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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 Project-Team: 2015 April 01

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1 Team members, visitors, external collaborators

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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. [136, 64, 97, 78]. 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 [72], 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 [147]. We investigated the interplay between four processes: nucleation, polymerization, depolymerization and fragmentation.

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

Cell population dynamics and its control
One of the important incentives for such model design, source of many theoretical works, is the challenging question of drug-induced drug resistance in cancer cell populations, described in more detail below in the Applicative axis 1, Cancer. The adaptive dynamics setting used consists of phenotype-structured integro-differential [or reaction-diffusion, when phenotype instability is added under the form of a Laplacian] equations describing the dynamic behavior of different cell populations interacting in a Lotka-Volterra-like manner that represents common growth limitation due to scarcity of expansion space and nutrients. The phenotype structure allows us to analyse the evolution in phenotypic traits of the populations under study and its asymptotics for two populations [128], [125, 124, 126]. Space may be added as a complementary structure variable provided that something is known of the (Cartesian) geometry of the population [127], which is seldom the case. A recent review of mathematical methods aiming at improving cancer treatments has been published in Physics of Life Reviews [18].

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 [75, 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 [54, 120, 160]. 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 [135].

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 [140], followed by [134, 119, 141, 77]. 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 [82].

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 [63]. 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 [63].

Models of population dynamics structured in phenotype The collaboration of Jean Clairambault with Emmanuel Trélat and Camille Pouchol (from September last year assistant professor at MAP5 Paris-Descartes, University of Paris), together now with Nastassia Pouradier Duteil, has been continued and presently leads us to a possible quantitative biological identification of the structuring phenotypes of the model developed in [146], through a beginning collaboration with an Indian systems biologist (Mohit Kumar Jolly, IIS Bangalore). Our motivation in this collaboration is to couple a physiologically based system of 6 ODEs developed by our Indian collaborator with our phenotype-structured cell population dynamics model [86, 88].

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 (Oxford). A feature of these models, in as much as conflicting continuous phenotypes (e.g., adhesivity vs. motility, or fecundity vs. viability, or fecundity vs. 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. This has been this year the object of a submitted article associating Frank Ernesto Alvarez Borges, José antonio Carrillo (Oxford) and Jean Clairambault [38], and this collaboration will be continued. In a simplified representation when the two phenotypes are just extreme values of a 1-d continuous phenotype (e.g., 0 for total adhesivity and no motility, 1 for no adhesivity and complete motility) this situation may be related to the previously described case, developed in [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

[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

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 [80]. An interesting consequence of this approach is the possibility to use the traditional finite volume approach to design numerical schemes able to capture the good behavior of such weak measure-valued solutions [109, 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 [151] with N. Sfakianakis (Heidelberg University), we extended the live-cell motility Filament Based Lamellipodium Model to incorporate the forces exerted on the lamellipodium of the cells due to cell-cell collision and cadherin induced cell-cell adhesion. We took into account the nature of these forces via physical and biological constraints and modelling assumptions. We investigated the effect these new components had in the migration and morphology of the cells through particular experiments. We exhibit moreover the similarities between our simulated cells and HeLa cancer cells.

In a second work done in collaboration with the group of biologist at IST (led by **Michael Sixt** Austria), we developed and analyzed a two-dimensional mathematical model for cells migrating without adhesion capabilities [118]. Cells are represented by their cortex, which is modelled as an elastic curve, subject to an internal pressure force. Net polymerization or depolymerization in the cortex is modelled via local addition or removal of material, driving a cortical flow. The model takes the form of a fully nonlinear degenerate parabolic system. An existence analysis is carried out by adapting ideas from the theory of gradient flows. Numerical simulations show that these simple rules can account for the behavior observed in experiments, suggesting a possible mechanical mechanism for adhesion-independent motility.

Free boundary problems for tumor growth

Fluid dynamic equations are now commonly used to describe tumor growth with two main classes of models: those which describe tumor growth through the dynamics of the density of tumoral cells subjected to a mechanical stress; those describing the tumor through the dynamics of its geometrical domain thanks to a Hele-Shaw-type free boundary model. The first link between these two classes of models has been rigorously obtained thanks to an incompressible limit in [139] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [121].

Since more realistic systems are used in the analysis of medical images, we have extended these studies to include active motion of cells in [138], viscosity in [143] 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 [142], see also Methodological axis 3. It is a fundamental but difficult issue to explain rigorously the emergence of instabilities in the direction transversal to the wave propagation. For a simplified model, a complete explanation is obtained in [122].

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), Politecnico di Torino and Politecnico di Milano,joint works on mathematics of tumor growth models.
- Joint work with Francesco Rossi (Università di Padova, Italy) and Benedetto Piccoli (Rutgers University, Camden, New Jersey, USA) on Developmental PDEs.
- Cooperation with Shugo Yasuda (University of Hyogo, Kobe, Japan) and Vincent Calvez (EPI Dracula) on the subject of bacterial motion.
- Cooperation with Nathalie Ferrand (INSERM), Michèle Sabbah (INSERM) and Guillaume Vidal (Centre de Recherche Paul Pascal, Bordeaux) on cell aggregation by chemotaxis.
- Nicolas Vauchelet, Université Paris 13

3.4 Methodological axis 3: Model and parameter identification combining stochastic and deterministic approaches in nonlocal and 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 [102], TRAIL treatment of HeLa cells [65], growth of multicellular spheroids [115], blood detoxification after drug-induced liver damage [150, 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 [137, 93], 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 [72]. 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) [94]. 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 [66, 112] and was the basis for Adélaïde Olivier's Ph.D thesis [133, 114] and of more recent work [132][100] (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 [56], 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 [104], was devoted to the stochastic modeling and analysis of protein aggregation, compared both with the deterministic approach traditionally developed in Mamba [147] and with experiments.

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 [61], [55]

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. Recently, we have also extended our approach to the study of Tumour-Immune System interac

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

In collaboration with Catherine Bonnet (Inria DISCO, Saclay) and François Delhommeau (St Antoine hospital in Paris), together with DISCO PhD students José Luis Avila Alonso and Walid Djema, this theme has led to common published proceedings of conferences: IFAC, ACC, CDC, MTNS [57, 59, 60, 71, 92, 58]. 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 [83, 84, 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 [73].

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 [76]. 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 [86, 88] and conference proceedings [85]. 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

[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, nevertheless 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

multicellularity and cancer, is also meant to endow us with an innovative methodology to apply *topological data analysis (TDA)* to investigate cancer genome data.

Modelling of TMZ induced drug resistance
Temozolomide (TMZ) is a standard chemotherapy treatment in patients with glioblastoma. Resistance to this drug is correlated to the presence of a specific enzyme, which activity in cancer cells creates a drug-induced cell death resistant phenotype. Understanding the transition of cancer cells to a resistant phenotype is still a topic of research where multiple hypothesis have been studied: From an adaptive process to an inherent resistance to treatment. It has been recently shown that if TMZ treatment does not significantly induce cell death in glioblastoma, it still generates a response in terms of the spatial arrangement of cell aggregates. Moreover, the coupling of TMZ with irradiation has been shown to generate a better response in patients compared with using irradiation alone. Therefore, understanding the mechanisms of glioblastoma reaction to TMZ treatment could open new therapeutic avenues. In the frame of the post-doctorate of Gissell Estrada Rodriguez, we developed a 2D mathematical model in [4], 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 [101]. Works by Schliess [150, 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 [79], 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 [95, 105], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [104].

In collaboration with Tom Banks first [62, 61] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [56], 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 [145]. 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 [144]. 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 [149], 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 [100].

[5] liedekerke:hal-01956017

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 [81]) 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 [161]. 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) [103] 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* [153, 74]: 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 [69], and through optimal control approach [70]. Concerning Wolbachia technique, we investigated general control principles [67] capable of spreading the infection.

We also considered the effects of hindrances to these strategies [32].

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

Mathematical epidemiology of infectious diseases

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

The issues raised by the effective implementation of the social distancing measures largely implemented on the Earth's surface during the whole year 2020, have been the focus of intense reflection. We contributed to this debate by studying optimal control policies aiming at reducing the total number of infected people during the whole epidemic outbreak, the so-called epidemic final size. In another research line, we established the equation fulfilled by the epidemic final size for a fully general SEIR model in a heterogenous population characterized by some trait in a discrete or continuous subset, and studied the uniqueness of its solution. This allowed to extend the use and meaningfulness of the classical concept of next-generation operator introduced by O. Diekmann et al. in 1990 [91]. Last, in cooperation with the Inria team NeCS (Inria Grenoble-Rhône-Alpes), we studied in a control theory perspective the effects of the testing policies in the dynamics and in the control of the epidemic.

