial capacity.

10.1.2 STIC/MATH/CLIMAT AmSud projects

NEMBICA

Title: NEw Methods for BIological Control of the Arboviruses

Program: STIC-AmSud

Duration: January 1, 2020 – (*missing: YEARMONTHEND*)

Local supervisor: Pierre-Alexandre Bliman

Partners:

- Gerdtzen (Chili)
- Universidad del Quindio
- Universidad nacional de Asuncion

Inria contact: Pierre-Alexandre Bliman

Summary: The present project is concerned with new strategies to control the spread of established diseases (such as e.g. dengue, chikungunya and Zika) and potentially emerging or reemerging diseases (e.g. Mayaro, Oropouche and Yellow fever) transmitted by mosquitoes *Aedes aegypti* and *Aedes albopictus*. Due especially to the widespread resistance to the insecticides traditionally used to control the vectors, the use of sterile insect (SIT – Sterile Insect Technique), of transgenic mosquitoes (RIDL – Release of Insect carrying Dominant Lethal gene) and/or of mosquitoes infected with the bacterium *Wolbachia* (which drastically reduces their vector competence), are considered as viable control alternatives. These biological control techniques envisage either the elimination of the vector in a locality (SIT or RIDL), or its local substitution by a population refractory to the arboviruses transmitted by these species (*Wolbachia*). How to achieve the releases on a large scale in order to maximize their effect is still a source of some central questions that we aim to study here. We will focus more specifically on the issues related to spatial spreading of the treatment, on observer techniques for estimating the number of mosquitoes during the releases, and on optimal and non-optimal control approaches. An important modeling effort will also be conducted on some key issues: we will assess the effects of the chemical and mechanical control methods on the success of the above techniques; the consequences of inter and intra-species competition in larval phase (an important issue so far overlooked); the questions raised by the use of self-propagating genetic mechanisms and the definition of associated efficacy measures; and develop genome scale model of *Wolbachia* in order to identify in the parasite-host relationship, crucial biological factors that could dynamically affect the dissemination.

10.1.3 Participation in other International Programs

Title: Modélisation de la biomécanique cellulaire et tissulaire - MOCETIBI

Program: IRP CNRS

Duration: January 2022 – December 2026

Local supervisor: Luis Almeida

Partners:

- Sorbonne Université
- Université Paris Cité
- Université Grenoble Alpes
- Politecnico di Torino
- Politecnico di Milano

Inria contact: Luis Almeida

10.2 National initiatives

Mamba (Marie Doumic and Philippe Robert) participates to the GDR "MeDyna" (mechanisms and dynamics of assemblies of peptides and proteins), coordinated by Stéphane Bressanelli from IBPC.

10.2.1 ANR

ANR ODISSE, 2020-2023 , headed by Vincent Andrieu, univ. of Lyon.

ANR InTelo 2017-2020 Telomere dynamics, headed by Teresa Teixeira (IBPC, Paris).

INCa/DGOS; PRT-K 2018-2021 Khê HOANG-XUAN, Hôpital Universitaire La Pitié Salpêtrière, Paris. Mathematical modeling at micro and macroscopic level of primary central nervous system lymphomas (PCNSL).

ANR ENERGENCE; 2023-2026 Diane Peurichard, RESTORE lab, Toulouse. ENERGY driven modelling of tissue architecture emerGENCE and homeorhesis.

10.2.2 ITMO Cancer 2016 - 2020, HTE call (heterogeneity of tumours in their ecosystems)

ITMO Cancer EcoAML Early leukaemogenesis in Acute Myelogenous Leukaemia (AML), 8 teams headed by François Delhommeau (CDR St Antoine, Paris).

ITMO Cancer MoGIIImaging Treatment-induced treatment resistance and heterogeneity in glioblastoma, 8 teams headed by Elizabeth Moyal (INSERM, Toulouse).

10.2.3 Inria Covid-19 mission

Pierre-Alexandre Bliman participates in the project HealthyMobility (Optimal Policies for Human Mobility to Control CoVID19-Epidemic Spread under Health and Economics Constraints), in cooperation with the Necs-Post team (CNRS, Gipsa, UGA, Inria), in the framework of Inria Covid-19 mission.

