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Activity Report 2019

Project-Team MAMBA

Modelling and Analysis for Medical and
Biological Applications

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

RESEARCH CENTER
Paris

THEME
**Modeling and Control for Life Sci-
ences**

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Project-Team MAMBA

Creation of the Team: 2014 January 01, updated into Project-Team: 2015 April 01

Keywords:

Computer Science and Digital Science:

- 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

1. Team, Visitors, External Collaborators

Research Scientists

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- Pierre-Alexandre Bliman [Inria, Senior Researcher, HDR]
- Jean Clairambault [Inria, Emeritus, HDR]
- Dirk Drasdo [Inria, Senior Researcher, HDR]
- Luis Lopes Neves de Almeida [CNRS, Senior Researcher, HDR]
- Diane Peurichard [Inria, Researcher]
- Nastassia Pouradier Duteil [Inria, Researcher, from Sep 2018]
- Philippe Robert [Inria, Senior Researcher, HDR]

Faculty Members

- Ayman Moussa [Univ Pierre et Marie Curie, Associate Professor, until Aug 2019]
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- Markus Schmidtchen [Sorbonne Université, from October 2019]
- Cécile Carrère [Sorbonne Université, Post-Doctoral Fellow, until Oct 2019]
- Jules Dichamp [Post-Doctoral Fellow, with IfADo Leibniz Institute, Dortmund (Germany)]
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- Florian Joly [Inria, Post-Doctoral Fellow, from May 2019 until Oct 2019]
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2. Overall Objectives

2.1. 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, which can be seen as active agents. Mathematically, they can be represented either explicitly as individuals with their dynamics modelled e.g. through branching trees and piecewise deterministic Markov processes (PDMP), 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) the 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 intracellular 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, among which we can quote: the collaboration with St Antoine Hospital in Paris within the Institut Universitaire de Cancérologie of Sorbonne Université (IUC, Luis Almeida, Jean Clairambault, Dirk Drasdo, Benoît Perthame); Institut Jacques Monod (Luis Almeida); INRA Jouy-en-Josas (VIM team, headed by Human Rezaei and Vincent Béringue (Marie Doumic and Philippe Robert); Wei-Feng Xue's team in the university of Canterbury (Marie Doumic and Philippe Robert); our collaborators within the HTE program (François Delhommeau at St Antoine, Thierry Jaffredo, and Delphine Salort at IBPS, Sorbonne Université, Paris; François Vallette at INSERM Nantes); Frédéric Thomas at CREEC, Montpellier; Hôpital Paul Brousse through ANR-IFlow and ANR-iLite; Institut de Biologie Physico-Chimique (IBPC, Paris, Teresa Teixeira's team; Marie Doumic); the close experimental collaborations that emerged through the former associated team QUANTISS (Dirk Drasdo), particularly at the Leibniz Institute for Working Environment and Human Factors in Dortmund, Germany; Yves Dumont at CIRAD, Montpellier.

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 4.3). 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 the question 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

Personnel Pierre-Alexandre Bliman, Jean Clairambault, Marie Doumic, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil, Philippe Robert

Project-team positioning

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. [135], [73], [99], [84]. 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 Tom Banks (USA), 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.

Scientific achievements

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 [78], 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.

In [96], the case of constant fragmentation rate and linear growth rate has been investigated in a deterministic approach, whereas similar questions were simultaneously raised but in a stochastic process approach in [75].

We also enriched the models by taking into account a nucleation term, modeling the spontaneous formation of large polymers out of monomers [147]. 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 [128], [125], [124], [126]. Space may be added as a complementary structure variable provided that something is known of the (Cartesian) geometry of the population [127], which is seldom the case.

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 [81], [110], 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 [61], [120], [156]. 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 [59].

Control 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. We have designed optimal control strategies to drive collective dynamics to consensus. In the case where consensus and clustering are situations to be avoided (for example in crowd dynamics), we designed control strategies to keep the system away from clustering.

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 [138], followed by [134], [119], [139], [83]. 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 [89].

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 homeostasis, 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 [72]. 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 [71].

Models of population dynamics structured in phenotype

The collaboration of Jean Clairambault with Emmanuel Trélat and Camille Pouchol (from September this 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 [146], 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 [13], [45].

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 [24]. 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 (Imperial College London). 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. 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 [24], 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.

Collaborations

- Nucleation, growth and fragmentation equations: **Klemens Fellner**, university of Graz, Austria, **Piotr Gwiazda**, Polish Academy of Sciences, Poland, **Christian Schmeiser**, university of Vienna.
- 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 MoGIIImaging (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.
- Mendelian inheritance and resistance in density-dependent population dynamics: **Pastor Pérez-Estigarríbia**, **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, **MAPMO**, **Orléans**, **Ewelina Zatorska**, University College London

3.3. Methodological axis 2: reaction and motion equations for living systems

Personnel

Luis Almeida, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil, Dirk Drasdo

Project-team positioning

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.

Scientific achievements

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 [117]. The extension to higher dimensions has been studied in [87]. 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 [109], [116].

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

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 [150] 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 [118]. 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 [137] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [121].

Since more realistic systems are used in the analysis of medical images, we have extended these studies to include active motion of cells in [136], viscosity in [141] and proved regularity results in [129]. 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 [140], 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 [122].

Two-way coupling of diffusion and growth

We are currently developing a mathematical framework for diffusion equations on time-evolving manifolds, where the evolution of the manifold is a function of the distribution of the diffusing quantity. The need for such a framework takes its roots in developmental biology. Indeed, 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. In addition to the elaboration of this theoretical framework, we also collaborate with a team of developmental biologists from Rutgers University (Camden, New Jersey) to develop a model for 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), 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

Personnel

Marie Doumic, Dirk Drasdo.

Project-team positioning

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 [103], TRAIL treatment of HeLa cells [74], growth of multicellular spheroids [115], blood detoxification after drug-induced liver damage [149], [107].

This naturally led 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 Tom Banks (Raleigh, USA) and Philippe Moireau (Inria M3DISIM) in inverse problems and data assimilation, and with numerous experimentalists.

Scientific achievements

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.

Estimation methods for growing and dividing populations

In this domain, all originated in two papers in collaboration with J.P. Zubelli in 2007 [143], [101], 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 [78]. 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) [97]. 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 [100],

a work which inspired also very recently other groups in statistics and probability [75], [112] and was the basis for Adélaïde Olivier's Ph.D thesis [132], [114] and of some of her more recent works [133][46] (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 [63], 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 [105], was devoted to the stochastic modeling and analysis of protein aggregation, compared both with the deterministic approach traditionally developed in Mamba [147] and with experiments.

Collaborations

- **Marc Hoffmann**, Université Paris-Dauphine, for the statistical approach to growth and division processes [100], **M. Escobedo**, Bilbao and **M. Tournus**, Marseille, for the deterministic approach.
- **Philippe Moireau**, Inria M3DISIM, for the inverse problem and data assimilation aspects [69], [62]

4. Application Domains

4.1. Introduction

The team has two 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. Newcomers in this applicative field are epidemiological modeling of propagation of insect vector-borne diseases by reaction-diffusion equations and of their optimal control, bacterial growth and wound healing.