Collaborations

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

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

5 Social and environmental responsibility

5.1 Footprint of research activities

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

6 Highlights of the year

Dirk Drasdo, one of the former members of MAMBA and its precursor BANG, left the team and co-founded the new team SIMBIOTX at INRIA Center Saclay-Ile de France together with Irene Vignon-Clementel (formerly team REO) starting 03/2021. The team SIMBIOTX works on SImulations in Medicine, BIOtechnology and ToXicology of multicellular systems, see details in and .

6.1 Awards

Gaëtan Vignoud received with three co-authors the award "Interne innovant" of “Trophées APinnov 2021” of the AP-HP for their contribution "Approche informatique de Deep Learning pour l’analyse vidéo du mouvement dans le cadre des syndromes parkinsoniens", see [90].

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" [158]; oscillatory behaviors 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 Individual and population approaches for calibrating division rates in population dynamics: Application to the bacterial cell cycle

Participants: Marie Doumic, Marc Hoffmann.

Modelling, analysing and inferring triggering mechanisms in population reproduction is fundamental in many biological applications. It is also an active and growing research domain in mathematical biology. In the book chapter [44], we review the main results developed over the last decade for the estimation of the division rate in growing and dividing populations in a steady environment. These methods combine tools borrowed from PDE’s and stochastic processes, with a certain view that emerges from mathematical statistics. A focus on the application to the bacterial cell division cycle provides a concrete presentation, and may help the reader to identify major new challenges in the field.

7.1.2 Heterogeneous aggregation: application to autophagy

Participants: Julia Delacour, Marie Doumic, Christian Schmeiser.

To date, there exists very few studies of heterogeneous aggregation, *i.e.* aggregates formation out of several monomeric species. Last year, we proposed a bimonomeric model of Becker-Döring type, capable of explaining damped oscillations observed in prion fibrils aggregates [96]; 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 [89], 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 [13], 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 [13], 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 .

7.1.3 Insights into protein filament division

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

The dynamics by which polymeric protein filaments divide can be described by the universal mathematical equations of 'pure fragmentation'. The rates of fragmentation reactions reflect the stability of the protein filaments towards breakage, which is of importance in biology and biomedicine for instance in governing the creation of amyloid seeds and the propagation of prions. In the numerical study [28], we devised from mathematical theory inversion formulae - analysed in their own right in previous studies [94] - to recover the division rates and division kernel information from time dependent experimental measurements of filament size distribution. The numerical approach to systematically analyze the behaviour of pure fragmentation trajectories was also developed. We illustrate how these formulae can be used, provide some insights on their robustness, and show how they inform the design of experiments to measure fibril fragmentation dynamics. These advances

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

Thanks to the thorough numerical investigation carried out in [28], we realized the limitation of the previous approaches. Whereas analysing the long-time dynamics allowed us to infer in a very efficient way the division rate characteristics, this does not provide enough information do infer the fragmentation *kernel*, *i.e.* the distribution of offspring sizes out of the breakage of a polymer. We thus developed a totally different approach in [43], where we considered *short-time* instead of *large-time* behaviour, which revealed strikingly informative. We first provided a new representation of the solution to the fragmentation equation as a power series in the Banach space of Radon measures endowed with the total variation norm. This representation is used to justify how the fragmentation kernel, which is one of the two key parameters of the fragmentation equation, can be recovered from short-time experimental measurements of the particle size distributions when the initial condition is a delta function. A new stability result for this equation is also provided using a Wasserstein-type norm. We exploit this stability to prove the robustness of our reconstruction formula with respect to noise and initial data.

7.1.4 Telomere-shortening and senescence in yeast cells

Participants: Marie Doumic, Hugo Martin, Teresa Teixeira, Zhou Xu.

Background Telomerase-negative cells have limited proliferation potential. In these cells, telomeres shorten until they reach a critical length and induce a permanently arrested state. This process called replicative senescence is associated with genomic instability and participates in tissue and organismal ageing. Experimental data using single-cell approaches in the budding yeast model organism show that telomerase-negative cells often experience abnormally long cell cycles, which can be followed by cell cycles of normal duration, before reaching the terminal senescent state. These series of non-terminal cell cycle arrests contribute to the heterogeneity of senescence, as we already established in previous studies [73], and likely magnify its genomic instability. Due to their apparent stochastic nature, investigating the dynamics and the molecular origins of these arrests has been difficult. In particular, whether the non-terminal arrests series stem from a mechanism similar to the one that triggers terminal senescence is not known.

In [19], we provide a mathematical description of sequences of non-terminal arrests to understand how they appear. We take advantage of an experimental data set of cell cycle duration measurements performed in individual telomerase-negative yeast cells that keep track of the number of generations since telomerase inactivation. Using numerical simulations, we show that the occurrence of non-terminal arrests is a generation-dependent process that can be explained by the shortest telomere reaching a probabilistic threshold length. While the onset of senescence is also triggered by telomere shortening, we highlight differences in the laws that describe the number of consecutive arrests in non-terminal arrests compared to senescence arrests, suggesting distinct underlying mechanisms and cellular states.

Replicative senescence is a complex process that affects cell divisions earlier than anticipated, as exemplified by the frequent occurrence of non-terminal arrests early after telomerase inactivation. The present work unravels two kinetically and mechanistically distinct generation-dependent processes underlying non-terminal and terminal senescence arrests. We suggest that these two processes are responsible for two consequences of senescence at the population level, the increase of genome instability on the one hand, and the limitation of proliferation capacity on the other hand.

7.2 Stochastic Models of Biological Systems

7.2.1 Stochastic models for spike-timing dependent plasticity

Participants: Philippe Robert, Gaëtan Vignoud.

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

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

In neuroscience, *synaptic plasticity* refers to the set of mechanisms driving the dynamics of neuronal connections, called *synapses* and represented by a scalar value, the *synaptic weight*. A Spike-Timing Dependent Plasticity (STDP) rule is a biologically-based model representing the time evolution of the synaptic weight as a functional of the past spiking activity of adjacent neurons. A general mathematical framework has been introduced in [26].

In this paper we develop and investigate a scaling approach of these models based on several biological assumptions. Experiments show that long-term synaptic plasticity evolves on a much slower timescale than the cellular mechanisms driving the activity of neuronal cells, like their spiking activity or the concentration of various chemical components created/suppressed by this spiking activity. For this reason, a scaled version of the stochastic model of [26] in [27] is introduced and a limit theorem, an averaging principle, is stated for a large class of plasticity kernels. A companion paper [25] is entirely devoted to the tightness properties used to prove these convergence results.

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

In these papers we consider a stochastic system with two connected nodes, whose unidirectional connection is variable and depends on point processes associated to each node. The *input* node is represented by an homogeneous Poisson process, whereas the *output* node jumps with an intensity that depends on the jumps of the input nodes and the connection intensity. We study a scaling regime when the rate of both point processes is large compared to the dynamics of the connection. In neuroscience, this system corresponds to a neural network composed by two neurons, connected by a single synapse. The strength of this synapse depends on the past activity of both neurons, the notion of *synaptic plasticity* refers to the associated mechanism. A general class of such stochastic models has been introduced in [26] and [27] to describe most of the models of long-term synaptic plasticity investigated in the literature. The scaling regime corresponds to a classical assumption in computational neuroscience that cellular processes evolve much more rapidly than the synaptic strength.

The central result of the paper is an averaging principle for the time evolution of the connection intensity. Mathematically, the key variable is the point process, associated to the output node, whose intensity depends on the past activity of the system. The proof of the result involves a detailed analysis of several of its unbounded additive functionals in the slow-fast limit, and technical results on interacting shot-noise processes.

7.2.2 On the Spontaneous Dynamics of Synaptic Weights in Stochastic Models with Pair-Based STDP.

Participants: Philippe Robert, Gaëtan Vignoud.

In [49] we investigate spike-timing dependent plasticity (STPD) in the case of a synapse connecting two neuronal cells. We develop a theoretical analysis of several STDP rules using Markovian theory. In this context there are two different timescales, fast neuronal activity and slower synaptic weight updates. Exploiting this timescale separation, we derive the long-time limits of a single synaptic weight subject to STDP. We show that the pairing model of presynaptic and postsynaptic spikes controls the synaptic weight dynamics for small external input, on an excitatory synapse. This result implies in particular that mean-field analysis of plasticity may miss some important properties of STDP. Anti-Hebbian STDP favors the emergence of a stable synaptic weight, but only for high external input. In the case of an inhibitory synapse the pairing schemes matter less, and we observe convergence of the synaptic weight to a non-null value only for Hebbian STDP. We extensively study different asymptotic regimes for STDP rules, raising interesting questions for future works on adaptive neuronal networks and, more generally, on adaptive systems.

Hawkes Processes In this project, stationary non-linear Hawkes processes are revisited by formulating the Hawkes dependence as a Markovian property on the space of non-negative sequences. A characterization of the associated point process is obtained in terms of the solution of stochastic differential equations. When the influence of past jumps decreases exponentially over time, the Palm measure of the associated stationary point process is expressed with the distribution of the stationary version of a one-dimensional Harris ergodic Markov chain. Finally a scaling result for some Hawkes processes exhibiting a blow-up phenomenon is derived.