11 Dissemination

Participants: Luis Almeida, Pierre-Alexandre Bliman, Giorgia Ciavolella, Jean Clairambault, Noemi David, Marie Doumic, Guillaume Garnier, Benoit Perthame, Diane Peurichard, Nastassia Pouradier Duteil.

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

Luis Almeida, Marie Doumic and Benoit Perthame organized (together with Vincent Calvez and Patricia Reynaud-Bouret) the one trimester program at IHP on Mathematical modeling of organization in living matter. from January to April 2022.

Luis Almeida and Benoit Perthame organized (together with Tommaso Lorenzi and Chloe Audebert) the Tissue growth and movement workshop, Paris, France, in January 2022.

Luis Almeida organized (together with Odo Diekmann) the Mathematical Epidemiology workshop, Paris, France, in February 2022.

Marie Doumic organized (together with Patricia Reynaud-Bouret and Marc Hoffmann) the Inverse Problems in Biology workshop, IHP, in March 2022.

Marie Doumic organized (together with Sara Merino, Christian Schmeiser and Pierre Degond) a programme in Vienna, Erwin Schroedinger Institut, in November 2022, on "Mathematical Methods for the Study of Self-organization in the Biological Sciences".

Luis Almeida, Giorgia Ciavolella, Jean Clairambault, Noemi David and Alexandre Poulain (together with Dimitrios Katsaounis, Theodoros Katsaounis and Nikolaos Sfakianakis) the MBMC 2022 Workshop and School, Heraklion, Greece, in August and September 2022.

Luis Almeida organized (together with Tommaso Lorenzi) the Modeling Cell and Tissue Biomechanics Workshop, Paris, France, in October 2022.

Luis Almeida organized (together with Carlota Rebelo) the Mathematical Modeling in Vector Control Workshop, Foz do Arelho, Portugal, in November 2022.

11.1.2 Scientific events: selection

Chair of conference program committees Philippe Robert is co-chair of the Sigmetrics/Performance 2022 conference.

Member of the conference program committees Pierre-Alexandre Bliman is member of the Program Committee of European Control Conference 2023.

Reviewer Pierre-Alexandre Bliman is reviewer for the conference IEEE Conference on Decision and Control 2022, and the IFAC World Congress 2023

11.1.3 Journal

Reviewer - reviewing activities

Marie Doumic is Editor in Chief of ESAIM: Proceedings and Surveys, and Associate Editor for Journal of Mathematical Biology, Kinetic and Related Models, and Bulletin des sciences mathématiques. Philippe Robert is Associate Editor of the journal “Stochastic Models”. Nastassia Pouradier Duteil is a guest editor for a Special Issue of OCAM entitled “Optimal control in therapeutics and epidemiology”. Diane Peurichard is regular reviewer for the journals Mathematics, JCOMP, Essaim: proceeding and surveys. Pierre-Alexandre Bliman is reviewer for Automatica, Bulletin of Mathematical Biology, Journal of Mathematical Biology and Nonlinear Analysis: Real World Applications.

11.1.4 Invited talks

Giorgia Ciavolella gave a talk in February 2022 at the Groupe de travail des thésards, LJLL, Sorbonne Université, Paris, France ; in March at the Seminar at Politecnico di Torino, Politecnico di Torino, Turin, Italy ; in June 2022 at the Nonlinear PDEs and Applications workshop, CNR, Rome, Italy ; in October 2022 at the Modelling cell and tissue biomechanics workshop, LJLL, Sorbonne Université, Paris, France. She presented a poster in January 2022 at the Tissue growth and movement, Membrane problems and application to cell invasion, Institut Henri Poincaré, Paris, France. She attended the workshop Mathematical modeling of organization in living matter, Institut Henri Poincaré, Paris, France.

Noemi David gave an invited talk in September 2022 at the Workshop Parabolic and kinetic models in population dynamics, Institut de Mathématiques de Toulouse ; in August at GAMM, Minisymposium Tissue growth: Analytical aspects and applications, Aachen; in July at the International Conference on Partial Differential Equations, Shanghai Jiao Tong University (SJTU), online ; in May at the Frontiers in numerical analysis of kinetic equations, INI, University of Cambridge - Seminar in April at the Frontiers in kinetic equations for plasmas and collective behaviour, INI, University of Cambridge. She presented posters at the conference Mathematical Modeling of Organization in Living Matter, CIRM, Marseille, and at the Workshop tissue growth and movement, IHP, Paris.

