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ACTIVITY REPORT

Project-Team

MAMBA

Modelling and Analysis for Medical and Biological Applications

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

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

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Project-Team MAMBA

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

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- Florian Joly [INSERM]
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2 Overall objectives

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

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

Biology and medicine presently face the difficulty to make sense of the data newly available by means of recent signal acquisition methods and to take appropriate actions through possible

treatment pathways. Modeling through agent-based or continuous models is a unique way to explain (model) experimental or clinical observations and then compute, control and predict the consequences of the mechanisms under study. These are the overall goals of Mamba.

3 Research program

3.1 Introduction

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

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

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

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

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

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

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

3.2 Methodological axis 1: Analysis and control for population dynamics

Population dynamics is a field with varied and wide applications, many of them being in the core of MAMBA interests - cancer, bacterial growth, protein aggregation. Their theoretical study also brings a qualitative understanding on the interplay between individual growth, propagation and reproduction in such populations. In the past decades, many results where obtained in the BANG team on the asymptotic and qualitative behavior of such structured population equations, see e.g. [135, 70, 98, 83]. Other Inria teams interested by this domain are Mycenae, Numed and Dracula, with which we are in close contacts. Among the leaders of the domain abroad, we can cite among others our colleagues Graeme Wake (New Zealand), Glenn Webb (USA), Jacek Banasiak (South Africa), Odo Diekmann (Netherlands), with whom we are also in regular contact. Most remarkably and recently, connections have also been made with probabilists working on Piecewise Deterministic Markov Processes (F. Malrieu at the university of Rennes, Jean Bertoin at the ETH in Zurich,

Vincent Bansaye at Ecole Polytechnique, Julien Berestycki at Cambridge, Amaury Lambert at College de France, M. Hoffmann at Paris Dauphine, Alex Watson in UCL, London and J. Bertoin in Zurich), leading to a better understanding of the links between both types of results – see also the Methodological axis 3.

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

Time asymptotics for nucleation, growth and division equations
Following the many results obtained in the BANG team on the asymptotic and qualitative behavior of structured population equation, we put our effort on the investigation of limit cases, where the trend to a steady state or to a steady exponential growth described by the first eigenvector fails to happen. In [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.

We also enriched the models by taking into account a nucleation term, modeling the spontaneous formation of large polymers out of monomers [146]. 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, 119, 158]. 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 [20].

Control and macroscopic limits of collective dynamics
The term *self-organization* is used to describe the emergence of complex organizational patterns from simple interaction rules in collective dynamics systems. Such systems are valuable tools to model various biological systems or opinion dynamics, whether it be the collective movement of animal groups, the organization of cells in an organism or the evolution of opinions in a large crowd.

A special case of self-organization is given by *consensus*, i.e. the situation in which all agents' state variables converge. Another phenomenon is that of *clustering*, when the group is split into clusters that each converge to a different state. A natural question in this framework is that of control: can the system be guided to a desired predetermined configuration? In the case when self-organization is not achieved naturally by the system, can it be driven to it? On the contrary, in the case where consensus and clustering are situations to be avoided (for example in crowd dynamics), can we design control strategies to keep the system away from clustering?

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

Models of neural network
Mean field limits have been proposed by biophysicists in order to describe neural networks based on physiological models. The various resulting equations are called integrate-and-fire, time elapsed models, voltage-conductance models. Their specific nonlinearities and the blow-up phenomena make their originality which has led to develop specific mathematical analysis [139], followed by [134, 118, 140, 82]. 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 [87].

Models of interacting particle systems
The organisation of biological tissues during development is accompanied by the formation of sharp borders between distinct cell populations. The maintenance of this cell segregation is key in adult tissue homeostatis, and its disruption can lead tumor cells to spread and form metastasis. This segregation is challenged during tissue growth and morphogenesis due to the high mobility of many cells that can lead to intermingling. Therefore, understanding the mechanisms involved in the generation and maintain of cell segregation is of tremendous importance in tissue morphogenesis, homeostasis, and in the development of various invasive diseases such as tumors. In this research axis, we aim to provide a mathematical framework which enables to quantitatively link the segregation and border sharpening ability of the tissue to these cell-cell interaction phenomena of interest [4]. 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 [4].

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 [145], 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 [90, 91].

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 [131]. 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 phenoytype-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. motility [1]) 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 [131], 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 Gwiązda, Polish Academy of Sciences, Poland; Christian Schmeiser, university of Vienna, through the associated team MaMoCeMa.
- Cell population dynamics and its control: Tommaso Lorenzi, former Mamba postdoc, now at the University of St. Andrews, Scotland, maintains a vivid collaboration with the Mamba team. He is in particular an external member of the HTE program MoGlImaging (see also Applicative axis 1). Emmanuel Trélat, Sorbonne Université professor, member of LJLL and of the CAGE Inria team, is the closest Mamba collaborator for optimal control. Benedetto Piccoli, Professor at Rutgers University (Camden, New Jersey), is collaborating on the analysis and control of collective dynamics. Nathalie Ayi, Sorbonne University, is participating in the development of graph-limit methods.
- Mendelian inheritance and resistance in density-dependent population dynamics: Pastor Pérez-Estigarribia, Christian Schaerer, Universidad Nacional de Asunción, Paraguay.
- Neural networks: Delphine Salort, Professor Sorbonne Université, Laboratory for computations and quantification in biology, and Patricia Reynaud, University of Nice, Maria Cáceres, University of Granada.
- Models of interacting particle systems: Pierre Degond, Imperial College London; Julien Barré, APMO, Orléans; Ewelina Zatorska, University College London; Sara Merino from the university of Vienna (through the associated team MaMoCeMa).

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

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

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

Aggregation equation

In the mathematical study of collective behavior, an important class of models is given by the aggregation equation. In the presence of a non-smooth interaction potential, solutions of such systems may blow up in finite time. To overcome this difficulty, we have defined weak measure-valued solutions in the sense of duality and its equivalence with gradient flows and entropy solutions in one dimension [116]. The extension to higher dimensions has been studied in [85]. An interesting

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

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, 117].

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 [149] 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 [16]. 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 [138] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [120].

Since more realistic systems are used in the analysis of medical images, we have extended these studies to include active motion of cells in [137], viscosity in [142] 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 [141], 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 [121].

Coupling of diffusion and growth

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

Migration of cells in extracellular matrix

A single cell based model has been developed that reproduces a large set of experimental observations of cells migrating in extracellular matrix based on physical mechanisms with mimimal 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 multiscale models

Direct parameter identification is a great challenge particularly in living systems in which part of parameters at a certain level are under control of processes at smaller scales. Mamba developed and addressed model and parameter identification methods and strategies in a number of mathematical and computational model applications including growth and fragmentation processes emerging in bacterial growth and protein misfolding, in liver regeneration [101], TRAIL treatment of HeLa cells [72], growth of multicellular spheroids [115], blood detoxification after drug-induced liver damage [148, 106].

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

Estimation methods for growing and dividing populations

In this domain, all originated in two papers in collaboration with J.P. Zubelli in 2007 [136, 94], whose central idea was to used 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) [95]. 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 [99], a work which inspired also very recently other groups in statistics and probability [73, 112] and was the basis for Adélaïde Olivier's Ph.D thesis [133, 114] and of more recent work [132][14] (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 [103], was devoted to the stochastic modeling and analysis of protein aggregation, compared both with the deterministic approach traditionally developed in Mamba [146] and with experiments.

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

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

Collaborations

- Marc Hoffmann, Université Paris-Dauphine, for the statistical approach to growth and division processes, Miguel Escobedo, Bilbao and Magali Tournus, Marseille, for the deterministic approach.
- Philippe Moireau, Inria M3DISIM, for the inverse problem and data assimilation aspects [68], [62]

4 Application domains

4.1 Introduction

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

4.2 Applicative axis 1: Focus on cancer

The MAMBA team designs and analyses mathematical models of tumor growth and therapy, at the cell population level, using agent-based or partial differential equations, with special interest in methodologies for therapeutic optimization using combined anticancer drug treatments. Rather than, or not only, modeling the effect of drugs on molecular targets, we represent these effects by their functional consequences on the fate of healthy and cancer cell populations: proliferation (velocity of the cell division cycle, decreasing it, e.g., by antagonizing growth factor receptors), apoptosis, cell death or senescence. Our goal in doing this is to circumvent the two main issues of anticancer therapy in the clinic, namely unwanted toxic side effects in populations of healthy

cells and emergence of drug-induced drug resistance in cancer cell populations. This point of view leads us to take into account phenomena of transient and reversible resistance, observed in many cancer cell populations, by designing and analyzing models of cell populations structured in continuous phenotypes, relevant for the description of the behavior of cell populations exposed to drugs: either degree of resistance to a given drug, or potential of resistance to drug-induced stress, proliferation potential, and plasticity. Such modeling options naturally lead us to 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.