7.2.3 A synaptic theory for procedural and sequence learning in the striatum

Participants: Jonathan Touboul, Laurent Venance, Gaëtan Vignoud.

In [159] Spike-Timing Dependent Plasticity (STDP) in the striatum is viewed as a substrate for the encoding of learning and memory. In particular, within this area, the medium-sized spiny neurons (MSNs) are thought to play a particular role in this task. They express anti-Hebbian plasticity at corticostriatal synapses, and their high thresholds require them to integrate many inputs to spike, and as such, their main role is to detect and integrate context elements to choose between different sensorimotor associations.

We develop a simple numerical model of the striatum, integrating cortical spiking inputs to study the role of anti-Hebbian STDP in sequence learning. In this model, cortical neurons are seen as binary input neurons and one striatal MSN is modeled as a leaky-integrate-and-fire neuron. Patterns, composed by sequences of cortical spikes, are presented to the MSN whose spiking binary pattern models the output of the circuit. Combined information from the output, reward and timing between the different spikes modify the intensity of each connection, through two mechanisms: anti-Hebbian STDP and reward signaling, using a simple additive three-factor learning rule. The network learning capacity is measured by a score, based on the prediction of rewarded and non-rewarded patterns. The learning dynamics and efficiency are compared between different settings (number of neurons, intensity of the plasticity, types of STDP, tolerance to random noise). Two important properties of the striatal networks, spiking latency and collateral inhibition have subsequently been added to the model and lead to an improvement of the global accuracy.

Altogether, these results suggest that anti-Hebbian STDP favors the learning of complete sequence of spikes, such as is needed in the striatum.

7.2.4 Movement disorders analysis using a deep learning approach

Participants: Gaëtan Vignoud.

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 developed a tool to compute an objective score of bradykinesia. A large database of videos showing parkinsonian patients performing MDS-UPDRS protocols has been acquired in a Movement Disorder unit. Several deep learning algorithms, including DeepLabCut®, were applied to detect a 2D skeleton of the hand composed of 21 predefined points, and transpose it into a 3D network. A two- and three-dimensional semi-automated analysis tool was then developed to study the evolution of several key parameters during the protocol repetitions.

7.3 Stochastic Chemical Networks

Participants: Lucie Laurence, Philippe Robert.

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

A chemical network is defined with three components

- A set of chemical species $\mathscr{S}$;
- 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 integers and the relation

$$p_a A p_b B \longrightarrow p_c C p_d D$$

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

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

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

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

The goal of this study is to find alternative ways to show results of stability and convergence in distribution. The general approach is to use some scaling arguments on the Markov process associated to the Chemical Reaction Network studied. Scaling in time and/or in space gets us some converging results, avoiding the usual search for a Lyapunov function. We also used averaging results in specific border cases. We are currently analyzing simple networks, binary (i.e. with complexes composed only of two molecules), and weakly reversible (i.e. with a graph weakly reversible).

7.4 Allocation of Resources in Prokaryotic Cells

Participants: Vincent Fromion, Philippe Robert, Jana Zaherddine.

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

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

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

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

A Model of Sequestration We worked on a model in which we have the same constant number N of polymerases and of 6S RNAs. By denoting $F_N(t)$ the number of free polymerases a time t, we proved in this model this convergence in distribution:

$$(\overline{F}_N(t)) \stackrel{def}{=} (\frac{F_N(t/\sqrt{N})}{\sqrt{N}}) \stackrel{\mathscr{D}}{\longrightarrow} (f(t))$$

such that $f'(t) = \mu - \lambda f^2(t)$ and $f(t) = \frac{F_N(0)}{\sqrt{N}}$ where λ and μ are respectively, the sequestration and desequestration rate. In particular, the number of free polymerases is of the order of $\sqrt{N}$ and the equilibrium point is $f_\infty \sqrt{\frac{\mu}{\lambda}}$.

We have also analyzed the fluctuations of $(\frac{F_N(t/\sqrt{N})}{\sqrt{N}})$ are of the order of $\sqrt[4]{N}$, by proving this convergence in distribution:

$$(\sqrt[4]{N}\,(\overline{F}_N(t) - f(t))) \stackrel{\mathscr{D}}{\longrightarrow} (\widehat{F}(t))$$

where $(\widehat{F}(t))$, the solution of the SDE

$$d\widehat{F}(t) = \sqrt{\mu + \lambda f^2(t)}dB(t) - 2\lambda f(t)\widehat{F}(t)dt$$

where $(B(t))$ is the standard Brownian motion in $\mathbb{R}$.

Model of Sequestration and mRNA Transcription In this model we take into consideration: the transcription of mRNA by a polymerase, the sequestration by the 6S RNA, as well as the production (at rate β_s) and the degradation (at rate δ_s) of 6S RNAs. The number of 6S RNAs is in particular not constant in this model. We denote by $S_N(t)$ the number of sequestered polymerases at time t.

Our main result in this model is this convergence in distribution:

$$(\frac{S_N(Nt)}{N}) \stackrel{\mathscr{D}}{\longrightarrow} (\overline{S}(t))$$

where $(\overline{S}(t))$ solution of the ODE $d\overline{S}(t) = \beta_s dt - \frac{\delta_s \mu}{\lambda} \frac{\overline{S}(t)}{1 - c_m - \overline{S}(t)} dt$ and c_m is the number of mRNA promoters.

For this model the number of sequestered polymerases is of the order of N. And we have an equilibrium point

$$S_\infty \ \frac{\beta_s \lambda}{\beta_s \lambda \ \delta_s \mu}(1 - c_m)$$

We are currently studying the fluctuations of $(\frac{S_N(Nt)}{N})$ in this case.

7.5 Analysis and control of populations of mosquitoes

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

Participants: Luis Almeida, Pierre-Alexandre Bliman, Martin 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 [155] 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 [155].

7.5.2 Optimal replacement strategies, application to Wolbachia

Participants: Luis Almeida, Pierre-Alexandre Bliman, Yannick Privat, Martin Strugarek, Nicolas Vauchelet.

We modelled and designed optimal release control strategy with the help of a least square problem. In a nutshell, one wants to minimize the number of uninfected mosquitoes at a given time horizon, under relevant biological constraints. We derived properties of optimal controls and studied a limit problem providing useful asymptotic properties of optimal controls [53, 33, 70].

7.5.3 Migration effects on biological control of dengue vectors

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

The main subject of this study is concerned with the effects of the migration of mosquitoes on the spread and sustainability of Wolbachia invasion. Recent works focused on the time dynamical systems or consider the spatial dynamics in an unbounded domain, typically the real line. Based on a previous work by M. Strugarek and N. Vauchelet, we studied more realistic situations by considering the spatial dynamics in a bounded domain, with Robin boundary conditions taking into account migration term. Existence and stability of the equilibrium points have been considered.

7.5.4 Oscillatory regimes in population models

Participants: Luis Almeida, Benoît Perthame, Martin Strugarek, Nicolas Vauchelet.

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 [156] 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 [157, 154] sufficient conditions for such a property to occur for monotone differential models with concave nonlinearities, and applied the obtained criterion to a two-dimensional model featuring juvenile and adult insect populations.

7.5.5 Feedback control principles for population replacement by *Wolbachia*

Participants: Pierre-Alexandre Bliman, Pastor Pérez Estigarribia, Christian 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 [67]. These principles were exemplified by two interval observer-based feedback control laws whose stabilizing properties were demonstrated when applied to a model retrieved from [68].

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 [135]. This allowed to model altogether the Mendelian inheritance of the resistance insecticide, and the maternal inheritance of Wolbachia [32].

7.5.6 Control of Mosquito populations using the Sterile Insect Technique

Participants: Luis Almeida, Jorge Estrada, Alexis Leculier, Nicolas Vauchelet, Yves Dumont, Olga Vasilieva, Hector Martinez.

The sterile insect technique consists in massive release of sterilized males in the aim to reduce the size of mosquitoes population or even eradicate it. In this work, we investigate the feasability of using the sterile insect technique as a barrier against invasion of a mosquito-free zone (e.g. an urban area) by the mosquitoes coming from outside. In [34] and [37] we were able to show (both analytical and numerical results) that performing the sterile insect technique on a sufficiently large band we may stop invasion. In [35] we were also able to extend this study to the feasability of implementing a Rolling Carpet strategy to increase the size of the mosquito-free area thanks to performing sterile male releases on a band that is moved towards the mosquito infected area at an appropriate speed depending on its size and on the number of sterile mosquitoes released.

7.6 Modelling and control in epidemiology

7.6.1 Social contacts and the spread of infectious diseases

Participants: Giacomo Dimarco, Benoit Perthame, Giuseppe Toscani, Mattia Zanella.