Marie Doumic gave a plenary talk at the PICO conference in Caen, October 2022, a Colloquium talk in December 2022 in Bielefeld, Germany, an invited talk at the workshop "population dynamics", Sorbonne Université. She gave a 4-hour course at the Summer School of the MMB chaire in Aussois, June 2022.

Guillaume Garnier participated to a math-bio conference in CIRM, Marseille, in March 2022, and to the MMB chaire summer school in Aussois in June 2022, and presented a poster at the Vienna programme "Mathematical Methods for the Study of Self-organization in the Biological Sciences", November 2022.

Jules Guilberteau gave a talk in April 2022 at the Groupe de travail des thésards, LJLL, Sorbonne Université, Paris, France, in June at the Congrès national d'analyse numérique (CANUM), Evian, France and in September at the European Conference of Mathematics and Theoretical Biology (ECMTB). He attended the School "diffusive systems" at the Hausdorff School for Advanced Studies in Mathematics in Bonn, Germany, in April.

Lucie Laurence and Philippe Robert attended to the "Chemical Reaction Networks" workshop in Torina from July 6 to July 8. Lucie Laurence has participated to the corresponding summer school in Torgnon from July 10 to July 16.

Nastassia Pouradier Duteil gave talks at the workshop "Mathematical challenges in modelling population dynamics" (SU, Paris), at the workshop "Round Meanfield" (Rome) and at the workshop "Kinetic and hydrodynamic descriptions in collective behavior" (Granada). She gave a mini-course at the 25th International Symposium on Mathematical Theory of Networks and Systems. She was invited to give a seminar at the University of Warwick.

Anaïs Rat gave seminar talks at IBPC and at CIRM, she supervised a team of highschool female students at the "stage des cigales" at CIRM in 2021, and participated to the research school "mathematical models and living matter organisation" at CIRM and to the trimester at IHP.

Philippe Robert gave a talk "Stochastic Models of Regulation of Transcription in Biological Cells" at the "12ème Atelier d'Evaluation de Performances" at INRIA Grenoble from July 4 to July 5. Philippe Robert gave a series of Lectures on "Stochastic Calculus with Poisson Processes" at the department of Mathematics of the University of North Carolina, Chapel-Hill from November 9 to November 19.

Jana Zaherddine gave a talk "Stochastic Models of Regulation of Transcription in Biological Cells" at the University of Tours on December, 8.

Diane Peurichard gave a talk in the workshop 'Mathematical Methods for the Study of Self-organization in the Biological Sciences' at the Erwin Schrodinger Institute, Wien, Austria in november 2022

Valeria Caliaro gave a talk at the ECMTB 2022 conference in the mini-symposium entitled 'Non-local models in mathematical biology', september 2022, Heidelberg

Pauline Chassonnery co-organized the workshop CARE at RESTORE, Toulouse on february 2023 Pauline Chassonnery gave a talk at the 'Mathematical Biology on the Mediterranean Conference', september 2022.

Marcel Fang gave a talk at the ECMTB 2022 conference, at 13th International Conference on Dynamical Systems applied to Biology and Natural Sciences (DSABNS) and at the European Control Conference 2022.

Pierre-Alexandre Bliman gave a talk at Imperial College, London; Oxford University; at CIRM workshop on Control theory and epidemilogy; at University of Lisbon; and during the Inverse Problems in Biology workshop held in IHP.

11.1.5 Scientific expertise

Pierre-Alexandre Bliman is expert for the Belgian Fonds National de la Recherche Scientifique.

11.1.6 Research administration

Marie Doumic is a member of the scientific council of INSMI and of the CID51 CNRS Committee (recruitment of junior and senior researchers in mathematics, computer science, physics and chemistry applied to biology).

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

Philippe Robert is teaching the master M2 course ‘Modèles Stochastiques de la Biologie Moléculaire’ at Sorbonne Université.