4.2. Applicative axis 1: Focus on cancer

Personnel

Luis Almeida, Jean Clairambault, Marie Doumic, Dirk Drasdo, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil.

Project-team positioning

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.

Scientific achievements

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 [66], [67], [68], [77], [95], [65]. 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 [90], [92], [124], [125], [127]. 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 [79].

Biomechanically mediated growth control of cancer cells

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 [123].

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 [43]. 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 [13], [45]. 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. Moreover it has been recently shown that TMZ treatment has an influence on the spatial structuration of cancer cell aggregates. In the frame of the HTE project MoGIIImaging and through the recent hiring of a post-doctoral candidate (Gissell Estrada Rodriguez), we are currently developing a mathematical framework to study and analyse the evolution of a population of glioblastoma cells that are exposed to TMZ. Based on the experimental data generated by our partner team led by F. Valette (Inserm Nantes), we propose a Keller-Segel type model for the formation of spheroid as a result of a chemoattractant produced by cancer

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, however 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

cells, and study the influence of a chemotherapeutic agent on the structuration of the cancer cell aggregates. By confronting the model results to experimental data, different modelling choices are currently explored to identify which key mechanisms could be responsible for the apparition of drug resistance in glioblastoma.

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 below).
- INSERM HTE laureate project MoGIImaging, 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), **Philippe Robert** (Inria RAP).
- TRAIL treatment: **Gregory Batt**, Inria Saclay and Inst. Pasteur (France)
- Biomechanical control of cancer cells: **Pierre Nassoy**, Bioimaging and Optofluidics Group, LP2N – UMR 5298. IOGS, CNRS & University of Bordeaux

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

Luis Almeida, Pierre-Alexandre Bliman, Marie Doumic, Dirk Drasdo, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil, Philippe Robert

Project-team positioning

The applications in this category span very different subjects from amyloid diseases, dengue fever, 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 [102]. Works by Schliess [149], [107] 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.

Scientific achievements

Amyloid disease

Application to protein aggregation in amyloid diseases is a long-standing interest of Mamba, dating back to 2010 [85], and developed through the collaboration with Human Rezaei's team at Inra. More recently, with Wei-Feng Xue in Canterbury, we investigated the intrinsic variability among identical experiments of nucleation [98], [106], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [105].

In collaboration with Tom Banks first [70], [69] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [63], we proposed new models and mechanisms.

Biological control of arboviroses

Sterile Insect Technique (SIT) [104] 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 disparition, of the target population.

A related technique is based on the infection by *Wolbachia* [111]. This symbiotic bacterium is maternally transmitted from infected females to their offspring, but induces *cytoplasmic incompatibility* [151], [80]: 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 [130].

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 [10], and through optimal control approach [42]. Concerning *Wolbachia* technique, we investigated general control principles [39] capable of spreading the infection.

Wound healing 1: epithelial tissues

We studied cell motion in epithelial gap closure, a form of collective cell migration that is a very widespread phenomenon both during development and adult life - it is essential for both the formation and for the maintenance of epithelial layers. Due to their importance, *in vivo* wound healing and morphogenetic movements involving closure of holes in epithelia have been the object of many studies. In our works ⁵ we considered wound healing and epithelial gap closure in both *in vivo* (in particular *drosophila* pupa) and *in vitro* (MDCK cell and human keratinocytes). We found some similarities in the geometry dependence of the wound closure strategies between these two situations, indicating the existence of conserved mechanisms that should be widespread across living beings. We are concentrating on the study of actin cable formation.

Wound healing 2: 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 [144]. 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 [145]. 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.

⁵ravasio:hal-01245750, vedula:hal-01298859

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 collaboration with S. Merino-Aceituno from the University of Vienna, efforts are being made in the development of a complete synthetic tissue model coupling the ECM and cell modelling with a vascularization model. A PhD project has been started to implement the coupled models and reduce the CPU time with the long-term goal to develop a usable software which would serve to investigate the role of different mechanisms in tissue development (not restricted to adipose tissues). Finally, further developments in collaboration with Imperial College London aim at pursuing the derivation of macroscopic PDE models from the agent-based formalisms.

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. The model construction is based on recent works where the authors developed a mathematical model given by ordinary differential equations (ODEs)[2] and a mathematical framework in 1D [3] showing that acceleration of the cell cycle is the major driver of regenerative spinal cord outgrowth in axolotls. Building on both mathematical models and 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 will be tested and compared with experimental data. 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. Model validation and calibration will be ensured by quantitative comparison with biological data already present in the literature and generated by the SysBio group of O. Chara, particularly the representative images of regenerative spinal cords after tail amputation. By varying the model parameters and observing the resulting alteration of the spinal cord size and architecture as a consequence of these variations, it will be possible to provide 'in silico' setting experiments to guide and plan future in vivo or ex vivo experiments. Altogether, the project is expected to provide a mechanistic understanding of the cellular mechanisms driving spinal cord regeneration, and to identify how spatial structuration can influence cell differentiation and growth.

[1] Rodrigo Albors A, Tazaki A, Rost F, Nowoshilow S, Chara O & Tanaka EM. 2015. Planar cell polarity-mediated induction of neural stem cell expansion during axolotl spinal cord regeneration. *Elife*. 4:e10230. [2] Rost F, Rodrigo Albors A, Mazurov V, Brusch L, Deutsch A, Tanaka EM & Chara O. 2016. Accelerated cell divisions drive the outgrowth of the regenerating spinal cord in axolotls. *Elife*. 5. pii: e20357. [3] Cura Costa E, Rodrigo Albors A, Tanaka EM & Chara O. Spatiotemporal distribution of cell proliferation rules spinal cord regeneration in the axolotl. MS in preparation.

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 ([52])

Modeling of morphogen diffusion in *Drosophila* oogenesis

In collaboration with a team of developmental biologists of Rutgers University (Camden, New Jersey), we have built a model for the diffusion of the Gurken morphogen during *Drosophila* oogenesis, taking into account a wide variety of biological mechanisms such as diffusion of the morphogen, reactions of components of the EGFR signaling pathway, movement of the source of morphogen, shift of the overlying follicle cells and growth of the egg chamber. This model, together with a complete numerical code developed in Matlab, provides a tool to understand how each mechanism influences the signal distribution. The overall aim of the project is to use this tool to guide future experiments, and to understand what mechanisms contribute to the different distributions of signal among species.

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 [148], 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 [46].

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 [123].

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 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. ([113]) 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.

(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.

(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.

(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 [108].

(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, CCl4 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 [17].

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 (Géraldine Cellière's PhD thesis [88]) 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 [157]. The work of that paper has been further advanced to adapt the procedures for clinical use (in preparation).