We introduce a mathematical description of the impact of contacts in the spread of infectious diseases by integrating an epidemiological dynamics with a kinetic modeling of population-based

contacts. The kinetic description leads to study the evolution over time of Boltzmann-type equations describing the number densities of social contacts of susceptible, infected and recovered individuals, whose proportions are driven by a classical SIR-type compartmental model in epidemiology. Explicit calculations show that the spread of the disease is closely related to moments of the contact distribution. Furthermore, the kinetic model allows to clarify how a selective control can be assumed to achieve a minimal lockdown strategy by only reducing individuals undergoing a very large number of daily contacts.

7.6.2 Immunity control by social distancing

Participants: Pierre-Alexandre Bliman, Michel Duprez, Yannick Privat, Nicolas Vauchelet.

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 [8] for optimal control on an interval with prescribed starting date, and in [7] in the case of free starting date.

7.6.3 Epidemic final size

Participants: Luis Almeida, Pierre-Alexandre Bliman, Grégoire Nadin, Benoît Perthame, Nicolas Vauchelet.

We considered in [5] 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.

7.6.4 Testing policies in the control of the Covid-19 epidemic

Participants: Pierre-Alexandre Bliman, Carlos Canudas de Wit, Alain Kibangou.

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 [20, 30, 31] 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.

7.6.5 Epidemic Dynamics with Reinfections

Participants: Pierre-Alexandre Bliman, Marcel Fang.

The phenomenon of reinfection, and particularly the counting of the number of reinfections, have been little studied so far. We considered here an infinite-dimensional system of ordinary differential equations (pretty much in the spirit of Becker-Döring system [96]) extending a usual SEIRS model and capable to count explicitly the number of reinfections of the individuals of the population. Having disentangled this underlying structure allows to express mean numbers of reinfections in the population. Also, we have demonstrated that measuring the number of infected individuals and the number of primo-infected individuals allows to collect more information on the system – more precisely, this may render observable and identifiable a simple SIS model which has none of this property when only one measurement is achieved.

7.6.6 Modelling of the population movements and epidemic spread

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

Modelling the movements and mixing of populations in complex urban environments is an important issue to attempt to reproduce epidemic dynamics. To begin the exploration of this question, we study in this methodological work the effects of various modelling options on the stability of the disease-free equilibrium of simple systems.

7.7 Focus on cancer

7.7.1 Analysis and numerics for mechanical models of tumor growth

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

This direction of research has been continued in [41]. Motivated by biological applications on tumour invasion through thin membranes, we study a porous-medium type equation where the density of the cell population evolves under Darcy's law and assuming continuity of both the density and flux velocity on the thin mem- brane which separates two domains. The complexity due to the presence of such layer and the drastically different scales and mobility rates between the membrane and the adjacent tissues, lead to consider the limit problem where the thickness of the membrane approaches zero. We recover the effective interface problem, and in particular, we are interested in the rigorous derivation of the transmission conditions on the limiting zero-thickness surface, already conjectured by Chaplain et al., which are compatible with nonlinear generalized Kedem-Katchalsky ones.

Collective motion of cells plays an important role and the case of self-propelled particles confined between two parallel plates has attracted a lot of attention. In [16], we considered cells moving with a constant speed while their direction changes by rotational diffusion. The probability distribution of such micro-organisms in confined environment is singular because particles accumulate at the boundaries. This leads us to distinguish between the probability distribution densities in the bulk and in the boundaries. They satisfy a degenerate Fokker-Planck system and we propose boundary conditions that take into account the switching between free-moving and boundary-contacting particles. Relative entropy property, a priori estimates and the convergence to an unique steady state are established. The steady states of both the PDE and individual based stochastic models are compared numerically.

7.7.2 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 [84, 126], has been summarised in [52], presented in more detail in [88], 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 [148]. 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.

7.7.3 Mathematical modeling of Tumour-Immune System interaction

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

In the setting of Emma Leschiera's thesis, we have studied the interaction between the tumor and the immune system. In particular, a first paper concerning the role of Intra-tumour heterogeneity (ITH) was recently accepted for publication in J. Theor. Biol. [47]. Several expoerimental papers that inspired this work, have shown that ITH has a strong impact on the efficacy of the immune response against solid tumours. In this work we considered that ITH can be measured both through the number of sub-populations of cancer cells expressing different antigens and through the percentage of immunogenic cells in a tumour. We proposed and implemented a spatially explicit stochastic individual-based model of the interaction dynamics between tumour cells and CD8+ T cells, which makes it possible to evaluate the contribution of these two aspects of ITH on anti-tumour immune response and which are able to retrieve several immunosurveillance scenarios (both successful and unsuccessful) identified in the experimental works.

In [36] we also developed an individual-based model for the coevolutionary dynamics between T-cells and tumour cells. We also formally derive the deterministic continuum limit of this individual-based model, which comprises a non-local partial differential equation for the phenotype distribution of tumour cells coupled with an integro-differential equation for the phenotype distribution of T-cells. We obtain results of the individual-based model, and show that there is a good agreement between them and analytical and numerical results of the continuum model.

We are now working on trying to model T-cell infiltration in solid tumours and to retrieve the notion of immunoscore which is a widely used tool to evaluate the chances of success of immunotherapy and an important information to guide the choice of a particular treatment or combination of treatments.

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

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

In the frame of the HTE project 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 [4]. Based on the experimental data generated by our partner team led by F. Valette (Inserm Nantes), we proposed a Keller-Segel type model where tumour aggregate formation is obtained as the result of nutrient-limited cell proliferation coupled with chemotaxis-based cell movement. The introduction of a chemotherapeutic treatment is supposed to induce mechanical changes at the cell level, with cells undergoing a transition from rigid bodies to semi-elastic entities. We analysed the influence of these individual mechanical changes on the properties of the aggregates obtained at the population level by introducing a nonlinear volume-filling chemotactic system of partial differential equations. The elastic properties of the cells were taken into account through the so-called squeezing probability, which allowed us to change the packing capacity of the aggregates, depending on the concentration of the treatment in the extracellular microenvironment. By confronting the model results to experimental data, we showed that the changes observed in cellular structures under a non-cytotoxic drug could be due to this mechanotransduction phenomenon. This study suggests a new mechanism which, if experimentally validated, opens interesting therapeutic avenues.

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

7.7.5 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 [152, 87]. In these articles, and in the invited conference paper [85], 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.

7.8 Macroscopic limit and asymptotic behavior of collective dynamics

7.8.1 Collective dynamics with time-varying weights

Participants: Nathalie Ayi, Nastassia Pouradier Duteil.

We have developed a model for collective dynamics with weights, in which each agent is described not only by its position, but also by a positive "weight of influence". The weights allow us to model a social hierarchy within the group, where the most 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.

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

In 2014, Medvedev used techniques from the recent theory of graph limit to derive rigorously the continuum limit of dynamical models on deterministic graphs. In our paper [6], we extended this idea to our collective dynamics model with time-varying weights, adopting the graph point of view. The central point of this approach consists of describing the infinite population by two functions $x(s)$ and $m(s)$ over the space of continuous indices s. The discrete system of ODEs is then shown to converge as N goes to infinity to a system of two non-local diffusive equations in the space of continuous indices. We showed that this approach is more general than the mean-field one, and the Graph Limit can be derived for a much greater variety of models. We established the existence and uniqueness of solutions to the models, and provided a rigorous mathematical justification for taking the graph limit in a general context.

In another paper [48], we derived the mean-field limit of this collective dynamics model with time-varying weights, for weight dynamics that preserve the total mass of the system as well as indistinguishability of the agents. The limit equation is a transport equation with source, where the (non-local) transport term corresponds to the position dynamics, and the (non-local) source term comes from the weight redistribution among the agents. We showed existence and uniqueness of the solution for both microscopic and macroscopic models and introduced a new empirical measure taking into account the weights. We obtained the convergence of the microscopic model to the macroscopic one by showing continuity of the macroscopic solution with respect to the initial data, in the Wasserstein and Bounded Lipschitz topologies.

Then, in [6], we proved the subordination of the mean-field limit to the graph one in the context of inditinguishability. This actually provides an alternative proof for the mean-field limit.

7.8.2 Consensus Formation in First-Order Graphon Models with Time-Varying Topologies

Participants: Benoît Bonnet, Nastassia Pouradier Duteil, Mario Sigalotti.

In a collaboration between MAMBA and the Inria team CAGE, centered around the post-doctoral position of Benoit Bonnet, we studied the large-time behavior of interacting particle systems modeled by graph dynamics.

Although the case of finite-dimensional Hegselmann-Krause systems is well-known in the literature, the question of understanding the formation of consensus in large interacting systems where the number of agents goes to infinity is less understood. Indeed, as explained in the previous paragraph, when the interaction kernels depend explicitly on the agent labels, the standard mean-field approach is not applicable. The latter can only account for systems whose dynamics are invariant under permutations, which greatly limits the admissible interaction models. Motivated by this observation, several recent contributions have been aiming at studying macroscopic approximations of collective dynamics which allow for more general and possibly asymmetric interaction functions. The corresponding approaches are based on the theory of graph limits introduced by Lovász and Segedy, and popularised by Medvedev.