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 [64, 66, 67, 77, 93, 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 [88, 89, 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 other cell types
Model simulations indicate that the response of growing cell populations on mechanical stress follows a simple universal functional relationship and is predictable over different cell lines and growth conditions despite the response curves look largely different. We developed a hybrid model strategy in which cells were represented by coarse-grained individual units calibrated in a high resolution cell model and parameterized each model cell by measurable biophysical and cell-biological parameters. Cell cycle progression in our model is controlled by volumetric strain, the latter being derived from a bio-mechanical relation between applied pressure and cell compressibility. After parameter calibration from experiments with mouse colon carcinoma cells growing against the resistance of an elastic alginate capsule, the model adequately predicts the growth curve in i) soft and rigid capsules, ii) in different experimental conditions where the mechanical stress is generated by osmosis via a high molecular weight dextran solution, and iii) for other cell types with different growth kinetics.

Our model simulation results suggest that the growth response of cell population upon externally applied mechanical stress is the same, as it can be quantitatively predicted using the same growth progression function [123]. This model has now been extended to compare the efficiency of different culturing methods, monolayer growth, multicellular spheroids growth and growth within elastic capsules. The methodology of culturing is relevant in terms of cell yield and cell homogeneity.

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

Free boundary multiphase models of tumor growth
Multiphase mechanical models are now commonly used to describe living tissues including tumour growth. The specific model we study here consists of two equations of mixed parabolic and hyperbolic type which extend the standard compressible porous media equation, including cross-reaction terms. We study the incompressible limit, when the pressure becomes stiff, which generates a free boundary problem. We establish the complementarity relation and also a segregation result. Several major mathematical difficulties arise in the two species case which are addressed in [9]. 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 [90, 91]. 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:

[2] Metazoa 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

[3] this latter point partly, however nicely, developed in Thomas Pradeu's book "The limits of the self", OUP 2012

[4] See on this point, e.g., Nils Baas: "On the philosophy of higher structures", Int. J. General Systems 2019

From an adaptive process to an inherent resistance to treatment. It has been recently shown that if TMZ treatment does not significantly induce cell death in glioblastoma, it still generates a response in terms of the spatial arrangement of cell aggregates. Moreover, the coupling of TMZ with irradiation has been shown to generate a better response in patients compared with using irradiation alone. Therefore, understanding the mechanisms of glioblastoma reaction to TMZ treatment could open new therapeutic avenues. In the frame of the post-doctorate of Gissell Estrada Rodriguez, we developed a 2D mathematical model in [31], suggesting a new possible mechanism for TMZ induced rearrangement of cancer cells (see section new results).

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

Collaborations

- AML modelling: Catherine Bonnet, DISCO Inria team, Saclay, and François Delhommeau, INSERM St Antoine (also collaborator in the INSERM HTE laureate project EcoAML, see below).
- INSERM HTE laureate project MoGlImaging, headed by E. Moyal (Toulouse): François Vallette, CRCNA and INSERM Nantes
- INSERM HTE laureate project EcoAML, headed by François Delhommeau, INSERM St Antoine: François Delhommeau, Thierry Jaffredo (IBPS), Delphine Salort (LCQB-IBPS)
- Adaptive dynamics to model drug resistance and optimal control to circumvent it:

  Alexandre Escargueil, Michèle Sabbah (1 PhD thesis in common), St Antoine Hospital, Paris

  Emmanuel Trélat (1 PhD thesis in common) at Inria team CAGE and Laboratoire Jacques-Louis Lions at Sorbonne Université.

  Frédéric Thomas at CREEC, Montpellier.

  Tommaso Lorenzi (Univ. of St Andrews).
- Telomere shortening: Teresa Teixeira and Zhou Xu (IBCP, Paris).
- Biomechanical control of cancer cells: Pierre Nassoy, Bioimaging and Optofluidics Group, LP2N – UMR 5298. IOGS, CNRS & University of Bordeaux; TreeFrog Pharmaceutics, 30 Avenue Gustave Eiffel Bâtiment A, 33600 Pessac
- EMT: Camille Pouchol (Université de Paris), Mohit Kumar Jolly (Indian Institute of Science, Bengalore)

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

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

model contribution to the biologically and/or medically relevant insights and aspects.

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

Different from these, Mamba has a strong focus on spatial-temporal modeling on the histological scale, integration of molecular processes in each individual cell, and single-cell (agent) based models [100]. Works by Schliess [148, 106] have been highlighted in editorials.

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

Amyloid disease

Application to protein aggregation in amyloid diseases is a long-standing interest of Mamba, dating back to 2010 [84], and developed through the collaboration with n rHuman Rezaei's team at Inra. More recently, with Wei-Feng Xue in Canterbury, we investigated the intrinsic variability among identical experiments of nucleation [96, 104], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [103].

In collaboration with Tom Banks first [69, 68] 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.

Wound healing: adipose tissues

After injury, if regeneration can be observed in hydra, planaria and some vertebrates, regeneration is rare in mammals and particularly in humans. In this research axis, we investigated the mechanisms by which biological tissues recover after injury. We explored this question on adipose tissue, using the mathematical framework recently developed in [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 [143]. The model successfully generated regeneration or scar formation as functions of few key parameters, and seemed to indicate that the fate of injury outcome could be mainly due to ECM rigidity.

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

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

In vitro construction of hepatic tissue for regenerative therapy consists in recapitulating mechanisms of embryonic development. However, implementing those mechanisms in a spatially and temporally coordinated way remains difficult. Specifically, the construction of bile ducts and in particular the controlled formation of luminal structures formed by cholangiocytes is a challenge. The team works on a high resolution individual-based computational model which can help in unravelling the mechanisms of initial bile duct lumen formation. Guided by the quantification of morphological features and expression of genes in developing bile ducts from embryonic mouse liver, hypotheses for the mechanisms of biliary lumen formation were generated and tested with the model. Our simulations with a hybrid simulation technology as developed in ref. [123] suggest that successful bile duct lumen formation primarily requires the simultaneous contribution of several mechanisms discussed in the literature.

Mathematical modelling of axolotl regeneration

Tissue response after injury/amputation induces one or two alternatives: scar formation versus

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

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

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

Bacterial population growth

We exploited all the methods developed to estimate the division rate of a population (see axis 3) to address a seminal question of biology: is it a size-sensing or a timing mechanism which triggers bacterial growth? In [147], 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 [14].

A new model for the emergence of blood capillary networks

In [58], we propose a new model for the emergence of blood capillary networks. We assimilate the tissue and extra cellular matrix as a porous medium, using Darcy's law for describing both blood and intersticial fluid flows. Oxygen obeys a convection-diffusion-reaction equation describing advection by the blood, diffusion and consumption by the tissue. Discrete agents named capillary elements and modelling groups of endothelial cells are created or deleted according to different rules involving the oxygen concentration gradient, the blood velocity, the sheer stress or the capillary

[5] liedekerke:hal-01956017

element density. Once created, a capillary element locally enhances the hydraulic conductivity matrix, contributing to a local increase of the blood velocity and oxygen flow. No connectivity between the capillary elements is imposed. The coupling between blood, oxygen flow and capillary elements provides a positive feedback mechanism which triggers the emergence of a network of channels of high hydraulic conductivity which we identify as new blood capillaries. We provide two different, biologically relevant geometrical settings and numerically analyze the influence of each of the capillary creation mechanism in detail. All mechanisms seem to concur towards a harmonious network but the most important ones are those involving oxygen gradient and sheer stress. This work offers a new paradigm for capillary network creation by placing the flow of blood at the central place in the process. The model proposed in [3] provides a proof of concept of this approach and elaborates a road map by which the model can be gradually improved towards a fully fledged simulator of blood capillary network formation. Such simulator would have huge potential for biological or clinical applications in cancer, wound healing, tissue engineering and regeneration.

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 was as 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. In addition, alternative mechanisms at the level of molecularly intermediated cell-cell communication discussed in the vast medical and biological literature have