Nastassia Pouradier Duteil is teaching a course on Mathematics in the Sorbonne University program RESPE “Retour aux Etudes Supérieures des Personnes Exilées”. She also supervised an L3 project on Evolutionary Games.

Marie Doumic is a part-time "professeuse chargée de cours" in Ecole Polytechnique (80 h/year), teaches probability (L3) and variationnal analysis of PDE (M1).

Diane Peurichard gave a 4h course for the 'Master de physique cellulaire', Strasbourg University on January 26th, 2023 entitled 'Mathematical modelling in biological systems'

Luis Almeida is in charge of the mathematical biology major of the M2 program of Sorbonne Université. He teaches the Introduction to Mathematical Biology M2 course.

Guillaume Garnier gave exercise classes in L1 (linear algebra and probabilities) and L3 (measure theory).

Pierre-Alexandre Bliman and Marcel Fang gave exercise classes at licence level in Sorbonne Université.

Nga Nguyen gave exercise classes at licence level in Université Sorbonne Paris-Nord.

11.2.2 Supervision

Nastassia Pouradier Duteil is the PhD advisor of Jules Guilberteau “Modeling and analysis of cell differentiation. Applications to the epithelial-mesenchymal transition”, from September 1st, 2020.

Philippe Robert is the PhD advisor of

- Lucie Laurence, “Stability of Stochastic Chemical Networks”, from September 1st 2021.
- Gaëtan Vignoud, “Plasticity of Stochastic Neural Networks”, from September 1st, 2018 with co-advisor Laurent Venance.
- Jana Zaherddine, “Stochastic Models of allocation of resources in prokaryotic cells”, from September 1st, 2020 with co-advisor Vincent Fromion.

Diane Peurichard is the PhD advisor of Valeria Caliaro (co-supervision with O. Chara) on the mathematical modelling of Axolotl regeneration from September 2019 and of Pauline Chassonnery (co-supervision with L. Casteilla, RESTORE, Toulouse) on the 3D mathematical modelling of adipose tissue morphogenesis from September 2020

Pierre-Alexandre Bliman is PhD advisor of Marcel Fang from September 2021, and PhD co-advisor of Nga Nguyen (September 2021) and Assane Savadogo (September 2020).

11.2.3 Juries

Philippe Robert has been the reviewer of Tien Cuong Phi’s PhD document “Décomposition de Kalikow pour des processus de comptage à intensité stochastique”, Université Côte d’Azur, defended on June, 14.

Diane Peurichard is a member of the jury for CRCN/ISFP positions at Inria Saclay, 2023.

Pierre-Alexandre Bliman has been member of the board of Douglas Madalena Martins’ Master thesis at COPPE - Universidade Federal de Rio de Janeiro

11.2.4 Interventions

Guillaume Garnier gave two lectures and a 4-hour course for highschool pupils at ENS, was a member of the committee of TFJM organised by the NGO Animath, and supervised the team of Sorbonne Université for the international competition iGEM (the team won the price "Best Plant Synthetic Biology project").

Nastassia Pouradier Duteil and Diane Peurichard took part in the scientific event for high school girls entitled "Master class lycéennes" organized by the Sephora Berrebi association on June 27, 2022. They organized an activity around collective behaviour.

Diane Peurichard together with Sophie Hecht organized a stand at the 'Fete de la science', in october 2022 at Grands moulins, Paris.

12 Scientific production

12.1 Major publications

- [1] L. Almeida, P.-A. Bliman, G. Nadin, B. Perthame and N. Vauchelet. 'Final size and convergence rate for an epidemic in heterogeneous population'. working paper or preprint. Oct. 2020. URL: <https://hal.sorbonne-universite.fr/hal-02981952>.
- [2] M. Doumic, S. Hecht and D. Peurichard. 'A purely mechanical model with asymmetric features for early morphogenesis of rod-shaped bacteria micro-colony'. In: *Mathematical Biosciences and Engineering* 17.6 (Oct. 2020), <http://aimspress.com/article/doi/10.3934/mbe.2020356>. URL: <https://hal.archives-ouvertes.fr/hal-02865566>.