In the article [39], we investigated the asymptotic formation of consensus for several classes of time-dependent cooperative graphon dynamics. We adapted the classical notion of scrambling coefficient to this setting, and leveraged it to establish sufficient conditions ensuring the exponential convergence to consensus with respect to the L^∞-norm topology. We then shifted our attention to consensus formation expressed in terms of the L^2-norm, and proved three different consensus result for symmetric, balanced and strongly connected topologies, which involved a suitable generalisation of the notion of algebraic connectivity to this infinite-dimensional framework. We then showed

that, just as in the finite-dimensional setting, the notion of algebraic connectivity that we proposed encodes information about the connectivity properties of the underlying interaction topology. We used the corresponding results to shed some light on the relation between L^2 and L^∞-consensus formation.

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

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

In [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.

7.8.4 Early morphogenesis of rod-shaped bacteria

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

To model the morphogenesis of rod-shaped bacterial micro-colony, several individual-based models have been proposed in the biophysical literature. When studying the shape of micro-colonies, most models present interaction forces such as attraction or filial link. In the article [98], 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.

7.8.5 A new model for the emergence of blood capillary networks

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

In [50], 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 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 [51] 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.

7.9 Modeling cell-fate transition

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

Cell-fate transition can be modeled by ordinary differential equations which describe the behavior of several molecules in interaction, and for which each stable equilibrium corresponds to a possible phenotype (or 'biological trait'). In the paper [17], we focused on simple ODE systems modeling two molecules which each negatively (or positively) regulate the other. It is well-known that such models may lead to monostability or multistability, depending on the selected parameters. However, extensive numerical simulations have led systems biologists to conjecture that in the vast majority of cases, there cannot be more than two stable points. Our main result is a proof of this conjecture. More specifically, we provided a criterion ensuring at most bistability, which is indeed satisfied by most commonly used functions. This includes Hill functions, but also a wide family of convex and sigmoid functions. We also determined which parameters lead to monostability, and which lead to bistability, by developing a more general framework encompassing all our results.

8 Bilateral contracts and grants with industry

8.1 Bilateral grants with industry

Participants: Gaëtan Vignoud, Philippe Robert.

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

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

9 Partnerships and cooperations

9.1 International initiatives

9.1.1 Associate Teams in the framework of an Inria International Lab or in the framework of an Inria International Program

Participants: Pierre-Alexandre Bliman, Cláudia Pio Ferreira.

MoCoVec

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

Duration: 2020 ->

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

Partners:

- Universidade Estadual Paulista

Inria contact: Pierre-Alexandre Bliman

Summary:

9.1.2 STIC/MATH/CLIMAT AmSud project

NEMBICA

Title: NEw Methods for BIological Control of the Arboviruses

Begin date: Wed Jan 01 2020

Local supervisor: Pierre-Alexandre Bliman

Partners:

- CIRAD
- UMR MISTEA
- Sorbonne Paris Nord
- Universidad de Buenos Aires
- Universidad Nacional de Salta
- Universidad de Chile
- Universidad del Quindio
- Universidad Autónoma de Occidente
- Universidad del Valle
- National University of Asuncion

Inria contact: Pierre-Alexandre Bliman

Summary: The present project is concerned with new strategies to control the spread of established diseases (such as e.g. dengue, chikungunya and Zika) and potentially emerging or reemerging diseases (e.g. Mayaro, Oropouche and Yellow fever) transmitted by mosquitoes Aedes aegypti and Aedes albopictus. Due especially to the widespread resistance to the insecticides traditionally used to control the vectors, the use of sterile insect (SIT – Sterile Insect Technique), of transgenic mosquitoes (RIDL – Release of Insect carrying Dominant Lethal gene) and/or of mosquitoes infected with the bacterium Wolbachia (which drastically reduces their vector competence), are considered as viable control alternatives. These biological control techniques envisage either the elimination of the vector in a locality (SIT or RIDL), or its local substitution by a population refractory to the arboviruses transmitted by these species (Wolbachia). How to achieve the releases on a large scale in order to maximize their effect is still a source of some central questions that we aim to study here. We will focus more

specifically on the issues related to spatial spreading of the treatment, on observer techniques for estimating the number of mosquitoes during the releases, and on optimal and non-optimal control approaches. An important modeling effort will also be conducted on some key issues: we will assess the effects of the chemical and mechanical control methods on the success of the above techniques; the consequences of inter and intra-species competition in larval phase (an important issue so far overlooked); the questions raised by the use of self-propagating genetic mechanisms and the definition of associated efficacy measures; and develop genome scale model of Wolbachia in order to identify in the parasite-host relationship, crucial biological factors that could dynamically affect the dissemination.

9.1.3 Participation in other International Programs

Fulbright Fellowship in Brandeis University. Gaëtan Vignoud has obtained a Fulbright Fellowship, as a visiting student researcher at Brandeis University, from October 2021 to March 2022. He will work with Pr. Jonathan D. Touboul on the switch between habitual and goal-directed behaviors in models of the striatum.

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

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

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

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.

9.3 Regional initiatives

MATHREGEN 2021-2023: MAthematical modeling of Tissue Homeostasis and REGENeration - Project Emergence Alliance Sorbonne University awarded to Diane Peurichard in collaboration with RESTORE, Toulouse

Summary: The goal of MATHREGEN is to open a therapeutic breakthrough in one of the great societal challenges that is regeneration of whole organs. To this aim, MATHREGEN proposes to study the mechanisms of tissue homeostasis and repair, via the development of innovative tools combining mathematical agent-based modelling, software development and sophisticated image processing techniques for calibration. This highly interdisciplinary project proposes a functional and simple view of complex biological systems, relying on the use of mathematical models to identify the main parameters involved in tissue repair coupled with state-of-the-art model calibration and model-data coupling methodologies. The experimental data provided by our biological partners will permit to test, validate and improve the underlying hypotheses of the models. If successful, this project will provide a list of key determinants that induce tissue reprogramming, suggesting new avenues for antiscarring therapies and tissue regeneration.

NoMicMac 2021-2023: Novel Microscopic-to-Macroscopic limit of short-range repulsion models - Project Emergence Alliance Sorbonne University awarded to Nastassia Pouradier Duteil

Summary: Large systems of interacting agents have long been the focus of a wide community of both mathematicians and applied scientists, captivated by the following question: how do globally organized patterns emerge in a system driven only by local interactions? Such behavior is ubiquitous in many systems, and understanding the emergence of patterns has many applications in crowd dynamics, animal group behavior (swarming, flocking, migration), and cells' organization in tissues. The classical approach to link microscopic and macroscopic models is a limit process called "mean-field limit". However, this approach has a main drawback: it does not take into account the intrinsic volume of the individuals, since they are approximated by their centers of mass. As a result, in many cases the limiting PDE fails to reproduce the behavior of the microscopic system, in particular when modeling congestion effects due to size constraints. The aim of this project is to address this issue by deriving rigorously a macroscopic limit for a microscopic model of a population subject to non-overlapping constraints, and to reveal the link between distance and density constraints.

10 Dissemination

Participants: All members.

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

General chair, scientific chair. Pierre-Alexandre Bliman was the scientific chair and organizer of the seminary of the STIC AmSud project NEMBICA, from September 20–24, 2021.

Member of the organizing committees. Diane Peurichard and Nastassia Pouradier Duteil co-organized, together with Chloé Audebert, a Mittag-Leffler summer school entitled "Multi-scale modeling for pattern formation in biological systems". The summer school gathered the participants around partial differential equations and numerical analysis applied to biological systems. It was composed of two courses of five hours each, one on partial differential equations and modeling of biological systems (taught by Marie-Therese Wolfram), and one on numerical analysis (taught by Magali Ribot). The rest of the school was organized around themed mini-symposia by all participants. Due to the pandemic, the school took place entirely online.

Marie Doumic and Diane Peurichard organized a minisymposium entitled 'Exploring the processes of bacteria self-organization using mathematical modelling and experimental studies' at the online SMB meeting, from June 13–17 2021.

10.1.2 Scientific events: selection

Chair of conference program committees. Marie Doumic was a member of the SMAI conference scientific committee and of the workshop "nonlocal models arising from mathematical biology"

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

Member of the conference program committees. Pierre-Alexandre Bliman was associate editor of the 2022 European Control Conference.

Reviewer. Pierre-Alexandre Bliman was reviewer for IEEE Conference on Decision and Control.

10.1.3 Journal

Member of the editorial boards. Jean Clairambault is Associate Editor of the journal "Frontiers in Applied Mathematics and Statistics", Section "Frontiers in mathematical biology", and Invited Editor of the journal "Mathematical Modelling of Natural Phenomena".