been implemented and are systematically assessed for their biological consequence at the tissue level. This permits an in-silico testing of alternative hypotheses contributing to a more efficient identification of informative future experiments.
(2) Liver disease: Degenerative liver diseases such as liver fibrosis and cirrhosis develop out of a disturbed balance of degenerative and regenerative processes. The model under (1) has thereby been extended by the formation of extracellular matrix, mimicked as fiber networks, to capture the disease process leading to liver fibrosis. In that process characteristic streets form that modify the mechanics, perfusion behavior and detoxification capacity of the liver. The model is now used to simulate disease pathways emerging from different administration schemes of drugs that are knowning to long-term lead to hepatocellular cancer.
(3) Consequence of liver fibrosis: Whole-slide scans from fibrotic liver in a mouse model has been analysed at different time points after emergence of the disease with regard to the degree of excess matrix to mimic the possible consequences of fibrotic inclusions on perfusion and function of liver within a multiscale model that considers ammonia detoxification in each individual hepatocyte as well as blood flow and transport processes in the liver lobule. This model has now be confronted on multimodal data in healthy liver, liver after a toxic dose of a drug, and fibrosis. The requirement to explain simultaneously all data sets in the same model imposes significant challenges for which solutions are currently explored.
(4) Bile flux: Bile flux has been for decades believed to be controlled by convection at the level of liver lobules as well as at the level of the entire organ. By a methodology based on correlative imaging for quantitative intravital flux analysis no directed advection was detectable in bile canaliculi at the resolution limit. Instead, after active transport across hepatocyte membranes bile salts within the liver lobules are transported in the canaliculi by a diffusion-dominated process. Only in the interlobular ducts i.e., at super-lobular level, diffusion is augmented by advection. In silico simulations of bile transport in real 3D bile network microarchitectures can quantitatively explain the data assuming diffusive transport as sole mechanism.
(5) Liver regeneration after partial hepatectomy (partial organ removal): Partial hepatectomy is an adequate therapy in case of diseases or events that destructed only part of the liver. A typical case is a primary tumor or a metastasis affecting only a single liver lobe. Within an biophysical agent-based model capturing many aspects of the cell mechanics we studied regrowth of liver after partial organ removal in mouse calibrated with multivariate experimental data. Our model predicts characteristic proliferation pattern that change from small animals (as mouse) to large animals (as pig).
(6) Bile duct ligation: Bile duct ligation (BDL) is an experimental procedure that mimics obstructive cholestatic disease. One of the early consequences of BDL in rodents is the appearance of so-called bile infarcts that correspond to Charcot-Gombault necrosis in human cholestasis. The mechanisms causing bile infarcts and their pathophysiological relevance are unclear. Therefore, intravital two photon–based imaging of BDL mice was performed with fluorescent bile salts (BS) and non-BS organic anion analogues. Key findings were followed up by matrix-assisted laser desorption ionization imaging, clinical chemistry, immunostaining, and gene expression analyses. Our group performed analysis of intravital imaging. The key finding is that bile microinfarcts occur in the acute phase after BDL in a limited number of dispersed hepatocytes followed by larger infarcts involving neighboring hepatocytes, and they allow leakage of bile from the BS-overloaded biliary tract into blood, thereby protecting the liver from BS toxicity; in the chronic phase after BDL, reduced sinusoidal BS uptake is a dominant protective factor, and the kidney contributes to the elimination of BS until cholemic nephropathy sets in[107].
(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[108].

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'ns PhD thesis [86]) 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 [159]. The work of that paper has been further advanced to adapt the procedures for clinical use (in preparation).

Collaborations

- Protein aggregation in amyloid diseases: Human Rezae's team at Inra Jouy-en-Josas (France) and W-F Xue's team in at university of Kent (Great Britain); Tom Banks at the North Carolina State University (USA) and Philippe Moireau (M3DISIM)
- Bacterial growth and division: Lydia Robert, Sorbonne Université (France)
- Liver research & toxicology: JG. Hengstler group (IfADo, Dortmund, Germany); R. Gebhardt (Univ. Leipzig); U. Klingmueller (DKFZ, Heidelberg); Irène Vignon-Clementel (INRIA, COMMEDIA)
- Growth in capsules and biomechanics: Pierre Nassoy, Institut dOptique Graduate School, Talence, France; Josef Kaes, Peter Debye Institute for Soft Matter Physics, Physics, Univ. Leipzig, Germany.
- Wound healing: (Adipose tissue regeneration) team of L. Casteilla (StromaLab, Toulouse). (Axolotl regeneration) team of O. Chara, SysBio group, Argentina.
- Diffusion of morphogen: Center for Computational and Integrative Biology, Rutgers University (Camden, New Jersey), joint work with Professor Nir Yakoby's Drosophila Laboratory

- Linking micro and macro-image information: Oliver Sedlaczek, Univ. and DKFZ Heidelberg, Kai Breuhahn, Univ. Heidelberg.

4.4 Applicative axis 3: Modelling and control in mathematical epidemiology

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

Biological control of arboviroses

Sterile Insect Technique (SIT) [102] 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* [150, 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 [75], and through optimal control approach [76]. Concerning Wolbachia technique, we investigated general control principles [6] capable of spreading the infection.

We also considered the effects of hindrances to these strategies [20, 48].

Mathematical epidemiology of infectious diseases

The current outbreak of Covid-19 resulted in the appearance of many novel experiences at individual and collective, biological and social, national and international levels, making this pandemic a full epistemological experience as well. Motivated by the great number of questions raised by this global event, some members of the team devoted part of their time to exploring more or less closely related scientific issues. One should notice however that this evolution constitutes indeed the continuation of a movement already initiated previously, and only accelerated by the current events.

The issues raised by the effective implementation of the social distancing measures largely implemented on the Earth's surface during the whole year 2020, have been the focus of intense reflection. We contributed to this debate by studying optimal control policies aiming at reducing the total number of infected people during the whole epidemic outbreak, the so-called epidemic final size. In another research line, we established the equation fulfilled by the epidemic final size for a fully general SEIR model in a heterogenous population characterized by some trait in a discrete or continuous subset, and studied the uniqueness of its solution. This allowed to extend the use and meaningfulness of the classical concept of next-generation operator introduced by O. Diekmann et al. in 1990 [92]. Last, in cooperation with the Inria team NeCS (Inria Grenoble-Rhône-Alpes), we studied in a control theory perspective the effects of the testing policies in the dynamics and in the control of the epidemic.

Collaborations

- Biological control of arboviroses: Nicolas Vauchelet (Université Paris 13); Yannick Privat (Université de Strasbourg); D. Villela, C. Struchiner (Fiocruz, Brazil); Jorge Zubelli (IMPA,

Brazil); Alain Rapaport (INRA-Montpellier), Y. Dumont (CIRAD-Montpellier); Ch. Schaerer, P. Pérez-Estigarribia (UNA, Paraguay), O. Vasilieva (Universidad del Valle, Cali, Colombia), D. Cardona-Salgado (Universidad Autónoma de Occidente, Cali, Colombia); Hervé Bossin (ILM, Papeete); René Gato and Misladys Rodriguez (Inst. Pedro Kouri, La Havane)

- Mathematical epidemiology of infectious diseases: Nicolas Vauchelet (Université Paris 13); Michel Duprez (Inria Nancy - Grand Est); Yannick Privat (Université de Strasbourg); Carlos Canudas de Wit (Inria Grenoble - Rhône-Alpes and CNRS); Alain Kibangou (Université Grenoble-Alpes).

5 Highlights of the year

Federica Bubba (July 1st, 1992 — June 25, 2020)

Federica was PhD student at Laboratoire Jacques-Louis Lions and Politecnico di Milano. She should have defended her thesis in July 2020. Her lifeless body was found in her room at the Politecnico student residence. The members of MAMBA team and of Laboratoire Jacques-Louis Lions lament the loss of this luminous and generous figure.

Here are two testimonies to remember her.

Federica obtained a degree in engineering between the Politecnico di Milano and the Ecole des Ponts et Chaussées. In 2016 she completed her engineering internship at UPMC under my supervision. She continued her M2 with us, and her internship was in fact the beginning of her thesis which she started in 2017. She was enrolled in a co-tutorship with Pasquale Ciarletta at the Politecnico. She spent two years at SU and since september 2019 she was in Milan.

From the beginning she had chosen to work in the field of mathematics for biology and biomechanics of living tissues. Her research led her to study the numerical modeling of cell movements by chemotaxis, tumor growth and to collaborate with the Saint-Antoine Hospital on the formation of cell aggregates that initiate collective movements (then metastasis).

Very active, curious and pragmatic, she was looking for concrete applications and efficient solutions in mathematics, often using numerical simulations. Within 3 years, she had become an accomplished researcher with collaborations in Paris, Scotland, Italy and Germany. She had created the association of Mathematical Engineers in Italy, an association that has more than 1500 members and she participated in humanitarian associations for learning italian to migrants.

With a decided and organized personality, she also had a collective sense that made her take responsibilities among the doctoral students of the laboratory. She was very much appreciated, her thesis had been submitted in May 2020, she was to join a postdoc she had carefully chosen, in Munster, Germany. After the big European cities, she told me that she wanted to return to a small town. Perhaps a little nostalgia for the San Severo of her childhood.

Benoît Perthame, Federica's PhD co-advisor

I met Federica for the first time at the beginning of my PhD. As she worked under the supervision of Benoît Perthame as well, we were “PhD siblings". She started her PhD one year before me, and I had the chance to work on subjects connected to her work. We often say among PhD students that the first year is a difficult period since we need to understand a new subject and adapt ourselves to do new things. Mine was very smooth, and Federica was the reason for that. She helped me a lot, explaining to me concepts that I found unclear at the time. She applied with me a pedagogy and patience that I found remarkable (especially knowing the silly questions I sometimes asked her). Working with her made me one of the witnesses of her exceptional research skills, and I still consider today Federica as a model. On a more personal side, I remember the conferences that we went to together. Especially, I remember the moment when we took the ferry on rough water to go to a conference on the island of Samos, in Greece. That way, we avoided taking a small propeller-driven plane to go to the island. But, Federica, I never knew if you took the boat because, like me, you were afraid of that “plane" or due to your inspiring action to reduce the carbon cost of your professional travels.

I told you, she is an example both in her works as well as her everyday actions. I could go on for days listing the admirable qualities that Federica had both on the personal and professional sides. She was an awesome colleague and friend.