Collaborations

- Biological control of arboviruses: **Nicolas Vauchelet** (Université Paris 13); **Grégoire Nadin** (LJLL, Sorbonne Université); **Yannick Privat** (Université de Strasbourg); **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).
- Protein aggregation in amyloid diseases: **Human Rezaei**'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 Université (France)

- Liver research & toxicology: **JG. Hengstler** group (IfADo, Dortmund, Germany); **R. Gebhardt** (Univ. Leipzig); **U. Klingmueller** (DKFZ, Heidelberg); **Irène Vignon-Clementel** (Inria, COMME-DIA)
- Growth in capsules and biomechanics: **Pierre Nassoy**, Institut dOptique Graduate School, Talence, France; **Josef Kaes**, Peter Debye Institute for Soft Matter Physics, Physics, Univ. Leipzig, Germany.
- Wound healing: **Patrizia Bagnerini** (Genova, Numerical methods), **Benoît Ladoux** (Institut Jacques Monod et Mechanobiology Institute Singapore, Biophysics) and **Antonio Jacinto** (CEDOC, Lisbon, Biology and Medicine). (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 Sedlaczek, Univ. and DKFZ Heidelberg, Kai Breuhahn, Univ. Heidelberg.

5. Highlights of the Year

5.1. Highlights of the Year

- Marie Doumic gave a plenary talk at the AIP Conference (Applied Inverse Problems) in Grenoble, July 8-12th (around 600 participants).
- Diane Peurichard and Nastassia Pouradier Duteil won a Mittag-Leffler and EWS-EMS Call to organize a summer school at the Mittag-Leffler institute in July 2020.
- the STIC AmSud cooperative project NEMBICA, between France, Chile, Paraguay and Colombia, headed by Pierre-Alexandre Bliman, has been accepted (2020-2021).

6. New Software and Platforms

6.1. TiQuant

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.

- Author: Dirk Drasdo
- Contact: Dirk Drasdo

6.2. TiSim

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.

- Participants: Andreas Buttenschoen, Dirk Drasdo, Eugenio Lella, Géraldine Cellière, Johannes Neitsch, Margaretha Palm, Nick Jagiella, Noémie Boissier, Paul van Liedekerke, Stefan Hoehme and Tim Johann
- Partner: IZBI, Université de Leipzig
- Contact: Dirk Drasdo

6.3. Platforms

6.3.1. *TiSim*

The deformable cell model [123], [52] has been integrated in addition to the center-based model in the software TiSim (Tissue Simulator), a follow-up of former CellSys [113]. Center-based models of cells represent forces between cells as forces between cell centers but lacks an explicit representation of cell shape. The deformable cell model represents cell shape explicitly. Applications are monolayers, multicellular spheroids and simulations of liver regeneration, whereby intracellular pathways can be integrated. The model shall be distributed as binary and will permit to use the deformable cell model to calibrate intercellular forces at high cell densities, where the two-body force models so far applied in center-based models fail.

6.3.2. *TiQuant*

This image processing and analysis software ([103]) now integrates a machine learning component. This is fundamental as it is more general and permits quicker adaptation to new images.

7. New Results

7.1. Direct and inverse Problems in Structured-population equations

7.1.1. *Modelling Polymerization Processes*

In 2017, we evidenced the presence of several polymeric species by using data assimilation methods to fit experimental data from H. Rezaei's lab [64]; new experimental evidence reinforced these findings [19], [35]. The challenges are now to propose mathematical models capable of tracking such diversity while keeping sufficient simplicity to be tractable to analysis.

In collaboration with Klemens Fellner from the university of Graz, we propose a new model, variant of the Becker-Döring system but containing two monomeric species, capable of displaying sustained though damped oscillations as is experimentally observed. We also proposed a statistical test to validate or invalidate the presence of oscillations in experimental highly nonstationary signals [55].

7.1.2. *Asymptotic behaviour of structured-population equations*

Pierre Gabriel and Hugo Martin studied the mathematical properties of a model of cell division structured by two variables – the size and the size increment – in the case of a linear growth rate and a self-similar fragmentation kernel [16]. They first show that one can construct a solution to the related two dimensional eigenproblem associated to the eigenvalue 1 from a solution of a certain one dimensional fixed point problem. Then they prove the existence and uniqueness of this fixed point in the appropriate L^1 weighted space under general hypotheses on the division rate. Knowing such an eigenfunction proves useful as a first step in studying the long time asymptotic behaviour of the Cauchy problem.

Etienne Bernard, Marie Doumic and Pierre Gabriel proved in [9] that for the growth-fragmentation equation with fission into two equal parts and linear growth rate, under fairly general assumptions on the division rate, the solution converges towards an oscillatory function, explicitly given by the projection of the initial state on the space generated by the countable set of the dominant eigenvectors of the operator. Despite the lack of hypo-coercivity of the operator, the proof relies on a general relative entropy argument in a convenient weighted L^2 space, where well-posedness is obtained via semigroup analysis. They also propose a non-dissipative numerical scheme, able to capture the oscillations.

Pierre Gabriel and Hugo Martin then extended this asymptotic result in the framework of measure solutions [50]. To do so they adopt a duality approach, which is also well suited for proving the well-posedness when the division rate is unbounded. The main difficulty for characterizing the asymptotic behavior is to define the projection onto the subspace of periodic (rescaled) solutions. They achieve this by using the generalized relative entropy structure of the dual problem.

7.1.3. *Estimating the division rate from indirect measurements of single cells*

7.1.3.1. *Marie Doumic and Adélaïde Olivier*

Is it possible to estimate the dependence of a growing and dividing population on a given trait in the case where this trait is not directly accessible by experimental measurements, but making use of measurements of another variable? The article [46] addresses this general question for a very recent and popular model describing bacterial growth, the so-called incremental or adder model - the model studied by Hugo Martin and Pierre Gabriel in [16]. In this model, the division rate depends on the increment of size between birth and division, whereas the most accessible trait is the size itself. We prove that estimating the division rate from size measurements is possible, we state a reconstruction formula in a deterministic and then in a statistical setting, and solve numerically the problem on simulated and experimental data. Though this represents a severely ill-posed inverse problem, our numerical results prove to be satisfactory.

7.2. Stochastic Models of Biological Systems

7.2.1. *Stochastic models for spike-timing dependent plasticity*

7.2.1.1. *Ph. Robert and G. Vignoud*

Synaptic plasticity is a common mechanism used to model learning in stochastic neural networks, STDP is a great example of such mechanisms. We develop a simple framework composed by two neurons and one synaptic weight, seen as stochastic processes and study the existence and stability of such distributions, for a wide range of classical synaptic plasticity models. Using two simple examples of STDP, the calcium-based

rule and the all-to-all pair-based rule, we apply stochastic averaging principles and obtain differential equations for the limit processes, based on the invariant distributions of the fast system when the slow variables are considered fixed. We study a general stochastic queue to approximate the calcium-based rule and are able to have an analytical solution for the invariant distribution of the fast synaptic processes. We also detail some simpler systems, either through some approximations or simulations to put into light the influences of different biologically-linked parameters on the dynamics of the synaptic weight.