Marie Doumic is Editor in Chief of ESAIM Proc. and Associate Editor of "Kinetic and Related Models", Bulletin des Sciences Mathématiques" and the Journal of Mathematical Biology.

Philippe Robert is Associate Editor of the journal "Stochastic Models".

Nastassia Pouradier Duteil is Guest Editor for the OCAM (Optimal Control Applications and Methods) special issue on "Optimal control in therapeutics and epidemiology".

Reviewer - reviewing activities. Nastassia Pouradier Duteil was a reviewer for the following journals: Communications in Mathematical Sciences, Journal of Mathematical Biology, SIAM Journal on Mathematical Analysis.

Diane Peurichard was a reviewer for the following journals: Mathematics, SIAM Journal on Mathematical analysis, JCOMP, European Journal of Applied Mathematics, Symmetry.

Pierre-Alexandre Bliman was reviewer for the following journals: Automatica, Communications in Nonlinear Science and Numerical Simulation, Communication Physics, Discrete and Continuous Dynamical Systems Series B, Journal of the Franklin Institute, IEEE Transactions on Automatic Control, Journal of Mathematical Biology, Journal of THeoretical Biology, Mathematical Biosciences, Mathematical Modelling of Natural Phenomena, Nonlinear Analysis: Real World Applications, International Journal of Robust and Nonlinear Control.

10.1.4 Invited talks

Jean Clairambault gave the following talks:

- A modelling view on drug resistance in cancer, reversible or not, and how to circumvent it. In-presence *Symposium UCAncer: Multidisciplinary approaches in cancer research*, Inria Sophia Antipolis, October 2021.
- Modelling plasticity of cancer cells and emergence of drug-induced drug resistance using adaptive cell population dynamics. *QBio Symposium on Bridging the scales: from single cells to cell populations, tissues and organs*, Institut Pasteur,virtual workshop, Paris, June 2021.
- Plasticity in cancer cells and emergence of drug-induced drug resistance: what consequences for therapeutics? *Virtual seminar, RUDN University, Moscow*, October 2021.

- From mathematical modelling of cancer cell plasticity to philosophy of cancer. *Applied analysis seminar, DISMA, Politecnico di Torino*, April 2021, *Bio Dynamics Days, LMAH & Courant Institute*, Le Havre ,virtual workshop, June 2021, *Conference on Mathematical Modelling in Biomedicine*, RUDN University, Moscow, international virtual meeting, October 2021.

Philippe Robert gave a talk “Stochastic Models of Neural Synaptic Plasticity” at the seminar “Stochastic Networks, Applied Probability, and Performance” on Oct 04, 2021.

Gaëtan Vignoud gave a talk “On the Spontaneous Dynamics of Synaptic Weights in Stochastic Models” at the 2021 International Conference on Mathematical Neuroscience - Digital Edition on 29th of June 2021. He has presented a poster “Movement disorders analysis using a deep learning approach” at IDAI Summer School 2021.

Nastassia Pouradier Duteil gave a seminar at the Online IntComSin Colloquium of Erlangen-Regensburg (Germany), “Continuum limits of collective dynamics with time-varying weights” on June 18, 2021. She also gave a presentation at the workshop “Numerical aspects of hyperbolic balance laws and related problems – Young Researchers Conference” in Verona (Italy) on Dec. 16, 2021.

Marie Doumic gave online Colloquiums for the university of Bonn (Germany) on February 2nd and for ECMTB on June 25th. She gave two talks as a two-week visiting fellow in the COLIBRI network of the university of Graz (Austria) from October 20th to November 2nd.

Diane Peurichard gave an (online) talk at the 15th International Conference on Free Boundary Problems on september 13th-17th and a talk at the Young Researcher Meeting for the conference "Numerical Aspects of Hyperbolic Balance Laws and Related Problems”, held from December 15 to December 17, 2021, at the University of Verona, Italy.

Pierre-Alexandre Bliman gave invited talks in the International Conference “Dynamical Systems Applied to Biology and Natural Sciences – DSABNS" (February 2021) and in the “Encontro nacional de modelagem matemática da Covid-19 (May 2021), presented communications at the conferences 2021 European Control Conference (June 2021) and at the seminaries Séminaire AFRIMath de modélisation mathématique (June 2021), GIPSA-Lab in Grenoble (July 2021), “Epidemics: modeling, identification, control" (October 2021), and in Universidade de Lisboa (October 2021).

10.1.5 Scientific expertise

Pierre-Alexandre Bliman was member of the Comités d’évaluation scientifique for the two ANR Calls for projects RA-Covid-19 and Résilience Covid-19, and expert for the ANR Appel spécifique - Action Liban.

10.1.6 Research administration

Marie Doumic is a member of the Scientific Council of INSMI (mathematical institute of the CNRS) and member of the interdisciplinary committee CID 51 of CNRS. She also represents Inria at CNFM (Comité National Français des Mathématiques).

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

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

Nastassia Pouradier Duteil is teaching a course on Mathematics in the Sorbonne University program RESPE “Retour aux Etudes Supérieures des Personnes Exilées”. She also gave a two-hour graduate-level course at the University of Erlangen-Nuremberg (online), entitled “Introduction to mean-field limits”.

Marie Doumic is a part-time "professeuse chargée de cours" in Ecole Polytechnique (67 h/year), teaches probability (L3) and variationnal analysis of PDE (M1).

Diane Peurichard is teaching the module ’Fondement des methodes numeriques’ (M1, 48h) and ’Approximation des équations aux dérivées partielles’ (M1,24h) at Sorbonne University. She gave

a 4h course for the 'Master de physique cellulaire', Strasbourg University on january 21th, 2022 entitled 'Mathematical modelling in biological systems'

10.2.2 Supervision

Jean Clairambault is a co-advisor of Frank Ernesto Alvarez Borges at Paris-Dauphine University

Philippe Robert is the PhD advisor of

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

Luis Almeida and Pierre-Alexandre Bliman supervised, together with Nicolas Vauchelet, the master M2 internship of Thi Quynh Nga Nguyen, now PhD student in the team with the same co-advisors.

Pierre-Alexandre Bliman was also the supervisor of Marcel Fang, presently PhD student in MAMBA team with the same advisor. Pierre-Alexandre Bliman is also co-supervisor of Assane Savadogo, together with the Professor Boureima Sangaré from Université Nazi Boni, Bobo-Dioulasso, in the framework of the IRD Programme Doctoral International "Modélisation des Systèmes Complexes".

Nastassia Pouradier Duteil and Diane Peurichard co-advised the M1 master thesis of Agathe Yvinec-Tolmer. Nastassia Pouradier Duteil advised the L2 internship of Maxime Guil. Nastassia Pouradier Duteil is currently co-advising with Camille Pouchol the PhD thesis of Jules Guilberteau.

Marie Doumic and Marc Hoffmann co-supervise, together with Lydia Robert from INRAE, Guillaume Garnier's Ph.D thesis, begun in October 2021.

Marie Doumic co-supervises Anaïs Rat's Ph.D with Magali Tournus from Ecole Centrale Marseille.

Diane Peurichard co-supervises the Phd of Pauline Chassonnery (ED Biologie-Santé-Biotechnologie, Toulouse) with Louis Casteilla (RESTORE, Toulouse)

Diane Peurichard co-supervises the PhD of Valeria Caliaro (Inria Paris) with Osvaldo Chara (Sysbio, Argentina and Technische Universität Dresden, Dresden, Germany)

Diane Peurichard and Luis Almeida supervised together the post-doctorate of Xinran Ruan (now professor at Capital Normal University, Beijin, China)

10.2.3 Juries

Jean Clairambault has been a reviewer of Giada Fiandaca's PhD thesis "Tumour phenotypic heterogeneity in a niche-construction evolutionary perspective: investigating the impact of trade-offs via a mathematical approach", Politecnico di Torino, defended on January 28, 2022.

Philippe Robert has been the reviewer of Pascal Helson's PhD document "Plasticity in networks of spiking neurons in interaction", Université Côte d'Azur, defended on March 29, 2021.

Pierre-Alexandre Bliman has been reviewer of Amidou Traore's PhD "Modélisation et contrôle d'un insecte ravageur", Université Joseph Ki-Zerbo, Ouagadougou and Université de Bordeaux, defended on February 19, 2021. He has also been reviewer of Souâd Yacheur's PhD "Modélisation et étude mathématique de la propagation d'une maladie vectorielle (paludisme) au sein d'une population", Université Aboubekr Belkaid, Tlemcen and Université de Lorraine, Metz, defended on December 16, 2021. last, he has been member of the panel of Muhammad Umar B. Niazi "Aggregated Monitoring of Large-scale Network Systems and Control of Epidemics", Université de Grenoble Alpes, defended on July 13, 2021.