Federica, I am so sad that you disappeared, but I am so happy to have known you.

For everything you shared with me, and in the name of all your colleagues: Thank you!

Alexandre Poulain, PhD student, Federica’s co-author

Federica’s bibliography

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2 important changes among MAMBA members in 2021:

- Grégoire Nadin, CR CNRS, joined MAMBA team. Former student at ENS Paris, Grégoire obtained PhD degree in 2008, under the supervision of H. Berestycki and F. Hamel, and Habilitation à diriger des recherches in 2018. Specialist of reaction-di‘fusion equations, including coupled and non-local, and of propagation phenomenon in space-time heterogeneous media, his research interests are focused on mathematical models in biology and ecology.

- Dirk Drasdo, DR Inria, just created a new Inria team, together with Irène Vignon-Clémentel, starting in 2021. The team Simbiotx, hosted at Inria Saclay-Î le-de-France Research Centre, started in February 2021.

Wei-Feng Xue, lecturer in biophysics at the university of Kent, Canterbury, UK, has been invited for one month, March 5th - April 5th, 2020, but the pandemic forced him to shorten his visit.

6 New software and platforms

6.1 New software

6.1.1 TiQuant

Name: Tissue Quantifier

Keywords: Systems Biology, Bioinformatics, Biology, Physiology

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

Author: Dirk Drasdo

Contact: Dirk Drasdo

6.1.2 TiSim

Name: Tissue Simulator

Keywords: Systems Biology, Bioinformatics, Biology, Physiology

Scientific Description: TiSim (Tissue Simulator) is a versatile and efficient simulation environment for tissue models. TiSim is a software for agent-based models of multicellular systems. It permits model development with center-based models and deformable cell models, it contains modules for monolayer and multicellular spheroid simulations as well as for simulations of liver lobules. Besides agent-based simulations, the flow of blood and the transport of molecules can be modelled in the extracellular space, intracellular processes such as signal transduction and metabolism can be simulated, for example over an interface permitting integration of SBML-formulated ODE models. TiSim is written in modern C++ , keeping central model constituents in modules to be able to reuse them as building blocks for new models. For user interaction, the GUI Framework Qt is used in combination with OpenGL for visualisation. The simulation code is in the process of being published. The modeling strategy and approaches slowly reach systems medicine and toxicology. The diffusion of software is a fundamental component as it provides the models that are complex and difficult to implement (implementing a liver lobule model from scratch takes about 2-2.5yrs) in form of a software to the developer and users who like to build upon them. This increases significantly the speed of implementing new models. Moreover, standardization is indispensible 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 ($\tilde{6}$0 MMs) + model development time ($\tilde{2}$64 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.

Authors: Margaretha Palm, Johannes Neitsch, Paul van Liedekerke, Dirk Drasdo, Stefan Hoehme, Tim Johann

Contacts: Dirk Drasdo, Stefan Hoehme, Tim Johann

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

Partner: IZBI, Université de Leipzig

6.2 New platforms

6.2.1 TiSim

The deformable cell model [123, 157] 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.

6.2.2 TiQuant

This image processing and analysis software ([101]) 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

The many results obtained during the last years have oriented us towards new research directions in the wide field of structured population equations: the study of the direct and inverse problem in the newly-proposed "adder model" [155]; oscillatory behaviours of such equations; the study of models for heterogeneous aggregation, *i.e.* where the aggregates are formed out of several monomeric species.

7.1.1 Heterogeneous aggregation: application to autophagy (J. Delacour, M. Doumic, C. Schmeiser, MaMoCeMa associated team)

To date, there exists very few studies of heterogeneous aggregation, *i.e.* aggregates formation out of several monomeric species. Last year, we proposed a bimonomeric model of Becker-Döring type, capable of explaining damped oscillations observed in prion fibrils aggregates [97]; however, in this study, we kept the standard formalism where a given aggregate is characterised by its size, *i.e.* by the number of monomers it contains, irrespective of the monomeric species.

In a different and still more complex direction, there is the case where each aggregate is formed out of two or more monomeric species, arranged in a particular way. This is typically the case of the aggregation of ubiquitinated cargo by oligomers of the protein p62. This is an important preparatory step in cellular autophagy, which has been Julia Delacour's Ph.D subject, defended in December 2020 [28], and co-supervised by M. Doumic and C. Schmeiser of the associated team MaMoCeMa. The dynamics of protein aggregation has been studied by mathematical modelling for several decades, but most models consider the aggregation of only one type of protein, which gives rise to models belonging to the class of nucleation-coagulation-fragmentation equations.Contrary to these studies, Julia Delacour's Ph.D thesis studied aggregates composed of two different types of particles with varying mixing ratios, which drastically increases the complexity of the problem. This phenomenon appears in autophagy, a natural mechanism of the cell which degrades unnecessary material.

Aggregation of ubiquitinated cargo by oligomers of the protein p62 is an important preparatory step in cellular autophagy. In a first study [40], a mathematical model for the dynamics of these heterogeneous aggregates in the form of a system of ordinary differential equations is derived and analyzed. Three different parameter regimes are identified, where either aggregates are unstable, or their size saturates at a finite value, or their size grows indefinitely as long as free particles are abundant. The boundaries of these regimes as well as the finite size in the second case can be computed explicitly. The growth in the third case (quadratic in time) can also be made explicit by formal asymptotic methods. The qualitative results are illustrated by numerical simulations. A comparison with recent experimental results permits a partial parametrization of the model.

In a more theoretical article [40], in collaboration with P. Smzolyan from the university of Vienna, the qualitative behavior of the model is analyzed, certain aspects of the previously conjectured asymptotics being proven rigorously. In particular, the stability of the zero state, where the model has a smoothness deficit is analyzed by a combination of regularizing transformations and blow-up techniques. On the other hand, in a different parameter regime, the existence of polynomially growing solutions is shown by Poincaré compactification, combined with a singular perturbation analysis .

7.1.2 Oscillatory asymptotic behaviour of structured-population equations (M. Doumic, H. Martin)

In [43], H. Martin and P. Gabriel proved, in the framework of measure solutions, that the equal mitosis equation present persistent asymptotic oscillations. This follows a previous study of the same phenomenon [71], carried out in an L^2 weighted norm. 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 (M. Doumic, A. 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 [14] adresses 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 [105]. 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, and pave the way for further improvements and theoretical estimates.

7.1.4 Insights into protein filament division (M. Doumic, W.F. Xue, M. Tournus, M. Escobedo)

The dynamics by which polymeric protein filaments divide can be described by the universal mathematical equations of 'pure fragmentation'. The rates of fragmentation reactions reflect the stability of the protein filaments towards breakage, which is of importance in biology and biomedicine for instance in governing the creation of amyloid seeds and the propagation of prions. In the numerical study [54], we devised from mathematical theory inversion formulae - analysed in their own right in previous studies [95] - to recover the division rates and division kernel information from time dependent experimental measurements of filament size distribution. The numerical approach to systematically analyze the behaviour of pure fragmentation trajectories was also developed. We illustrate how these formulae can be used, provide some insights on their robustness, and show how they inform the design of experiments to measure fibril fragmentation dynamics. These advances

are made possible by our central theoretical result on how the length distribution profile of the solution to the pure fragmentation equation aligns with a steady distribution profile for large times.

In the biological article [5], we applied these methods to compare the stability towards breakage of several protein fibrils. The division of amyloid protein fibrils is required for the propagation of the amyloid state and is an important contributor to their stability, pathogenicity, and normal function. Here, we combine kinetic nanoscale imaging experiments with analysis of a mathematical model to resolve and compare the division stability of amyloid fibrils. Our theoretical results show that the division of any type of filament results in self-similar length distributions distinct to each fibril type and the conditions applied. By applying these theoretical results to profile the dynamical stability toward breakage for four different amyloid types, we reveal particular differences in the division properties of disease-related amyloid formed from α-synuclein when compared with non-disease associated model amyloid, the former showing lowered intrinsic stability toward breakage and increased likelihood of shedding smaller particles. Our results enable the comparison of protein filaments' intrinsic dynamic stabilities, which are key to unraveling their toxic and infectious potentials.

7.2 Stochastic Models of Biological Systems

7.2.1 Stochastic models for spike-timing dependent plasticity (Ph. Robert and G. Vignoud)

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

If numerous models of neuronal cells have been proposed in the mathematical literature, few of them include a variable for the time-varying strength of the connection. In [53], a new, general, mathematical framework to study the phenomenon of synaptic plasticity associated to STDP rules is introduced. A system composed of two neuronal cells connected by a single synapse is investigated and a stochastic process describing its dynamical behavior is presented and analyzed. The notion of *plasticity kernel* is introduced as a key component of plastic neural networks models. We show that a large number of STDP rules from neuroscience and physics applied to neural systems can be represented by this formalism.