12.2 Publications of the year

International journals

- [3] L. Almeida, C. Audebert, E. Leschiera and T. Lorenzi. 'A hybrid discrete-continuum modelling approach to explore the impact of T-cell infiltration on anti-tumour immune response'. In: *Bulletin of Mathematical Biology* (2022). URL: <https://hal.archives-ouvertes.fr/hal-03722100>.
- [4] L. Almeida, J. Bellver Arnau and Y. Privat. 'Optimal release strategies for mosquito population replacement'. In: *Applied Mathematics and Optimization* (2022). URL: <https://hal.archives-ouvertes.fr/hal-03212761>.
- [5] L. Almeida, M. Duprez, Y. Privat and N. Vauchelet. 'Optimal control strategies for the sterile mosquitoes technique'. In: *Journal of Differential Equations* 311 (22nd Feb. 2022), pp. 229–266. DOI: [10.1016/j.jde.2021.12.002](https://doi.org/10.1016/j.jde.2021.12.002). URL: <https://hal.archives-ouvertes.fr/hal-02995414>.
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- [8] F. E. Alvarez, J. A. Carrillo and J. Clairambault. 'Evolution of a structured cell population endowed with plasticity of traits under constraints on and between the traits'. In: *Journal of Mathematical Biology* (4th Nov. 2022). URL: <https://hal.archives-ouvertes.fr/hal-03344894>.
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- [10] P.-A. Bliman and Y. Dumont. 'Robust control strategy by the Sterile Insect Technique for reducing epidemiological risk in presence of vector migration'. In: *Mathematical Biosciences* (June 2022), p. 108856. DOI: [10.1016/j.mbs.2022.108856](https://doi.org/10.1016/j.mbs.2022.108856). URL: <https://hal.archives-ouvertes.fr/hal-03699418>.

- [11] B. Bonnet, N. Pouradier Duteil and M. Sigalotti. ‘Consensus Formation in First-Order Graphon Models with Time-Varying Topologies’. In: *Mathematical Models and Methods in Applied Sciences* (2022). URL: <https://hal.archives-ouvertes.fr/hal-03418399>.
- [12] G. Ciavolella. ‘Effect of a membrane on diffusion-driven Turing instability’. In: *Acta Applicandae Mathematicae* (20th Feb. 2022). URL: <https://hal.archives-ouvertes.fr/hal-03231369>.
- [13] P. Degond, A. Manhart, S. Merino-Aceituno, D. Peurichard and L. Sala. ‘How environment affects active particle swarms: a case study’. In: *Royal Society Open Science* 9 (2022), p. 220791. URL: <https://hal.archives-ouvertes.fr/hal-03684115>.
- [14] J. Delacour, M. Doumic, S. Martens, C. Schmeiser and G. Zaffagnini. ‘A mathematical model of p62-ubiquitin aggregates in autophagy’. In: *Journal of Mathematical Biology* 84.3 (1st Mar. 2022). DOI: [10.1007/s00285-021-01659-2](https://doi.org/10.1007/s00285-021-01659-2). URL: <https://hal.archives-ouvertes.fr/hal-02548223>.
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International peer-reviewed conferences

- [27] M. Fang and P.-A. Bliman. ‘Modelling, Analysis, Observability and Identifiability of Epidemic Dynamics with Reinfections’. In: ECC 2022 - European Control Conference. London, United Kingdom, 12th July 2022. URL: <https://hal.inria.fr/hal-03541732>.

Conferences without proceedings

- [28] P. Berardi, S. Mattarocci, R. Langston, P. Jolivet, G. Charvin, M. Doumic, Z. Xu and M. T. Teixeira. ‘How the shortest telomere in the cell signals senescence’. In: EMBO Workshop on Telomere function and evolution in health and disease. Troia, Portugal, 6th Sept. 2022. URL: <https://hal.science/hal-03960641>.
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Scientific book chapters

- [30] L. Almeida, J. Bellver Arnau, M. Duprez and Y. Privat. ‘Minimal cost-time strategies for mosquito population replacement’. In: *Optimization and Control for Partial Differential Equations*. Vol. 29. Radon Series on Computational and Applied Mathematics. De Gruyter, 11th Mar. 2022. URL: <https://hal.archives-ouvertes.fr/hal-02532677>.
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Doctoral dissertations and habilitation theses