Diane Peurichard is a member of the selection commitee for the CRCN/ISFP positions 2022, Inria Saclay

Diane Peurichard is a member of the selection commitee for the CRCN positions at INRAE 2022 "Modèles dynamiques pour la modélisation en écologie microbienne"

Diane Peurichard is a member of the selection commitee for the MCF positions 2022, Université de Montpellier (section 26, EDPs appliquées à la dynamique des populations)

10.3 Popularization

Marie Doumic gave a conference at the Mathpark seminar of Institut Henri Poincaré on December 11.

10.3.1 Internal or external Inria responsibilities

Diane Peurichard is member of the CDT (Commission de Développement Technologique) at Inria Paris

Diane Peurichard is member of the CSD (Comité de Suivi Doctoral) at Inria Paris

Diane Peurichard is member of the pôle ecoute at Sorbonne Université (instance in charge of support of researchers regarding communication problems, discomfort, harrassement issues etc)

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, B. Aymard, D. Peurichard, P. Kennel, A. Lorsignol, F. PLOURABOUE, L. Casteilla and P. Degond. 'A new model for the emergence of blood capillary networks'. In: *Networks & Heterogeneous Media* 16 (2021), pp. 91–138. DOI: 10.3934/nhm.2021001. URL: https://hal.archives-ouvertes.fr/hal-03409948.

[4] L. Almeida, G. Estrada-Rodriguez, L. Oliver, D. Peurichard, A. Poulain and F. M. Vallette. 'Treatment-induced shrinking of tumour aggregates: A nonlinear volume-filling chemotactic approach'. In: *Journal of Mathematical Biology* (2021). DOI: 10.1007/s00285-021-01642-x. URL: https://hal.archives-ouvertes.fr/hal-02906240.

[5] L. Almeida, P.-A. Bliman, G. Nadin, B. Perthame and N. Vauchelet. 'Final size and convergence rate for an epidemic in heterogeneous population'. In: *Mathematical Models and Methods in Applied Sciences* 31.05 (2021), pp. 1021–1051. URL: https://hal.sorbonne-universite.fr/hal-02981952.

[6] N. Ayi and N. Pouradier Duteil. 'Mean-field and graph limits for collective dynamics models with time-varying weights'. In: *Journal of Differential Equations* (25th Oct. 2021). DOI: 10.1016/j.jde.2021.07.010. URL: https://hal.inria.fr/hal-03065067.

[7] P.-A. Bliman and M. Duprez. 'How Best Can Finite-Time Social Distancing Reduce Epidemic Final Size?' In: *Journal of Theoretical Biology* (4th Feb. 2021), p. 110557. DOI: 10.1016/j.jtbi.2020.110557. URL: https://hal.inria.fr/hal-02953047.

[8] P.-A. Bliman, M. Duprez, Y. Privat and N. Vauchelet. 'Optimal Immunity Control and Final Size Minimization by Social Distancing for the SIR Epidemic Model'. In: *Journal of Optimization Theory and Applications* 189.2 (2021), pp. 408–436. DOI: 10.1007/s10957-021-01830-1. URL: https://hal.archives-ouvertes.fr/hal-02862922.

[9] N. Boissier, D. Drasdo and I. Vignon-Clementel. 'Simulation of a detoxifying organ function: Focus on hemodynamics modeling and convection-reaction numerical simulation in microcirculatory networks'. In: *International Journal for Numerical Methods in Biomedical Engineering* 37.2 (2021). DOI: 10.1002/cnm.3422. URL: https://hal.inria.fr/hal-03135175.

[10] B. Bonnet and E. Flayac. 'Consensus and Flocking under Communication Failures for a Class of Cucker-Smale Systems'. In: *Systems and Control Letters* 152 (1st June 2021), p. 104930. URL: https://hal.archives-ouvertes.fr/hal-02087941.

[11] N. David and B. Perthame. 'Free boundary limit of tumor growth model with nutrient'. In: *Journal de Mathématiques Pures et Appliquées* (2021). URL: https://hal.archives-ouvertes.fr/hal-02515263.

[12] T. Dębiec, B. Perthame, M. Schmidtchen and N. Vauchelet. 'Incompressible limit for a two-species model with coupling through Brinkman's law in any dimension'. In: *Journal de Mathématiques Pures et Appliquées* (2021). URL: https://hal.archives-ouvertes.fr/hal-02461406.

[13] J. Delacour, M. Doumic, S. Martens, C. Schmeiser and G. Zaffagnini. 'A mathematical model of p62-ubiquitin aggregates in autophagy'. In: *Journal of Mathematical Biology* 84.3 (1st Mar. 2022). DOI: 10.1007/s00285-021-01659-2. URL: https://hal.archives-ouvertes.fr/hal-02548223.

[14] G. Dimarco, B. Perthame, G. Toscani and M. Zanella. 'Social contacts and the spread of infectious diseases'. In: *Journal of Mathematical Biology* (2021). URL: https://hal.sorbonne-universite.fr/hal-02934939.

[15] S. Fischer, M. Dinh, V. Henry, P. Robert, A. Goelzer and V. Fromion. 'BiPSim: a flexible and generic stochastic simulator for polymerization processes'. In: *Scientific Reports* 11.1 (Dec. 2021). DOI: 10.1038/s41598-021-92833-5. URL: https://hal.inria.fr/hal-03288602.

[16] J. Fu, B. Perthame and M. Tang. 'Fokker–Plank System for Movement of Micro-organism Population in Confined Environment'. In: *Journal of Statistical Physics* 184.1 (July 2021). DOI: 10.1007/s10955-021-02760-y. URL: https://hal.sorbonne-universite.fr/hal-03278860.

[17] J. Guilberteau, C. Pouchol and N. Pouradier Duteil. 'Monostability and bistability of biological switches'. In: *Journal of Mathematical Biology* (20th Nov. 2021). URL: https://hal.sorbonne-universite.fr/hal-03190534.

[18] M. Kuznetsov, J. Clairambault and V. Volpert. 'Improving cancer treatments via dynamical biophysical models'. In: *Physics of Life Reviews* (21st Oct. 2021), pp. 1–84. URL: https://hal.archives-ouvertes.fr/hal-03390854.

[19] H. Martin, M. Doumic, M. T. Teixeira and Z. Xu. 'Telomere shortening causes distinct cell division regimes during replicative senescence in Saccharomyces cerevisiae'. In: *Cell & Bioscience* 11.1 (9th Oct. 2021). DOI: 10.1186/s13578-021-00693-3. URL: https://hal.archives-ouvertes.fr/hal-03374435.

[20] M. U. B. Niazi, A. Kibangou, C. Canudas de Wit, D. Nikitin, L. Tumash and P.-A. Bliman. 'Modeling and Control of Epidemics through Testing Policies'. In: *Annual Reviews in Control* 52 (14th Oct. 2021), pp. 554–572. DOI: 10.1016/j.arcontrol.2021.09.004. URL: https://hal.archives-ouvertes.fr/hal-02986566.

[21] S. Nordmann and B. Perthame. 'Dynamics of concentration in a population structured by age and a phenotypic trait with mutations. Convergence of the corrector'. In: *Journal of Differential Equations* (2021). URL: https://hal.archives-ouvertes.fr/hal-02437168.

[22] A. Poulain and K. Schratz. 'Convergence, error analysis and longtime behavior of the Scalar Auxiliary Variable method for the nonlinear Schrödinger equation'. In: *IMA Journal of Numerical Analysis* (18th Nov. 2021). DOI: 10.1093/imanum/drab082. URL: https://hal.archives-ouvertes.fr/hal-03088926.

[23] N. Pouradier Duteil and B. Piccoli. 'Control of collective dynamics with time-varying weights'. In: *Springer INdAM Series* (9th Aug. 2021). URL: https://hal.archives-ouvertes.fr/hal-02995844.

[24] N. Pouradier Duteil and F. Salvarani. 'Kinetic approach to the collective dynamics of the rock-paper-scissors binary game'. In: *Applied Mathematics and Computation* 388 (Jan. 2021). DOI: 10.1016/j.amc.2020.125496. URL: https://hal.archives-ouvertes.fr/hal-02491580.

[25] P. Robert and G. Vignoud. 'Averaging Principles for Markovian Models of Plasticity'. In: *Journal of Statistical Physics* 183.3 (9th June 2021), pp. 47–90. URL: https://hal.archives-ouvertes.fr/hal-02973366.

[26] P. Robert and G. Vignoud. 'Stochastic Models of Neural Plasticity'. In: *SIAM Journal on Applied Mathematics* 81.5 (9th Sept. 2021), pp. 1821–1846. URL: https://hal.archives-ouvertes.fr/hal-02973362.

[27] P. Robert and G. Vignoud. 'Stochastic Models of Neural Plasticity: A Scaling Approach'. In: *SIAM Journal on Applied Mathematics* 81.6 (16th Nov. 2021), pp. 2362–2386. URL: https://hal.inria.fr/hal-03256017.