Mathematical models of biological neural networks are associated to a rich and complex class of stochastic processes. When the connectivity of the network is fixed, various stochastic limit theorems, such as mean-field approximation, chaos propagation and renormalization have been used successfully to study the qualitative properties of these networks. Experiments show that long-term synaptic plasticity evolves on a much slower timescale than the cellular mechanisms driving the activity of neuronal cells. For this reason a scaling model of our stochastic model is also introduced and averaging principles for a sub-class of plasticity kernels are stated, and proved in [52]. These results are used to analyze two STDP models widely used in applied physics: *Pair-based rules* and *calcium-based rules*. We compare results of computational neuroscience on models of timing-based synaptic plasticity with our results derived from averaging principles. A class of discrete models of STDP rules is also introduced and studied for the analytical tractability of its solutions in the light of averaging principles.

In [52], we consider a simple *plastic* neural network whose *connectivity/synaptic strength* $(W(t))$ depends on a set of activity-dependent processes to model *synaptic plasticity*, a well-studied mechanism from neuroscience. It has been observed experimentally that its dynamics occur on much slower timescale than that of the main cellular processes. The purpose of this paper is to establish limit theorems for the distribution of $(W(t))$ with respect to the fast timescale of neuronal processes.

The central result obtained is an averaging principle for the stochastic process $(W(t))$. Mathematically, the key variable is the point process whose jumps occur at the instants of neuronal

spikes. A thorough analysis of several of its unbounded additive functionals is achieved in the slow-fast limit. Additionally, technical results on interacting shot-noise processes are developed and used in the general proof of the averaging principle. A comparison with classical related results of statistical physics in neuroscience is done in [53].

7.2.2 Online Sequence Learning In The Striatum With Anti-Hebbian Spike-Timing-Dependent Plasticity (G. Vignoud, J.D. Touboul (Brandeis University), L. Venance (Collège de France))

Cortico-striatal synaptic plasticity is viewed as a substrate for procedural learning. In particular, medium-sized spiny neurons (MSNs) integrate context elements to choose between different sensorimotor associations. They express anti-Hebbian spike-timing dependent plasticity (STDP) at corticostriatal synapses. Therefore, we questioned the impact of STDP on learning in the striatum To do so, we developed a simple 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 modeled as binary neurons sending their input to one MSN, modeled as a leakyintegrate-and-fire neuron. Patterns are defined by temporal sequences of spikes from the input neurons, presented sequentially to the MSN whose spiking binary pattern models the output of the circuit. Combining 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. A subset of patterns induce a "reward" consisting on an increase in the synaptic weights associated with the input neurons active during these patterns. The learning dynamics and efficiency are studied in different settings (number of neurons, intensity of the plasticity, types of STDP, tolerance to random noise, strategies to end learning). A second MSN which inhibits the other cell improves the global accuracy. We also investigated the persistence of learning, by shutting off/on the dopaminergic plasticity, and compared it to DMS/DLS experimental and behavioral experiments.

7.2.3 A synaptic theory for procedural and sequence learning in the striatum (G. Vignoud, J.D. Touboul (Brandeis University), L. Venance (Collège de France))

Spike-Timing Dependent Plasticity (STDP) can be viewed as a substrate for procedural learning in the striatum. Here, we explore how STDP rules at play in striatum provide an efficient support for learning sequences. Biologically, it has been shown that striatal projecting neurons (SPNs) require the coincidence of many spikes to fire, and play a role in sensory-motor integration. SPNs express anti-Hebbian STDP at corticostriatal synapses: a pre-synaptic spike followed by a post-synaptic spike leads to depression, whereas the reverse pairing leads to potentiation. In computational neurosciences, models for learning sequences have used gradient descent in a Perceptron-like way. Recently, anti-Hebbian STDP has been applied for learning of spike times or in a decoding task. Nevertheless, how the specific properties of SPNs combine with anti-Hebbian learning to enable sequence learning, and the efficiency of that learning, remain unknown.

We undertake a computational study of the role of anti-Hebbian plasticity at SPNs. We first consider on SPN modeled as an integrate-and-fire neuron, receiving feedforward input from multiple cortical neurons through synapses subject to anti-Hebbian STDP. Following precisely timed sequences of spikes from cortical neurons, SPNs are able to selectivity respond only to those stimulations that are followed by a global LTP signal (e.g., modeling reward following a successful task). Considering two bursting SPNs (adaptive nonlinear IF neurons) connected through lateral inhibition (both properties observed experimentally in SPNs) allow learning of a wider array of sequences. We will explore how this learning capacity depends on the number of cells, on the type and intensity of plasticity, as well as its robustness to noise. To conclude, we show that anti-Hebbian STDP, bursting, lateral inhibition of SPNs combine to endow the system with the ability to learn to decode temporal sequences.

7.2.4 Movement Disorders Analysis Using a Deep Learning Approach (C. Desjardins, Q. Salardaine, G. Vignoud, B. Degos)

Bradykinesia is defined as a motor slowness and is associated with decrement of the amplitude and/or the speed of movement. Bradykinesia is a key parkinsonian feature yet subjectively assessed by the MDS-UPDRS score making reproducible measurements and follow-up challenging. Using a deep learning inspired approach, we have developed a tool to compute an objective score of bradykinesia.

Method. A large database of videos showing parkinsonian patients performing MDS-UPDRS protocols has been acquired in a Movement Disorder unit. We applied a detection algorithm based on the existing DeepLabCut [1] software to detect 21 different and characteristic points of the hand on a 2-d projection. Another deep learning approach is then used to transpose this 2-d projection on a 3-d hand model, leading to a full 3-d geometrical description of the 21 points as a function of time.

We analyzed separately all three tests of upper limb bradykinesia as described in the MDS-UPDRS. Firstly, for the "finger tapping" protocol, we computed the geometrical distance between the tips of the index and the thumb, leading to a precise detection of the amplitude, speed and acceleration of the tapping. Then, for the "hand movements", we analyzed the speed and amplitude at which the patient performed successive fist openings and closings, to have a precise estimation of its evolution over time. Finally, the "pronation-supination movements of hands" are assessed by the wrist rotation angle, computed thanks to the 3-d position of several key hand joints.

7.2.5 The Stability of Non-Linear Hawkes Processes (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 $t\in\mathbb{R}$ 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.

7.2.6 Stochastic Chemical Networks (L. Laurence and Ph. Robert)

The general goal of this work, started in September 2020, is of developing a scaling approach to analyze stochastic models of chemical networks. A chemical network is defined with three components

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

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

$$p_aAp_bB \longrightarrow p_cCp_dD$$

is an edge of the graph corresponding to the transformation of the complex p_aAp_bB (p_a copies of A and p_b copies of B) into the complex p_cCp_dD. The rate at which such reaction occurs is

$$\prod_{i0}^{p_a-1}(x_A-i)\prod_{i0}^{p_b-1}(x_B-i)$$

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

The main goal of this study is of giving the conditions under which the state of the chemical network is converging in distribution. We have started with simple examples: a cyclic network, i.e. whose graph is a loop and a network proposed by Agazzi and Mattingly.

7.2.7 Allocation of Resources in Prokaryotic Cells (V. Fromion (INRAE), Ph. Robert, J. Zaherddine)

The objective of this starting PhD work (September 2020) is of designing and analyzing stochastic models of allocation of resources for protein production of bacteria cells. We have started to analyze the impact of the production of sRNA (small RNAs) as an agent to modulate the number of free polymerases.

7.3 Analysis and control of populations of mosquitoes

7.3.1 Control Strategies for Sterile Insect Techniques (L. Almeida, P.-A. Bliman, M. Strugarek)

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 (L. Almeida, P.-A. Bliman, Y. Privat, M. Strugarek, N. Vauchelet)

We modelled and designed optimal release control strategy with the help of a least square problem. In a nutshell, one wants to minimize the number of uninfected mosquitoes at a given time horizon, under relevant biological constraints. We derived properties of optimal controls and studied a limit problem providing useful asymptotic properties of optimal controls [60, 76].

7.3.3 Oscillatory regimes in population models (M. Strugarek, L. Dufour, N. Vauchelet, L. Almeida, B. Perthame, D. Villela)

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 [153] 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 [154, 151] 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* (P.-A. Bliman, P. Pérez Estigarribia, Ch. Schaerer)

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 [6]. These principles were exemplified by two interval observer-based feedback control laws whose stabilizing properties were demonstrated when applied to a model retrieved from [74].

In order to tackle the issue of mosquito population control in presence of insecticide, we developed a class of fast-slow models for adaptive resistance evolution [20]. This allowed to model altogether the Mendelian inheritance of the resistance insecticide, and the maternal inheritance of Wolbachia [48].

7.4 Modelling and control in epidemiology

7.4.1 Immunity control by social distancing (P.-A. Bliman, M. Duprez (Inria Nancy Grand Est), Y. Privat (Université de Strasbourg), N. Vauchelet (Université Paris 13))

The current outbreak of Covid-19 and the entailed implementation of social distancing on an unprecedented scale, led to a renewed interest in modelling and analysis of the nonpharmaceutical intervention strategies to control infectious diseases. The term "social distancing" (including, but not limited to, "physical distancing") refers to attempts to directly reduce the infecting contacts within the population. In absence of vaccine or therapy, such containment strategies constitute probably the only mid-term option. An issue of interest is to understand how one can minimize the epidemic final size, or equivalently the total number of individuals infected during the outbreak, given maximal social distancing duration and intensity. Voluntarily ignoring many features important in the effective handling of a human epidemic, we investigated this question on a simple SIR model. A complete answer was given in [37] for optimal control on an interval with prescribed starting date, and in [7] in the case of free starting date.