7.2.2. Online Sequence Learning In The Striatum With Anti-Hebbian Spike-Timing-Dependent Plasticity

7.2.2.1. G. Vignoud. Collaboration with J. Touboul (Brandeis University)

Spike-Timing Dependent Plasticity (STDP) in the striatum is viewed as a substrate for procedural learning. Striatal projecting neurons (SPNs) express anti-Hebbian plasticity at corticostriatal synapses, (a presynaptic cortical spike followed by a postsynaptic striatal spike leads to the weakening of the connection, whereas the reverse pairing leads to potentiation). SPNs need to integrate many inputs to spike, and as such, their main role is to integrate context elements to choose between different sensorimotor associations. In this work, we develop a simple numerical model of the striatum, integrating cortical spiking inputs to study the role of anti-Hebbian STDP in pattern recognition and sequence learning. Cortical neurons are seen as binary input neurons and one striatal SPN is modeled as a leaky-integrate-and-fire neuron. Combined informations from the output, reward and timing between the different spikes modify the intensity of each connection, through two mechanisms: anti-Hebbian STDP and dopaminergic signaling, using three-factor learning rules. We have added a second output neuron with collateral inhibition which leads to an improvement of the global accuracy. In another project, we studied the dynamics of learning, by shutting off/on the dopaminergic plasticity, and compare it to DMS/DLS experimental and behavioral experiments. We show that anti-Hebbian STDP favors the learning of complete sequence of spikes, such as is needed in the striatum, whereas, even if Hebbian STDP helps to correlate the spiking of two connected neurons, it is not sufficient to integrate of long sequences of correlated inputs spikes.

7.2.3. D1/D2 detection from action-potential properties using machine learning approach in the dorsal striatum

7.2.3.1. G. Vignoud. Collaboration, with Team Venance (CIRB/Collège de France)

Striatal medium spiny neurons (MSNs) are segregated into two subpopulations, the D1 receptor-expressing MSNs (the direct striatonigral pathway) and the D2 receptor-expressing MSNs (the indirect striatopallidal pathway). The fundamental role of MSNs as output neurons of the striatum, and the necessary distinction between D1- and D2-expressing neurons accentuate the need to clearly distinguish both subpopulations in electrophysiological recordings in vitro and in vivo. Currently, fluorescent labelling of the dopaminergic receptors in mice enables a clear differentiation. However, multiplying in vivo the number of genetic markers (optogenetics, fluorescence) hinders possibilities for other genetic manipulations. Moreover, electrophysiological properties of fluorescent neurons can slightly differ from “native” cells and false-positive can be observed. The lack of a proper way to separate D1- and D2-MSNs based on electrophysiological properties led us to devise a detection algorithm based on action potential profile. We used more than 450 D1/D2 labelled MSNs from in vitro patch-clamp recordings (different experimentalists, different setups and protocols), to characterize and identify properties that facilitate the MSN discrimination. After analyzing passive and active MSN membrane properties, we built an extensive dataset and fed it into classical machine learning classification methods. The training of the different algorithms (k-nearest neighbors, random forest, deep neural networks, ...) was performed with the scikit-learn Python library, and the optimized classifier was able to correctly discriminate neurons in the dorsolateral striatum at 76% (and up to 83% if we allow the classifier to reject some MSNs). This study developed an efficient classification algorithm for D1/D2-MSNs, facilitating cell discrimination without specific genetic fluorescent labelling, leaving some room for other genetic markers and optogenetic labeling.

7.2.4. The Stability of Non-Linear Hawkes Processes

7.2.4.1. Ph. Robert and G. Vignoud

We have investigated the asymptotic properties of self-interacting point processes introduced by Kerstan (1964) and Hawkes and Oakes (1974). These point processes have the property that the intensity at some point $t \in (-\infty, +\infty)$ is a functional of all points of the point process before t . Such a process is said to be stable if it has a version whose distribution is invariant by translation. By using techniques of coupling and Markovian methods, we have been able to obtain some existence and uniqueness results with weaker conditions than in the current literature.

7.2.5. Mathematical Models of Gene Expression

7.2.5.1. Ph. Robert

In Robert [30] we analyze the equilibrium properties of a large class of stochastic processes describing the fundamental biological process within bacterial cells, *the production process of proteins*. Stochastic models classically used in this context to describe the time evolution of the numbers of mRNAs and proteins are presented and discussed. An extension of these models, which includes elongation phases of mRNAs and proteins, is introduced. A convergence result to equilibrium for the process associated to the number of proteins and mRNAs is proved and a representation of this equilibrium as a functional of a Poisson process in an extended state space is obtained. Explicit expressions for the first two moments of the number of mRNAs and proteins at equilibrium are derived, generalizing some classical formulas. Approximations used in the biological literature for the equilibrium distribution of the number of proteins are discussed and investigated in the light of these results. Several convergence results for the distribution of the number of proteins at equilibrium are in particular obtained under different scaling assumptions.

7.2.6. Stochastic modelling of molecular motors

7.2.6.1. Marie Doumic, Dietmar Oelz, Alex Mogilner

It is often assumed in biophysical studies that when multiple identical molecular motors interact with two parallel microtubules, the microtubules will be crosslinked and locked together. The aim of the article [4] is to examine this assumption mathematically. We model the forces and movements generated by motors with a time-continuous Markov process and find that, counter-intuitively, a tug-of-war results from opposing actions of identical motors bound to different microtubules. The model shows that many motors bound to the same microtubule generate a great force applied to a smaller number of motors bound to another microtubule, which increases detachment rate for the motors in minority, stabilizing the directional sliding. However, stochastic effects cause occasional changes of the sliding direction, which has a profound effect on the character of the long-term microtubule motility, making it effectively diffusion-like. Here, we estimate the time between the rare events of switching direction and use them to estimate the effective diffusion coefficient for the microtubule pair. Our main result is that parallel microtubules interacting with multiple identical motors are not locked together, but rather slide bidirectionally. We find explicit formulae for the time between directional switching for various motor numbers.

7.3. Analysis and control of mosquito populations

7.3.1. Control Strategies for Sterile Insect Techniques

We proposed different models to serve as a basis for the design of control strategies relying on releases of sterile male mosquitoes (*Aedes spp*) and aiming at elimination of wild vector population. Different types of releases were considered (constant, periodic or impulsive) and sufficient conditions to reach elimination were provided in each case [152]. We also estimated sufficient and minimal treatment times. A feedback approach was introduced, in which the impulse amplitude is chosen as a function of the actual wild population [152].

7.3.2. *Optimal replacement strategies, application to Wolbachia*

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 [8], [42].

7.3.3. *Oscillatory regimes in population models*

Understanding mosquitoes life cycle is of great interest presently because of the increasing impact of vector borne diseases. Observations yields evidence of oscillations in these populations independent of seasonality, still unexplained. We proposed [33] a simple mathematical model of egg hatching enhancement by larvae which produces such oscillations that conveys a possible explanation.

On the other hand, population oscillations may be induced by seasonal changes. We considered a biological population whose environment varies periodically in time, exhibiting two very different “seasons”, favorable and unfavorable. We addressed the following question: the system’s period being fixed, under what conditions does there exist a critical duration above which the population cannot sustain and extincts, and below which the system converges to a unique periodic and positive solution? We obtained [153], [154] sufficient conditions for such a property to occur for monotone differential models with concave nonlinearities, and applied the obtained criterion to a two-dimensional model featuring juvenile and adult insect populations.