- [32] J. Bellver Arnau. ‘Optimal mosquito release strategies for vector-borne disease control’. Sorbonne Université, 14th Dec. 2022. URL: <https://hal.science/tel-03953920>.
- [33] G. Ciavolella. ‘Reaction-diffusion equations with membrane conditions describing tumor invasion’. Sorbonne Université; Università degli studi di Roma "Tor Vergata" (1972-....), 4th Oct. 2022. URL: <https://theses.hal.science/tel-03935724>.
- [34] N. David. ‘Incompressible limit and well-posedness of PDE models of tissue growth’. Sorbonne Universites, UPMC University of Paris 6, 4th July 2022. URL: <https://hal.science/tel-03916210>.
- [35] E. Leschiera. ‘Mathematical models of tumour-immune interactions: discrete and continuum approaches’. Sorbonne Universites, UPMC University of Paris 6, 10th Oct. 2022. URL: <https://hal.archives-ouvertes.fr/tel-03869890>.
- [36] G. Vignoud. ‘Synaptic plasticity in stochastic neuronal networks’. Sorbonne Université, 8th Apr. 2022. URL: <https://theses.hal.science/tel-03640150>.

Reports & preprints

- [37] L. Almeida, J. Bellver Arnau, Y. Privat and C. Rebelo. *Vector-borne disease outbreak control via instant vector releases*. 19th Oct. 2022. URL: <https://hal.archives-ouvertes.fr/hal-03577751>.

- [38] L. Almeida, A. Léculier, G. Nadin and Y. Privat. *Optimal control of bistable travelling waves: looking for the spatial distribution of a killing action to block a pest invasion*. 12th Oct. 2022. URL: <https://hal.archives-ouvertes.fr/hal-03811940>.
- [39] L. Almeida, C. Audebert, E. Leschiera and T. Lorenzi. *Discrete and continuum models for the coevolutionary dynamics between CD8+ cytotoxic T lymphocytes and tumour cells*. 9th Nov. 2022. URL: <https://hal.archives-ouvertes.fr/hal-03348931>.
- [40] L. Almeida, P.-A. Bliman, N. Nguyen and N. Vauchelet. *Steady-state solutions for a reaction-diffusion equation with Robin boundary conditions: Application to the control of dengue vectors*. 14th Sept. 2022. URL: <https://hal.archives-ouvertes.fr/hal-03775887>.
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- [44] J. Clairambault. *Mathematical modelling of cancer growth and drug treatments: taking into account cell population heterogeneity and plasticity*. 28th Nov. 2022. URL: <https://hal.inria.fr/hal-03938411>.
- [45] N. David. *Phenotypic heterogeneity in a model of tumor growth: existence of solutions and incompressible limit*. 11th Apr. 2022. URL: <https://hal.archives-ouvertes.fr/hal-03636939>.
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- [51] A. Léculier and N. Nguyen. *A control strategy for Sterile Insect Techniques using exponentially decreasing releases to avoid the hair-trigger effect*. 14th Nov. 2022. URL: <https://hal-univ-paris13.archives-ouvertes.fr/hal-03851525>.
- [52] D. Peurichard, X. Ruan and G. Estrada-Rodriguez. *Asymptotic preserving schemes for nonlinear kinetic equations leading to volume-exclusion chemotaxis in the diffusive limit*. 2nd Nov. 2022. URL: <https://hal.inria.fr/hal-03950098>.
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- [55] P. Robert and G. Vignoud. *A Palm Space Approach to Non-Linear Hawkes Processes*. 23rd Dec. 2022. URL: <https://hal.inria.fr/hal-03911583>.

- [56] Y. Yin, K. Breuhahn, H.-U. Kauczor, O. Sedlacek, I. Vignon-Clementel and D. Drasdo. *Diffusion-weighted MRI -guided needle biopsies permit quantitative tumor heterogeneity assessment and cell load estimation*. 23rd June 2022. URL: <https://hal.inria.fr/hal-03702898>.
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Other scientific publications

- [59] C. Elbar, B. Perthame and J. Skrzeczkowski. ‘Pressure jump and radial stationary solutions of the degenerate Cahn-Hilliard equation (Extended version)’. In: *Comptes Rendus. Mécanique* (2023). URL: <https://hal.science/hal-03696545>.

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