7.4.2 Epidemic final size (L. Almeida, P.-A. Bliman, G. Nadin, B. Perthame, N. Vauchelet)

We considered in [32] a general SEIR epidemic model in a heterogenous population characterized by some trait in a discrete or continuous subset of a finite-dimensional space. The incubation and recovery rates governing the evolution of each homogenous subpopulation depend upon this trait, and no restriction is assumed on the contact matrix that defines the probability for an individual of a given trait to be infected by an individual with another trait. We derived and studied the final size equation fulfilled by the limit distribution of the population. Our main contribution was to prove the uniqueness of this solution among the distributions smaller than the initial condition. The results are shown to remain valid in presence of diffusion term. They generalize previous works corresponding to finite number of traits or to rank 1 contact matrix.

7.4.3 Testing policies in the control of the Covid-19 epidemic (P.-A. Bliman, C. Canudas de Wit (NeCS, Inria Grenoble-Rhône-Alpes) A. Kibangou (Gipsa-lab))

Testing for the infected cases is one of the most important mechanisms to control an epidemic. It enables to isolate the detected infected individuals, thereby limiting the disease transmission to the susceptible population. We presented in [46] an epidemic model that incorporates the testing rate as a control input. The proposed model differentiates the undetected infected from the detected infected cases, who are assumed to be removed from the disease spreading process in the population. The model has been estimated and validated for Covid-19 data in France, and two testing policies were proposed and evaluated by predicting the number of active intensive care unit (ICU) cases and the cumulative number of deaths.

7.5 Analysis and numerics for mechanical models of tumor growth

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

New directions of research have been initiated for the analysis of PDE models arising in biology. Firstly, in contact with CNR in Roma, we have studied the use of the Kedem-Katchalsky conditions to represent the effect of a membrane, the analysis is presented in [10] based on Pierre's method for parabolic systems as improved in [18]. Secondly, because living tissues can be seen as multi-phasic mixtures (different cells have different mechanical properties), the degenerate and singular

Cahn-Hilliard equation is widely used in the domain to represent the proportion of cancer cells. In [21], we proposed a relaxation approach, compatible for the energy decay, which allows to reduce this fourth order equation to a system of two second order equations and thus to use standard finite elements softwares. It is also possible to keep two cell densities rather than a proportion and one arrives to systems of porous media equations (cells move in anextra-cellular matrix with properties well describes by a porous media model). In this context, the pressure law is stiif and it is relevant to study the limiting free boundary problem. The first result in this direction is derived in [9]. When the nutrients are included in the model, specific theoretical difficulties arise and this is treated in [38] thanks to a new remarkable estimate on the porous media equation.

From the numerical side, to preserve energy properties, the Scalar Auxiliary Variable method is very efficient and has been proposed by J. Chen and his collaborators a few years ago. We have used this method in the context of chemotaxis [49], and extended to the nonlinear Schroedinger equation in [50].

7.6 Focus on cancer

7.6.1 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 [89, 126], has been summarised in [59], presented in more detail in [91], and has been the object of the PhD thesis work of Camille Pouchol, see above "Cell population dynamics and its control" . In collaboration with F. Vallette's INSERM team in Nantes, it gave rise to the publication of the article [24]. It is now oriented, thanks to work underway by Frank Ernesto Alvarez Borges, Jean Clairambault, and Stéphane Mischler , in particular towards the mathematical representation of *bet hedging* in cancer, namely a supposed optimal strategy consisting for cancer cell populations under life-threatening cell stress in diversifying their phenotypes according to several resistance mechanisms, such as overexpression of ABC transporters (P-glycoprotein and many others), of DNA repair enzymes or of intracellular detoxication processes. According to different deadly insults the cancer cell population is exposed to, some phenotypes may be selected, any such successful subpopulation being able to store the cell population genome (or subclones of it if the cell population is already genetically heterogeneous) and make it amenable to survival and renewed replication.

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

In the frame of the HTE project MoGlImaging and the post-doctorate of Gissell Estrada Rodriguez, we developed a 2D mathematical model to study and analyse the evolution of a population of glioblastoma cells that are exposed to TMZ [31]. Based on the experimental data generated by our partner team led by F. Valette (Inserm Nantes), we proposed a Keller-Segel type model where tumour aggregate formation is obtained as the result of nutrient-limited cell proliferation coupled with chemotaxis-based cell movement. The introduction of a chemotherapeutic treatment is supposed to induce mechanical changes at the cell level, with cells undergoing a transition from rigid bodies to semi-elastic entities. We analysed the influence of these individual mechanical changes on the properties of the aggregates obtained at the population level by introducing a nonlinear volume-filling chemotactic system of partial differential equations. The elastic properties of the cells were taken into account through the so-called squeezing probability, which allowed us to change the packing capacity of the aggregates, depending on the concentration of the treatment in the extracellular microenvironment. By confronting the model results to experimental data, we showed that the changes observed in cellular structures under a non-cytotoxic drug could be due to this mechanotransduction phenomenon. This study suggests a new mechanism which, if experimentally validated, opens interesting therapeutic avenues.

7.6.3 Plasticity in cancer cell populations and philosophy of cancer

From a biological point of view, adaptive dynamics and its asymptotics rely on the so-called *plasticity* of cancer cell populations, i.e., their ability to easily change their phenotypes, thanks to their poor differentiation, to adapt to a changing environment, in particular to develop resistance to cancer treatments. This point of view has been reviewed, from a biological, mathematical and 'philosophy of cancer' point of view in [25, 11]. In these articles, and in the invited conference paper [27], is particularly developed the idea according to which cancer is characterized, not so much as a default of control on cell proliferation, but at least equally as a default of control on cell differentiations. This idea is not new (in particular it has been put forward in Marta Bertolaso's book of 2016 "Philosophy of cancer", Springer Publ.), nevertheless it could lead to modeling developments that should complement the classical models based on sheer proliferation of cell populations, and possibly open the way to new therapeutic tracks, provided that can be found actual means of control and reestablishment of physiological cell differentiation, that so far exist for very few cancer diseases (e.g., for acute promyelocytic leukemia).

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

7.7 Single Cell-based Modeling, biomechanics, Liver regeneration, and liver function

7.7.1 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 [156]. 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.

7.7.2 Simulation of a detoxifying organ function: focus on hemodynamics modeling and convection-reaction numerical simulation in microcirculatory networks

When modelling a detoxifying organ function, an important component is the impact of flow on the metabolism of a compound of interest carried by the blood. In ref. [8] we study the effects of red blood cells (such as the Fahraeus-Lindqvist effect and plasma skimming) on blood flow in typical microcirculatory components such as tubes, bifurcations and entire networks, with particular emphasis on the liver as important representative of detoxifying organs. In one of the plasma skimming models, under certain conditions, oscillations between states are found and analysed in a methodical study to identify their causes and influencing parameters.
The flow solution obtained is then used to define the velocity at which a compound would be transported. A convection-reaction equation is studied to simulate the transport of a compound in blood and its uptake by the surrounding cells. Different types of signal sharpness have to be handled depending on the application to address different temporal compound concentration profiles. To permit executing the studied models numerically stable and accurate, we here extend existing transport schemes to handle converging bifurcations, and more generally multi-furcations. We study the accuracy of different numerical schemes as well as the effect of reactions and of the network itself on the bolus shape. Even though this study is guided by applications in liver micro-architecture, the proposed methodology is general and can readily be applied to other capillary network geometries, hence to other organs or to bioengineered network designs.

7.7.3 Intravital dynamic and correlative imaging reveals diffusion-dominated canalicular and flow-augmented ductular bile flux

Since the late 1950s transport of bile in the liver has been described by the 'osmotic concept', according to which bile flows in the canaliculi towards the ducts, in reverse direction to the blood flow in the sinusoids, the capillaries in the liver lobules. Liver lobules are the smallest repetitive anatomical and funtional units of liver. Until recently, it has been impossible to measure flow in canaliculi and ducts because of their small dimensions. In ref. [26] imaging techniques have now been established that allow the direct flux analysis in bile canaliculi of the intact liver in living organisms. Experimental findings were directly confronted with the results of computer simulations performed in intravital images to infer the influence of diffusion versus advection contributions. In contrast to the prevailing osmotic concept recent evidence indicates that the transport of small molecules in canalicular bile is diffusion dominated, while flow may be negligibly small. Only in the interlobular ducts, diffusion seems augmented by flow. These findings may have important consequences for the development of therapies for liver diseases that impact on function and architecture of the biliary system.