7.3.4. *Feedback control principles for population replacement by Wolbachia*

The issue of effective scheduling of the releases of *Wolbachia*-infected mosquitoes is an interesting problem for Control theory. Having in mind the important uncertainties present in the dynamics of the two populations in interaction, we attempted to identify general ideas for building release strategies, which should apply to several models and situations [39]. These principles were exemplified by two interval observer-based feedback control laws whose stabilizing properties were demonstrated when applied to a model retrieved from [76].

7.4. **Bacterial motion by Rerun and tumble**

Collective motion of chemotactic bacteria such as *Escherichia coli* relies, at the individual level, on a continuous reorientation by runs and tumbles. It has been established that the length of run is decided by a stiff response to a temporal sensing of chemical cues along the pathway. We describe a novel mechanism for pattern formation stemming from the stiffness of chemotactic response relying on a kinetic chemotaxis model which includes a recently discovered formalism for the bacterial chemotaxis [142]. We prove instability both for a microscopic description in the space-velocity space and for the macroscopic equation, a flux-limited Keller-Segel equation, which has attracted much attention recently. A remarkable property is that the unstable frequencies remain bounded, as it is the case in Turing instability. Numerical illustrations based on a powerful Monte Carlo method show that the stationary homogeneous state of population density is destabilized and periodic patterns are generated in realistic ranges of parameters. These theoretical developments are in accordance with several biological observations.

This motivates also our study of traveling wave and aggregation in population dynamics of chemotactic cells based on the FLKS model with a population growth term [86]. Our study includes both numerical and theoretical contributions. In the numerical part, we uncover a variety of solution types in the one-dimensional FLKS model additionally to standard Fisher/KPP type traveling wave. The remarkable result is a counter-intuitive backward traveling wave, where the population density initially saturated in a stable state transits toward an unstable state in the local population dynamics. Unexpectedly, we also find that the backward traveling wave solution transits to a localized spiky solution as increasing the stiffness of chemotactic response. In the theoretical part, we obtain a novel analytic formula for the minimum traveling speed which includes the counter-balancing effect of chemotactic drift vs. reproduction/diffusion in the propagating front. The front propagation speeds of numerical results only slightly deviate from the minimum traveling speeds, except for the localized spiky solutions, even for the backward traveling waves. We also discover an analytic solution of unimodal traveling wave in the large-stiffness limit, which is certainly unstable but exists in a certain range of parameters.

Another activity concerns the relation between the tumbling rate and the internal state of bacteria. The study [58] aims at deriving models at the macroscopic scale from assumptions on the microscopic scales. In particular we are interested in comparisons between the stiffness of the response and the adaptation time. Depending on the asymptotics chosen both the standard Keller-Segel equation and the flux-limited Keller-Segel (FLKS) equation can appear. An interesting mathematical issue arises with a new type of equilibrium equation leading to solution with singularities.

7.5. Numerical methods for cell aggregation by chemotaxis

Three-dimensional cultures of cells are gaining popularity as an in vitro improvement over 2D Petri dishes. In many such experiments, cells have been found to organize in aggregates. We present new results of three-dimensional in vitro cultures of breast cancer cells exhibiting patterns. Understanding their formation is of particular interest in the context of cancer since metastases have been shown to be created by cells moving in clusters. In the paper [82], we propose that the main mechanism which leads to the emergence of patterns is chemotaxis, i.e., oriented movement of cells towards high concentration zones of a signal emitted by the cells themselves. Studying a Keller-Segel PDE system to model chemotactical auto-organization of cells, we prove that it is subject to Turing instability if a time-dependent condition holds. This result is illustrated by two-dimensional simulations of the model showing spheroidal patterns. They are qualitatively compared to the biological results and their variability is discussed both theoretically and numerically.

This motivates to study parabolic-elliptic Keller-Segel equation with sensitivity saturation, because of its pattern formation ability, is a challenge for numerical simulations. We provide two finite-volume schemes that are shown to preserve, at the discrete level, the fundamental properties of the solutions, namely energy dissipation, steady states, positivity and conservation of total mass [131]. These requirements happen to be critical when it comes to distinguishing between discrete steady states, Turing unstable transient states, numerical artifacts or approximate steady states as obtained by a simple upwind approach. These schemes are obtained either by following closely the gradient flow structure or by a proper exponential rewriting inspired by the Scharfetter-Gummel discretization. An interesting fact is that upwind is also necessary for all the expected properties to be preserved at the semi-discrete level. These schemes are extended to the fully discrete level and this leads us to tune precisely the terms according to explicit or implicit discretizations. Using some appropriate monotonicity properties (reminiscent of the maximum principle), we prove well-posedness for the scheme as well as all the other requirements. Numerical implementations and simulations illustrate the respective advantages of the three methods we compare.

7.6. Focus on cancer

Modelling Acute Myeloid Leukaemia (AML) and its control by anticancer drugs by PDEs and Delay Differential equations

This theme has continued to be developed in collaboration with Catherine Bonnet, Inria DISCO (Saclay) [93], [94]. Without control by drugs, but with representation of mutualistic interactions between tumor cells and their surrounding support stromal cells, it has also, in collaboration with Delphine Salort and Thierry Jaffredo (LCQB-IBPS) given rise to a recent work by Thanh Nam Nguyen, hired as HTE and ERC postdoctoral fellow at LCQB, submitted as full article [24].

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 [128], [127] and later continued in [91], [92], [126], has been recently summarised in [60] and has been the object of the PhD thesis work of Camille Pouchol, see above “Cell population dynamics and its control”. It is now oriented, thanks to work underway by Cécile Carrère, Jean Clairambault, Tommaso Lorenzi and Grégoire Nadin, 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.

Philosophy of cancer biology

This new research topic in Mamba, dedicated to explore possibly underinvestigated, from the mathematical modelling point of view, parts of the field of cancer growth, evolution and therapy, has been the object of a presentation by Jean Clairambault at the recent workshop “Philosophy of cancer biology”

<https://www.philinbiomed.org/event/philosophy-of-cancer-biology-workshop/>.

This workshop gathered most members worldwide of this small, but very active in publishing, community of philosophers of science whose field of research is “philosophy of cancer”, as they call it themselves. This topic offers a clear point of convergence between mathematics, biology and social and human sciences.

7.7. Deformable Cell Modeling: biomechanics and Liver regeneration

- Biomechanically mediated growth control of cancer cells The key intriguing novelty was that the same agent-based model after a single parameter has been calibrated with growth data for multicellular spheroids without application of external mechanical stress by adapting a single parameter, permitted to correctly predict the growth speed of multicellular spheroids of 5 different cell lines subject of external mechanical stress. Hereby the same mechanical growth control stress function was used without any modification [123]. The prediction turned out to be correct independent of the experimental method used to exert the stress, whereby once a mechanical capsule has been used, once dextran has been used in the experiments.
- Regeneration of liver with the Deformable Cell Model. The key novelty was the implementation of the model itself, but an interesting novel result is that the DCM permits closure of a pericentral liver lobule lesion generated by drug-induced damage with about 5 times smaller active migration force due to the ability of the cell to strongly deform and squeeze into narrow spaces between the capillaries. This finding stresses that a precise mechanical description is important in view of quantitatively correct modeling results [155]. The deformable cell model however could be used to calibrate the interaction forces of the computationally much cheaper center-based model to arrive at almost the same results.