7.7.4 Bayesian inference of a parametric random ellipsoid from its orthogonal projections

The interface between experiments and models at tissue microarchitecture are histological images, that need to be segmented and quantitatively analyzed. Sometimes 3D information has to be inferred from 2D images. The article by de Langlard et. al. [122] focuses on a new method for the inference of a parametric random ellipsoid from the observations of its 2D orthogonal projections. The proposed method enables to recover some 3D morphological characteristics of a population of independent and identically distributed spheroids thanks to the only observations of its projected ellipses. In many applications such as in histological images, ellipsoids arise as a simple, but realistic, model for given objects e.g. cell nuclei [159]. For example, ellipsoidal models are frequently encountered to represent cells or aggregates of cells (tumor). The proposed method can be applied to infer 3D morphological characteristics of such objects when only their orthogonal projections are observed through 2D images.

7.8 The role of actin protrusion dynamics in cell migration through a degradable viscoelastic extracellular matrix: a computational model

Actin protrusion dynamics plays an important role in the regulation of three-dimensional (3D) cell migration [15]. We present a computational model of cell migration through a degradable viscoelastic ECM. The cell is modeled as an active deformable object that captures the viscoelastic behavior of the actin cortex and the subcellular processes underlying 3D cell migration. The ECM is regarded as a viscoelastic material, with or without anisotropy due to fibrillar strain stiffening, and modeled by means of the meshless Lagrangian smoothed particle hydrodynamics (SPH) method. ECM degradation is captured by local fluidization of the material and permits cell migration through the ECM. By simulations, we demonstrate that changes in ECM stiffness and cell strength affect cell migration and are accompanied by changes in number, lifetime and length of protrusions.

7.9 Macroscopic limit and control of collective dynamics

7.9.1 Collective dynamics with time-varying weights

We have developed a model for collective dynamics with weights, in which each agent is described not only by its position, but also by a positive "weight of influence". The weights allow us to model a social hierarchy within the group, where the most influencial agents (the ones with the largest weights) have a larger impact on the behavior of the group. Moreover, the weights of influence are susceptible to evolve in time, which models the changing social hierarchy. In [51], we formulated a control problem of consensus type, in which the objective is to drive all agents to a final target

point under suitable control constraints. We studied controllability with and without constraints on the total mass of the system, and designed control strategies with the steepest descent approach.

Related to the aforementioned models of opinion dynamics with time-varying weights, we explored the natural question of the large population limit with two different approaches: the now classical mean-field limit and the more recent graph limit. We established the existence and uniqueness of solutions to the models [35], and provided a rigorous mathematical justification for taking the graph limit in a general context. Then, establishing the key notion of indistinguishability, which is a necessary framework to consider the mean-field limit, we prove the subordination of the mean-field limit to the graph one in that context. This actually provides an alternative (but weaker) proof for the mean-field limit.

7.9.2 Kinetic approach to the collective dynamics of the rock-paper-scissors binary game

The binary zero-sum game rock-paper-scissors provides a simple framework for any two-player contest where each player has an equal probability of winning, losing or tying. It is one of the subclasses of three-strategy games, and it has been generalized in many ways (for example, punishment games and reward games), both in the static and in the evolutionary contexts. In [23], we introduced a kinetic version of the rock-paper-scissors game, in which instead of the well-studied inter-species competition, each agent within the unique population can compete with all the other agents. We proved existence and uniqueness of the solution of the kinetic equation and subsequently we proved the rigorous derivation of the quasi-invariant limit for two meaningful choices of the domain of definition of the independent variables. We showed that the domain of definition of the problem plays a crucial role and heavily influences the behavior of the solution. The rigorous proof of the relaxation limit does not need the use of entropy estimates for ensuring compactness.

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

In [3], we modeled and studied the patterns created through the interaction of collectively moving self-propelled particles (SPPs) and elastically tethered obstacles. Simulations of an individual-based model reveal at least three distinct large-scale patterns: travelling bands, trails and moving clusters. This motivated the derivation of a macroscopic partial differential equations model for the interactions between the self-propelled particles and the obstacles, for which we assumed large tether stiffness. The result is a coupled system of non-linear, non-local partial differential equations. By performing a linear stability analysis, we showed that patterning was expected if the interactions are strong enough and allowed for the predictions of pattern size from model parameters. The macroscopic equations revealed that the obstacle interactions induce short-ranged SPP aggregation, irrespective of whether obstacles and SPPs are attractive or repulsive.

7.9.4 Early morphogenesis of rod-shaped bacteria (M. Doumic, S. Hecht, D. Peurichard)

To model the morphogenesis of rod-shaped bacterial micro-colony, several individual-based models have been proposed in the biophysical literature. When studying the shape of micro-colonies, most models present interaction forces such as attraction or filial link. doumic:hal-0286556In the article [13], we propose a model where the bacteria interact only through non-overlapping constraints. We consider the asymmetry of the bacteria, and its influence on the friction with the substrate. Besides, we consider asymmetry in the mass distribution of the bacteria along their length, and the division follows the so-called "adder model" (see Section 7.1). These new modelling assumptions allow us to retrieve mechanical behaviours of micro-colony growth without the need of interaction such as attraction. We compare our model to various sets of experiments, discuss our results, and propose several quantifiers to compare model to data in a systematic way. We now aim at deriving a space-and-size structured population equation as the macroscopic limit of a simplified version of this model.

8 Bilateral contracts and grants with industry

8.1 Bilateral grants with industry

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

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

9 Partnerships and cooperations

9.1 International initiatives

9.1.1 Inria associate team not involved in an IIL

MoCoVec

Title: MoCoVec

Duration: 2020 - 2022

Coordinator: Pierre-Alexandre Bliman

Partners:

- Instituto de Biociências, Universidade Estadual Paulista (Brazil)

Inria contact: Pierre-Alexandre Bliman

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

MaMoCeMa

Title: MaMoCeMa

Duration: 2018 - 2020

Coordinator: Marie Doumic

Partners:

- Wolfgang Pauli Institute, University of Vienna (Austria)

Inria contact: Marie Doumic

Summary: 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 are presently maintained and ensured by the sabbatical of Marie Doumic -MAMBA team leader-, 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).

9.1.2 Participation in other international programs

STIC AmSud 20-STIC-05 NEMBICA

Title: *New Methods for Biological Control of the Arboviruses*

Duration: 2020 - 2021

Coordinator: Pierre-Alexandre Bliman

Partners:
- 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 Quindio, Universidad Autónoma de Occidente and Universidad del Valle (Colombia)
- National University of Asuncion (Paraguay).

Inria contact: Pierre-Alexandre Bliman

Summary: The main focus of this project is modeling and analysis, using mathematical methods, of new strategies aimed at controling 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

9.2 National initiatives

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

9.2.1 ANR

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.

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

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

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

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

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

9.2.3 Inria Covid-19 mission

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

9.2.4 BMBF

BMBF "LiSyM" This project establishes **li**ver **sys**tems medicine approaches to understand disease pathways and consequences of liver disease on liver function. The project is a large network projects linking many partners all over Germany.

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

Dirk Drasdo organized the minisymposium on "Cells" at the Conference on the virtual physiological human, VPH2020, in Paris, on invitation.

Member of the organizing committees Marie Doumic was a member of the scientific committee of the workshop PDE-MANS held in Granada, January 8-16, 2020.

10.1.2 Scientific events: selection

Chair of conference program committees Benoit Perthame was a co-chair of the semester "Quantum and Kinetic Problems: Modeling, Analysis, Numerics and Applications" held in Singapore, 30 september 2019 - 31 March 2020.

Member of the conference program committees

- Pierre-Alexandre Bliman is Member of the Conference Editorial Board of the European Control Conference, 2020
- Emma Leschiera and Alexandre Poulain co-organized (together with Hugo Martin and Angélique Perrillat-Mercerot) the conference IbOMaN : Interplay between Oncology, Mathematics and Numerics: focus on pre-treatment studies, June 22-23, online
- Jesús Bellver Arnau participated in the organization of the Rencontre M2-Doctorants du LJLL.

Reviewer

- Pierre-Alexandre Bliman is Reviewer for the IFAC World Congress, 2020

10.1.3 Journal

Member of the editorial boards

- Philippe Robert is Associate Editor of the journal “Stochastic Models”
- Dirk Drasdo is Associated Editor for Journal of Theoretical Biology, Royal Society Open Science, and The Scientific World Journal.
- Marie Doumic is Editor in Chief of ESAIM-Proc. and Associate Editor of the Journal of Mathematical Biology, of Kinetic and Related Models and of the Bulletin des sciences mathématiques

Reviewer - reviewing activities

- Pierre-Alexandre Bliman is Reviewer for the journals Applied Mathematical Modelling, Annual Reviews in Control, Automatica, Communications in Nonlinear Science and Numerical Simulation, Complex Systems, IEEE Control Systems Letters, IEEE Transactions on Automatic Control, International Journal of Biomathematics, Journal of Mathematical Biology, Journal of Optimization Theory and Applications, Mathematical Biosciences and Engineering, Mathematical Methods in the Applied Sciences, Physica D: Nonlinear Phenomena, International Journal of Robust and Nonlinear Control, Systems and Control Letters
- J. Clairambault has been in 2020 a reviewer for the journals Entropy, BBA Reviews Cancer, Journal of Clinical Medicine, eLife, PLoS Computational Biology, Bulletin of Mathematical Biology, Frontiers in Genetics, Frontiers in Oncology, Journal of Theoretical Biology, Physical Biology, Mathematical Medicine and Biology, Vietnam Journal of Mathematics, Mathematical Biosciences and Engineering, Biosystems, Computers in Biology and Medicine.
- Noemi David has been reviewer for the European Journal of Applied Mathematics EJAM.