8. Partnerships and Cooperations

8.1. 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.

8.1.1. ANR

8.1.1.1. ANR Blanc 2014-2018 “Kibord”

This project gathers several members of the MAMBA team together with the ENS Cachan and Université Paris-Dauphine on the mathematical study of PDE models with application to biology.

8.1.1.2. ANR iLITE 2016 - 2020

Jean-Charles Duclos-Vallée, Paul Brousse Hospital, Villejuif. Partners are several departments in Paul Brousse Hospital, ENS Cachan, University of Compiègne and several companies all over France, and COMMEDIA team, Inria Paris. The pursued objective is the bioengineering design of an artificial liver intended for liver replacement.

8.1.1.3. ANR InTelo 2017-2020

Telomere dynamics, headed by Teresa Teixeira (IBPC, Paris).

8.1.1.4. 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).

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

8.1.2.1. ITMO Cancer EcoAML

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

8.1.2.2. ITMO Cancer MoGImaging

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

8.2. International Initiatives

- **STIC AmSud 20-STIC-05**

- Title: New Methods for Biological Control of the Arboviruses
- International Partner (Institution - Laboratory - Researcher):
 CIRAD (Montpellier), UMR MISTEA (Montpellier), Université Paris 13, Université de Bordeaux, Université de Strasbourg, Université Paris-Dauphine - PSL; Universidad de Buenos Aires and Universidad Nacional de Salta (Argentina); Universidad de Chile (Chile); Universidad del Quindío, Universidad Autónoma de Occidente and Universidad del Valle (Colombia); National University of Asuncion (Paraguay).
- Duration: 2020 - 2021
- Start year: 2020
- The main focus of this project is modeling and analysis, using mathematical methods, of new strategies aimed at controlling the spread of the dengue fever and other vector-borne diseases similar to Dengue and transmitted by Aedes mosquitoes, like Chikungunya and Zika virus.
- The key topics are the following.
 - * Spatial aspects of biological control techniques
 - * Estimation issues for vector-borne epidemics
 - * Optimal and non-optimal control approaches for biological control techniques
 - * Modelling the effects of conventional control methods on the success of biological control
 - * Modelling the competition effects in larval phase during biological control
 - * Modelling and efficacy measures for self-propagating genetic interventions
 - * Genome-scale models for Wolbachia

- **ERC Advanced grant No 740623 ADORA**

ADORA is the acronym for *Asymptotic approach to spatial and dynamical organizations*.

Adora ERC project aims at understanding of spatial, social and dynamical organization of large numbers of agents, presently a fundamental issue in science. ADORA focuses on problems motivated by biology because, more than anywhere else, access to precise and numerous data has opened the route to novel and complex mathematical models. The addressed problems are written in terms of

nonlinear partial differential equations. The flux-limited Keller-Segel system, the integrate-and-fire Fokker-Planck equation, kinetic equations with internal state, nonlocal parabolic equations and constrained Hamilton-Jacobi equations are among examples of the equations under investigation.

The role of mathematics is not only to understand the analytical structure of these new problems, but it is also to **explain the qualitative behavior of solutions and to quantify their properties.** The challenge arises here because these goals should be achieved through a hierarchy of scales. Indeed, the problems under consideration share the common feature that the large scale behavior cannot be understood precisely without access to a hierarchy of finer scales, down to the individual behavior and sometimes its molecular determinants.

Major difficulties arise because the numerous scales present in these equations have to be discovered and singularities appear in the asymptotic process which yields deep compactness obstructions. Our vision is that **the complexity inherent to models of biology can be enlightened** by mathematical analysis and a classification of the possible asymptotic regimes.

However an enormous effort is needed to uncover the equations intimate mathematical structures, and bring them at the level of conceptual understanding they deserve being given the applications motivating these questions which range from medical science or neuroscience to cell biology.

8.2.1. *MaMoCeMa*

Title: Mathematical modeling of cell motility and of autophagy

International Partner (Institution - Laboratory - Researcher):

University of Vienna (Austria) - Wolfgang Pauli Institute - Christian Schmeiser

Start year: 2018

Numerous fruitful collaborations have been developed these last years between the WPI and the Inria team MAMBA. Diane Peurichard – newly recruited permanent member of the team MAMBA-worked two years (2016-2017) with Christian Schmeiser -member of the present project- through a post-doctoral contract at the university of Vienna. In collaboration with the biologists of IST, they developed mathematical tools to understand how cells move through adhesion-based and adhesion-free motion with applications in cancer development, prevalent theme of the team MAMBA. Collaborations WPI-MAMBA have been maintained and ensured by the sabbatical of Marie Doumic (2016-2018) -, working at the university of Vienna with Christian Schmeiser and the PhD student Julia Delacour. They have initiated a collaboration on the mathematical modeling of autophagy, which requires both C. Schmeiser's expertise in biomechanics and M. Doumic's knowledge on aggregation processes. This team will also benefit of the strong links that C. Schmeiser has developed with the two biologists teams of S. Martens (on autophagy) and M. Sixt (on cell movement).

8.2.2. *Participation in Other International Programs*

- **BMBF (Germany) / LiSym; 2016-2020** LiSym addresses liver diseases and regeneration, namely, steatosis, fibrosis and cirrhosis, and acute on chronic liver failure. (Dirk Drasdo)
- **BMBF (Germany) / MSDILI; 2016-2019** MS-DILI addresses multiscale modeling of drug-induced liver disease focusing on the role of APAP. Dirk Drasdo participates in this project. (Dirk Drasdo)

8.3. International Research Visitors

Visitors in Paris (LJLL) invited by J. Clairambault: Zineb Kaïd, PhD student, University Abou Bekr Belkaïd, Tlemcen, Nov. 25 - Dec. 13; Jean-François Mascari, researcher, IAC-CNR, Rome, Dec. 9-13.

Visitors in Paris (Inria) invited by D. Drasdo: Jieling Zhao, Postdoc from IfADo, Jules Dichamp, Postdoc from ifADo, Paul van Liedekerke, Research engineer from IfADo.

Visitors in Paris (LJLL) invited by D. Peurichard and M. Doumic: P. Degond (Imperial College London) Nov 20 - 22, C. Schmeiser (University of Vienna), Dec. 1 - 7, Claudia Wyrzen (University of Vienna) feb 4-8 2019, M. Tournus and M. Escobedo (February 18-22), .

Visitors in Paris (LJLL) invited by P. A. Bliman: Prof. Héctor Jairo Martínez Romero (Universidad del Valle, Cali, Colombia) for two weeks, together with Oscar Eduardo Escobar Lasso, PhD student who was present one month.