10.1.4 Invited talks

- Many Mamba members have been invited to the semester on "Quantum and Kinetic Problems: Modeling, Analysis, Numerics and Applications" held in Singapore, 30 September 2019 - 31 March 2021:

  Benoît Perthame gave a 4-hour course on 16-17 January and a public lecture on 20 January

  Marie Doumic, Gissell Estrada-Rodriguez, Diane Peurichard and Xinran Ruan gave invited talks at the workshop on mathematical biology held on 20-23 January

- Many Mamba members have participated to the thematic month on Mathematical Issues in Biology held at CIRM, Marseille, from 3 February to 6 March:

  Marie Doumic gave a 4,5h-course on the "PDE and Probability school" held on 3-7 February

  Gissell Estrada-Rodriguez, Sophie Hecht gave an invited talk on the workshop "PDE and Probability school" held on 3-7 February

  Jean Clairambault gave an invited talk to the workshop "Mathematical Models in Evolutionary Biology" held on February 10-14

- Jean Clairambault gave an invited talk at the virtual "2nd International Symposium on Mathematical and Computational Oncology" (ISMCO) on October 9

10.1.5 Participation to scientific events

- Pierre-Alexandre Bliman delivered in March a talk at Departamento de Matemáticas, Universidad del Valle, Cali, Colombia.
- Valeria Caliaro presented a poster during the thematic month on Mathematical Issues in Biology held at CIRM, Marseille (Research school - PDE and Probability for Biology), February 3–7; and the Conference - Mathematics of Complex Systems in Biology and Medicine, February 24-28. She also gave a short talk at a seminar organized by the University of Verona on November 4.
- Giorgia Ciavolella delivered an online talk at the “Giornata Giovani IAC-CNR"", Online talk".
- Noemi David Research presented two posters, at the School - PDE and Probability for Biology, held February 3-7 at CIRM, Marseille, France; and at the Conference - Mathematics of Complex Systems in Biology and Medicine, held February 24-28, CIRM, Marseille,France. She also presented talks during the session of Café Mamba on October 5; and in the *Groupe de Travail des Thésards*, LJLL, on November 18.
- Emma Leschiera presented a poster in the conference *Mathématiques des systèmes complexes en biologie et en médecine*, February 24-28. She also delivered talks in the framework of two internal seminaries, at the Laboratory of Computational and Quantitative Biology (LCQ), Sorbonne Université; and at StAMBio, the Mathematical Biology Group at University of St Andrews.
- Alexandre Poulain gave a talk at the conference PDE and Probability for Biology, February 2020, CIRM; and at CANUM-J: Congrès d’Analyse Numérique pour les Jeunes - 2020, December 3-4.

10.1.6 Leadership within the scientific community

- Dirk Drasdo is associated with IfADo Leibniz Institute, having directed three research engineers/postdoccs from that institute.
- Dirk Drasdo co-leads a workpackage in the network grant ANR-iLite.

10.1.7 Scientific expertise

- Pierre-Alexandre Bliman is member of the Scientific committee of the ANR Call for projects Recherche-Action sur Covid-19 (RA-COVID-19). He is also expert for the ANR Call for projects Flash call COVID-19, and for FAPESP (São Paulo state, Brazil).
- Pierre-Alexandre Bliman is member of the Scientific committee of the MATH AmSud international program.

10.1.8 Research administration

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

10.2 Teaching - Supervision - Juries

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

- B. Perthame and N. Pouradier Duteil, “Mathematical Models for Neurosciences”, M1 course, Sorbonne Université
- D. Drasdo, “Agent-based models of tissue organization”, Paris 24 h / yr, M2 course, Sorbonne Université, 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 Sorbonne Université, "Fondements des méthodes numériques", 40h
- D. Peurichard, M1 TD in Sorbonne Université, "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”, Sorbonne Université
- M. Doumic, 67h as a part-time "professoresse chargée de cours" at Ecole Polytechnique
- Ph. Robert, M2 Course, "Modèles Stochastiques de la Biologie Moléculaire", Sorbonne Université

Supervision

- PhD in progress:
  - P.-A. Bliman was co-supervisor of the PhD student Pastor E. Pére-Estigarribia (with Ch. Schaerer, at Universidad Nacional de Asunción, Paraguay), defended October 15. He is co-supervisor of Assane Savadogo (with B. Sangaré, Université Nazi Boni, Burkina Faso);
  - 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 (with Yannick Privat, Université de Strasbourg);
  - M. Doumic is Julia Delacour’s co-supervisor (with Christian Schmeiser, Vienna - defended in December 2020), and Anaïs Rat co-supervisor (with Magali Tournus, Centrale Marseille - begun in October 2019);
  - B. Perthame is Alexandre Poulain’s supervisor, Giorgia Ciavolella’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);
  - D. Peurichard is Valeria Caliaro’s supervisor;
  - P. Robert is Gaëtan Vignoud’s co-supervisor, Jana Zaherddine co-supervisor;
  - N. Pouradier Duteil is co-supervising the PhD thesis of Jules Guilberteau on Mathematical Modeling of Cell Differentiation.

Committees

- J. Clairambault was a member of the ANR evaluation panel “Mathematics and their interactions for biology and health”.
- J. Clairambault was a member and chair of the PhD defence Committee of Florian Lavigne, defended September 22, Avignon.
- J. Clairambault was a reviewer for the PhD thesis of Martina Conte, defended January 15, 2021, Bilbao.
- 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’s habilitation defence committees: Pierre Gabriel, 13 January 2021 (MD chair), Virginie Ehrlacher, 10 December 2020
- M. Doumic’s Ph.D defence committees: Kokou Kevin Atsou (MD reviewer), 18 December 2020; Virgile Andreani (MD chair), 17 December 2020; Léo Darrigade (MD reviewer), 16 December 2020; Julia Delacour (MD supervisor), 14 December 2020;
- N. Pouradier Duteil was a member of the Inria/Inrae PhD selection committee.
- N. Pouradier Duteil is a member of the “Conseil du Laboratoire” at Laboratoire Jacques-Louis Lions.
- D. Peurichard is a member of the Inria "Commission des emplois scientifiques" for selecting PhD, delegation and post-doctoral candidates at Inria.
- Ph. Robert. Reviewer of HDR of Romain Yvinec, 02/12/2020, Université de Tours. Member of Jury of PhD Defense of Eustache Besançon, 08/12/2020, Institut Polytechnique de Paris.
- P.-A. Bliman. Reviewer and Member of the PhD defence committee of Nicolas Martin, Université Grenoble-Alpes, February 19. Member of the PhD defence committee of Nelson Barroso, Inria Lille - Nord Europe, December 18.

10.3 Popularization

- Emma Leschiera and her advisor Chloé Audebert participated in a speed meeting with students from a middle school in Nanterre.
- In a book chapter [57] (in French) two subfields of in-silico biology is described: QSAR modelling and the modelling of virtual organs down to micro-architectural level as a complement to animal experimentation, because they enable experiments to be interpreted, guide the optimisation of their design, and facilitate the extrapolation from in vitro to in vivo toxicity. The chapter positions the tools from these two disciplines in the context of the Adverse Outcome Pathways (AOP) which is a recently established toxicological construct that connects, in a formalized, transparent and quality-controlled way, mechanistic information to apical endpoints for regulatory purposes.

11 Scientific production

11.1 Major publications

[1] L. Almeida, P.-A. Bliman, G. Nadin, B. Perthame and N. Vauchelet. ‘Final size and convergence rate for an epidemic in heterogeneous population’. working paper or preprint. Oct. 2020. URL: https://hal.sorbonne-universite.fr/hal-02981952.

[2] M. Doumic, S. Hecht and D. Peurichard. ‘A purely mechanical model with asymmetric features for early morphogenesis of rod-shaped bacteria micro-colony’. In: *Mathematical Biosciences and Engineering* 17.6 (Oct. 2020), http://aimspress.com/article/doi/10.3934/mbe.2020356. URL: https://hal.archives-ouvertes.fr/hal-02865566.

11.2 Publications of the year

International journals

[3] P. Aceves-Sanchez, P. Degond, E. E. Keaveny, A. Manhart, S. Merino-Aceituno and D. Peurichard. 'Large-Scale Dynamics of Self-propelled Particles Moving Through Obstacles: Model Derivation and Pattern Formation'. In: *Bulletin of Mathematical Biology* 82.10 (Oct. 2020). DOI: 10.1007/s11538-020-00805-z. URL: https://hal.archives-ouvertes.fr/hal-03138284.

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Other scientific publications

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11.3 Other

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