Visitors in Paris (LJLL) invited by B. Perthame: Shugo Yasuda (University of Hyogo, Kobe, Japan), Min Tang (SJTU, China), Maria Caceres (Granada, Spain), Zhenan Zhou (Peking University), Weizhu Bao (Singapore university).

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events: Organisation

9.1.1.1. General Chair, Scientific Chair

- J. Clairambault has organised with Stylianos Xanthopoulos (University of the Aegean), Nikolaos Sfakianakis (University of St. Andrews), Nikos Kavallaris (University of Chester) and Pierre-Alexandre Bliman the Summer school and workshop *MBMC-Samos 2019* “Mathematical Biology on the Mediterranean Conference”, Samos island, Greece, September 1-14, see <http://actuarweb.aegean.gr/mbmc2019>. This conference, envisioned to be the first of a series of such MBMCs, consisted of two twin events, the Summer school and the workshop (1st and 2nd week) that were funded by Inria DGDS and DPEI, together with EMS and ESMTB.
- Dirk Drasdo is member of the Program committee of the SBMC 2020 (Heidelberg, Germany), May, 25-27.
- L. Almeida, B. Perthame and D. Peurichard coordinate a math-bio work group every month at LJLL
- D. Peurichard and D. Drasdo coordinate the internal ‘Open MAMBA seminar’ - seminar for PhD and post-doctoral students of the MAMBA team
- Pierre-Alexandre Bliman, together with Christian Schaerer (Polytechnic School, Universidad Nacional de Asunción, Paraguay), organized the Workshop on Advanced Control Techniques for Mosquito-Borne Diseases 2019 (WTAEM 2019) 11–17 november 2019, <https://sites.google.com/view/wtaem/wtaem>
- Benoit Perthame organized a France-China summer school 1-5 july 2019 (partnership LIA-SFMA, Institute of Natural Science and Department of mathematics, Shanghai Jiao Tong University)

9.1.1.2. Member of the Organizing Committees

- On October 7th and 8th, Marie Doumic co-organized the symposium *Deciphering the functional mechanisms of biological macromolecules* with Raphaël Guérois (CEA) and Marc Baaden (IBPC).
- Marie Doumic was a member of the organisation committee for the 50th anniversary of J-L. Lions laboratory (November 27-29).
- Marie Doumic co-organised the Workshop “Mathematical Models in Cancer”, August 1-2, Vienna, Austria.

9.1.2. Scientific Events: Selection

9.1.2.1. Member of the Conference Program Committees

- Pierre-Alexandre Bliman was in the Editorial Board of the conference “European Control Conference”, Naples (Italy), 25-28 June 2019.

9.1.2.2. Reviewer

- Pierre-Alexandre Bliman, reviewer for the conferences IEEE Conference on Decision Control, European Control Conference.

- Dirk Drasdo, CELLMECH 2019 (June 3-6, 2019): Quantitative single-cell-based modelling reveals predictable response of growing tumour spheroids on external mechanical stress, and how this informs liver regeneration
- Dirk Drasdo, 3rd Workshop on BioFabrication & Cancer, 24-25.09.2019: Quantitative single-cell-based modelling reveals predictable response of growing tumour spheroids on external mechanical stress, and how this informs liver regeneration

9.1.3. Journal

9.1.3.1. Member of the Editorial Boards

- Dirk Drasdo is associate editorial member of J. Theor. Biol. Royal Society Open Science, and The Scientific World Journal.
- Marie Doumic is associate editor of Kinetic and Related Models and of the Journal of Mathematical Biology.
- Diane Peurichard and Nastassia Pouradier Duteil are guest editors of a special issue for the journal Mathematical Biosciences and Engineering, planned in september 2020.
- Benoit Perthame is associate editor of Bol. SeMA, Milan Journal of Mathematics, M3AS, Mathematical Medicine and Biology (IMA journal), Comm. in PDE,

9.1.3.2. Reviewer - Reviewing Activities

We reviewed for:

BBA Reviews Cancer, Mathematical Modelling of Natural Phenomena, Mathematical Biosciences, Mathematical Biosciences and Engineering, Bioinformatics, BBA Molecular Cell Research, Computers in Biology and Medicine, Biosystems, J Math Biol, Cancer Research, Bull Math Biol, J Theor Biol, Science Advances ; Symmetry, Mathematical Biosciences and Engineering ; IEEE Transactions on Automatic Control, Mathematical Biosciences; Transactions of the London Mathematical Society, Journal of Mathematical Biology; Annales de l'Institut Henri Lebesgue, SIAM Applied Math, J. Math. Biol, Asymptotic Analysis.

9.1.4. Invited Talks

- P.-A. Bliman's presentations at seminars and workshops:
 - Laboratoire Analyse, Géométrie et Applications UMR 7539, Université Paris 13, February 2019;
 - Institut de Mathématiques de Bordeaux UMR 5251, March 2019;
 - Universidad Nacional de Asunción, Asunción, Paraguay, March 2019 Université de Guyane, Cayenne, April 2019;
 - Universidade Federal de Amapá, Macapá, Brazil, April 2019;
 - Laboratoire Jacques-Louis Lions, Sorbonne Université, Paris, June 2019;
 - COPPE, Universidade Federal de Rio do Janeiro, Brazil, July 2019;
 - Fifth International Conference on Computational and Mathematical Population Dynamics, Fort Lauderdale (FL), USA May 2019;
 - Mathematical Biology on the Mediterranean Conference, Samos, September 2019;
 - Workshop on Advanced Control Techniques for Mosquito-Borne Diseases 2019, Asunción, Paraguay, November 2019.
- J. Clairambault's presentations at seminars and workshops:
 - Maths club Paris VII, January 2019;
 - LJLL 50-year anniversary, Roscoff March 2019;

- Seminar Math-Bio, LAGA, Université Paris XIII, Villetaneuse, April 2019;
- Mathematical Methods and Models in Biosciences Conference, IMPAN, Bedlewo, Poland, June 2019;
- Mathematical Biology on the Mediterranean Conference, Samos, Greece, September 2019;
- Symposium on Modelling approaches for cancer therapy, Cité scientifique, Lille, September 2019;
- Q-Bio symposium Pasteur Institute, December 2019.
- D. Peurichard’s presentations at seminars and workshops:
 - Colloque d’ouverture 50 ans du LJLL, Roscoff, March 2019;
 - ICIAM 9th International Congress on Industrial and Applied Mathematics, Valencia, July 15th-19th;
 - Math and cancer workshop in Vienna, 1-3th August, 2019;
 - MAMOVI days (MATHématiques de la MODélisation du VIVant), Tours, 4th-6th Sep, 2019;
 - Mathematical Biology on the Mediterranean Conference, Samos, Greece, September 2019;
 - PDE-biology workshop, Orsay, 25-26 Nov 2019;
 - Math-bio seminar, Bordeaux, December, 2019.
- N. Pouradier Duteil’s presentations at seminars and workshops:
 - Colloque d’ouverture 50 ans du LJLL, Roscoff, March 2019;
 - Journées Picard, Roscoff, March 2019;
 - Séminaire du laboratoire Jacques-Louis Lions, Paris, March 2019;
 - Workshop “PDEs and Applications in Life Sciences”, Penn State, USA, October 2019;
 - INdAM workshop "Recent advances in kinetic equations and applications", Rome, Italy, November 2019.
- M. Doumic’s presentations at seminars, workshops and conferences:
 - Inria-KAIST (Korean Advanced Institute of Science and Technology) meeting, Paris, March 28th.
 - Amiens PDE seminar, May 27th.
 - PDE Day, June 7th, Le Havre.
 - Four-hour course at the 2019 Summer School on Mathematical Biology, July 1-4, Shanghai.
 - Plenary talk at the AIP 2019 Conference (Applied Inverse Problems), July 7-11, Grenoble.
 - First meeting of MeDyNa GDR, October 7-10, Sainte Montaine.
 - DEA conference in Krakow, September 18-20.
 - CENTURI Conference in Marseille, November 18th, with W-F. Xue.

9.1.5. Leadership within the Scientific Community

Dirk Drasdo is member of the scientific leadership board of the German flagship project LiSyM (Liver Systems Medicine) financed by BMBF (Germany).

Marie Doumic is a member of the board of the GDR Medyna (self-assembly of peptides and proteins).

9.1.6. Scientific Expertise

M. Doumic is a member of ITMO BMSV (interdisciplinary institute for structural and biomolecular basis of living matter) experts’ committee, representing Inria.

M. Doumic is a member of the scientific committee of the mathematical institute INSMI of CNRS, and a member of the interdisciplinary committee CID 51 of CNRS.

9.1.7. Research Administration

- Dirk Drasdo is associated with IfADo Leibniz-Institute. He directs a research group bi-localized at Inria de Paris and IfADo, Dortmund.
- Dirk Drasdo is member of the scientific leadership board of the German flagship project LiSyM (Liver Systems Medicine) financed by BMBF (Germany).
- D. Peurichard is a member of the CSD (Comité de Suivi Doctoral) at Inria
- P.-A. Bliman is the coordinator of the ECOS-Nord project C17M01 “News methods for control of dengue and arboviroses”, and international coordinator of the STIC AmSud project 20-STIC-05 “New Methods for Biological Control of the Arboviruses” epidemics”.
- M. Doumic is a member of the organisation committee for mentorship at Inria Paris.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Most non permanent researchers have teaching activities in Sorbonne Université. We detail below only some of the teaching activities of permanent researchers.

- N. Pouradier Duteil, “Travaux de Recherche Encadrés”, 10h, M1, Jussieu
- D. Drasdo, “Agent-based models of tissue organization”, Paris 24 h / yr, M2 course, UPMC, Paris, France
- D. Drasdo: "Integrated and spatial-temporal multiscale modeling of liver guide in vivo experiments in healthy & chronic disease states: a blue print for systems medicine?", M2 course, 1 h, Ecole Polytechnique, France
- D. Peurichard, TD M1 in Jussieu, "Fondements des méthodes numériques", 40h
- D. Peurichard, M1 TD in Jussieu, "Approximation des EDP", 24h
- D. Peurichard, M2 4 hours course in Strasbourg in the interdisciplinary program entitled 'Physique Cellulaire'
- B. Perthame, M2 course “Introduction to mathematical biology”
- M. Doumic, M2 Course "Inverse Problems in Population Dynamics"

(24 hours)

9.2.2. Supervision

PhD in progress:

- P.-A. Bliman is co-advisor of the PhD student Pastor E. Pére-Estigarribia (with Ch. Schaerer, at UNA, Paraguay);
- L. Almeida is Emma Leschiera’s co-supervisor (with Chloé Audebert, Sorbonne Université, and Tommaso Lorenzi, St Andrew’s university) and Jesus Bellver Arnau’s supervisor;
- M. Doumic is Mathieu Mezache’s co-supervisor (with H. Rezaei, Inra - defended in December 2019), Cécile della Valle’s co-supervisor (with Philippe Moireau, Inria Saclay), Julia Delacour’s co-supervisor (with Christian Schmeiser, Vienna), Hugo Martin’s co-supervisor (with Pierre Gabriel, Université de Versailles-St Quentin - defended in July 2019), Adrien Ellis’ co-supervisor (with Marc Hoffmann, Université Paris Dauphine - begun in October 2019) and Anaïs Rat co-supervisor (with Magali Tournus, Centrale Marseille - begun in October 2019);

- B. Perthame is Alexandre Poulain's supervisor, Giorgia Ciavovella's co-supervisor (with Roberto Natalini, Roma), Federica Bubba's co-supervisor (with Pasquale Ciarletta, Politecnico di Milano) and Noemi David's co-supervisor (with, University of Bologna);
- Diane Peurichard is Valeria Caliaro's supervisor;
- Philippe Robert is Gaëtan Vignoud's advisor.

M2 internship: P.-A. Bliman was Mahamadou Sylla's advisor; M. Doumic was Adrien Ellis' advisor; D. Peurichard was Valeria Caliaro's advisor; Luis Almeida is Jesus Bellver Arnau's supervisor and Jorge Hernandez co-supervisor.

9.2.3. Committees

- J. Clairambault's international project evaluation activity in 2019: ICREA, EPSRC
- J. Clairambault's PhD defence committees: Ghassen Haddad (JC supervisor), Paris March 1st; Mohammed Ladjimi, Lille, September 25.
- J. Clairambault is member of the ANR evaluation panel "Mathematics and their interactions for biology and health"
- M. Doumic is a member of the interdisciplinary committee 51 of CNRS (CID51): selection committee for junior and senior research scientists of CNRS.
- M. Doumic was a member of the Inria Paris research center selection committee for junior scientists.
- M. Doumic's Ph.D defence committees: Hugo Martin (MD supervisor), July Paris, Frédérique Robin (MD chair), September 26, Paris; Emma Horton (MD reviewer), November 14th, Bath; Mathieu Mezache (MD supervisor), December 17th, Paris; Samuel Nordmann, October 11th, Paris.
- D. Peurichard is a member of the Inria "Commission des emplois scientifiques" for selecting PhD, delegation and post-doctoral candidates at Inria.
- D. Peurichard is a member of the ARP/SRP selection committee for Inria.

9.3. Popularization

Diane Peurichard presented a talk in the framework of the "Remise des prix des Olympiades de mathématiques de Paris" (prize for national mathematics competition for young french students), Wednesday 29th, June 2019.

Diane Peurichard presented her work at the Inria scientific days in Lyon from June 5th- 7th, 2019.

At the occasion of scientific seminars, Pierre-Alexandre Bliman gave interviews to TV channels in Paraguay: Paraguai TV (March 28, 2019); and in Brazil: Globo Amapá (April 16, 2019), Balanço Geral AP (April 17th, 2019).

Marie Doumic gave a presentation of her research for middle-school pupils in internship (December 2019) and for highschool mathematics teachers (March 2019, in Lille), and did "speed-dating interviews" with high school students (February 12th, NGO "Sephora Berrebi").

Benoit Perthame gave public talks at Tamkang university (Taipei) and Nancy.

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