[28] M. Tournus, M. Escobedo, W.-F. Xue and M. Doumic. 'Insights into the dynamic trajectories of protein filament division revealed by numerical investigation into the mathematical model of pure fragmentation'. In: *PLoS Computational Biology* 17.9 (3rd Sept. 2021), e1008964. DOI: 10.1371/journal.pcbi.1008964. URL: https://hal.archives-ouvertes.fr/hal-03131754.

[29] N. Vartak, G. Guenther, F. Joly, A. Damle-Vartak, G. Wibbelt, J. Fickel, S. Jörs, B. Begher-Tibbe, A. Friebel, K. Wansing, A. Ghallab, M. Rosselin, N. Boissier, I. Vignon-Clementel, C. Hedberg, F. Geisler, H. Hofer, P. Jansen, S. Hoehme, D. Drasdo and J. Hengstler. 'Intravital dynamic and correlative imaging reveals diffusion-dominated canalicular and flow-augmented ductular bile flux'. In: *Hepatology* 73.4 (Apr. 2021), pp. 1531–1550. DOI: 10.1002/hep.31422. URL: https://hal.inria.fr/hal-03135253.

International peer-reviewed conferences

[30] M. U. B. Niazi, C. Canudas de Wit, A. Kibangou and P.-A. Bliman. 'Optimal Control of Urban Human Mobility for Epidemic Mitigation'. In: CDC 2021 - 60th IEEE Conference on Decision and Control. Austin, United States, 13th Dec. 2021. URL: https://hal.archives-ouvertes.fr/hal-03185149.

[31] M. U. B. Niazi, A. Kibangou, C. Canudas de Wit, D. Nikitin, L. Tumash and P.-A. Bliman. 'Effective Testing Policies for Controlling an Epidemic Outbreak'. In: CDC 2021 - 60th IEEE Conference on Decision and Control. Austin, United States, 13th Dec. 2021. URL: https://hal.archives-ouvertes.fr/hal-03185142.

[32] P. E. Pérez Estigarribia, P.-A. Bliman and C. E. Schaerer. 'Modelling and control of Mendelian and maternal inheritance for biological control of dengue vectors'. In: ECC 2021 - European Control Conference. Rotterdam / Virtual, Netherlands, 29th June 2021. URL: https://hal.inria.fr/hal-03004882.

Reports & preprints

[33] L. Almeida, J. Bellver Arnau and Y. Privat. *Optimal release strategies for mosquito population replacement*. 29th Apr. 2021. URL: https://hal.archives-ouvertes.fr/hal-03212761.

[34] L. Almeida, J. Estrada and N. Vauchelet. *The sterile insect technique used as a barrier control against reinfestation*. 2nd Apr. 2021. URL: https://hal.archives-ouvertes.fr/hal-02615391.

[35] L. Almeida, A. Leculier and N. Vauchelet. *Analysis of the "Rolling carpet" strategy to eradicate an invasive species*. 15th June 2021. URL: https://hal.archives-ouvertes.fr/hal-03261142.

[36] L. Almeida, C. Audebert, E. Leschiera and T. Lorenzi. *Discrete and continuum models for the coevolutionary dynamics between CD8+ cytotoxic T lymphocytes and tumour cells*. 20th Sept. 2021. URL: https://hal.archives-ouvertes.fr/hal-03348931.

[37] L. Almeida, J. Estrada and N. Vauchelet. *Wave blocking in a bistable system by local introduction of a population: application to sterile insect techniques on mosquito populations*. 13th Oct. 2021. URL: https://hal.archives-ouvertes.fr/hal-03377080.

[38] F. E. Alvarez, J. A. Carrillo and J. Clairambault. *Evolution of a structured cell population endowed with plasticity of traits under constraints on and between the traits*. 20th Sept. 2021. URL: https://hal.archives-ouvertes.fr/hal-03344894.

[39] B. Bonnet, N. Pouradier Duteil and M. Sigalotti. *Consensus Formation in First-Order Graphon Models with Time-Varying Topologies*. 7th Nov. 2021. URL: https://hal.archives-ouvertes.fr/hal-03418399.

[40] G. Ciavolella. *Effect of a membrane on diffusion-driven Turing instability*. 14th Oct. 2021. URL: https://hal.archives-ouvertes.fr/hal-03231369.

[41] G. Ciavolella, N. David and A. Poulain. *Effective interface conditions for a model of tumour invasion through a membrane*. 20th May 2021. URL: https://hal.archives-ouvertes.fr/hal-03231456.

[42] J. Delacour, C. Schmeiser and P. Szmolyan. *Long-time behaviour of a model for p62-ubiquitin aggregation in cellular autophagy*. 12th Feb. 2021. URL: https://hal.archives-ouvertes.fr/hal-03140178.

[43] M. Doumic, M. Escobedo and M. Tournus. *An inverse problem: recovering the fragmentation kernel from the short-time behaviour of the fragmentation equation*. 19th Dec. 2021. URL: https://hal.archives-ouvertes.fr/hal-03494439.

[44] M. Doumic and M. Hoffmann. *Individual and population approaches for calibrating division rates in population dynamics: Application to the bacterial cell cycle*. 30th Aug. 2021. URL: https://hal.archives-ouvertes.fr/hal-03328781.

[45] M. Fang and P.-A. Bliman. *Modelling, Analysis, Observability and Identifiability of Epidemic Dynamics with Reinfections*. 24th Jan. 2022. URL: https://hal.inria.fr/hal-03541732.

[46] S. Hoehme, J. Boettger, S. Hammad, B. Begher-Tibbe, P. Bucur, E. Vibert, R. Gebhardt, J. G. Hengstler and D. Drasdo. *A predictive computational model shows that biomechanical cell cycle progression control can explain liver regeneration after partial hepatectomy*. 9th Feb. 2021. URL: https://hal.archives-ouvertes.fr/hal-03136097.

[47] E. Leschiera, T. Lorenzi, S. Shen, L. Almeida and C. Audebert. *A mathematical model to study the impact of intra-tumour heterogeneity on anti-tumour CD8 + T cell immune response*. 16th Nov. 2021. URL: https://hal.archives-ouvertes.fr/hal-03283699.

[48] N. Pouradier Duteil. *Mean-field limit of collective dynamics with time-varying weights*. 8th Mar. 2021. URL: https://hal.archives-ouvertes.fr/hal-03164226.

[49] P. Robert and G. Vignoud. *On the Spontaneous Dynamics of Synaptic Weights in Stochastic Models with Pair-Based STDP*. 16th Nov. 2021. URL: https://hal.inria.fr/hal-03430167.

11.3 Cited publications

[50] P. Aceves-Sanchez, B. Aymard, D. Peurichard, P. Kennel, A. Lorsignol, F. Plouraboue, L. Casteilla and P. Degond. 'A new model for the emergence of blood capillary networks'. In: *Networks and Heterogeneous Media* 16 (2021), pp. 91–138.

[51] 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), p. 129. DOI: 10.1007/s11538-020-00805-z. URL: https://hal.archives-ouvertes.fr/hal-03138284.

[52] L. Almeida, R. H. Chisholm, J. Clairambault, T. Lorenzi, A. Lorz, C. Pouchol and E. Trélat. 'Why Is Evolution Important in Cancer and What Mathematics Should Be Used to Treat Cancer? Focus on Drug Resistance'. In: *Trends in Biomathematics: Modeling, Optimization and Computational Problems: Selected works from the BIOMAT Consortium Lectures, Moscow 2017*. Springer International Publishing, Aug. 2018, pp. 107–120. URL: https://hal.inria.fr/hal-01945593.

[53] L. Almeida, Y. Privat, M. Strugarek and N. Vauchelet. 'Optimal releases for population replacement strategies: application to wolbachia'. In: *SIAM Journal on Mathematical Analysis* 51.4 (2019), pp. 3170–3194.

[54] L. Alphey. 'Genetic control of mosquitoes'. In: *Annual review of entomology* 59 (2014).

[55] A. Armiento. 'Inverse problems and data assimilation methods applied to protein polymerisation'. Theses. Université Paris 7 - Diderot, Jan. 2017. URL: https://hal.inria.fr/tel-01447286.

[56] A. Armiento, M. Doumic, P. Moireau and H. Rezaei. 'Estimation from Moments Measurements for Amyloid Depolymerisation'. In: *Journal of Theoretical Biology* (Mar. 2016). DOI: 10.1016/j.jtbi.2016.02.037. URL: https://hal.archives-ouvertes.fr/hal-01248255.

[57] J. L. Avila Alonso, C. Bonnet, E. Fridman, F. Mazenc and J. Clairambault. 'Stability analysis of PDE's modelling cell dynamics in Acute Myeloid Leukemia'. In: *53rd IEEE Conference on Decision and Control*. Los Angeles, United States, Dec. 2014. URL: https://hal.inria.fr/hal-01110304.

[58] J. L. Avila Alonso, C. Bonnet, J. Clairambault, H. Ozbay, S.-I. Niculescu, F. Merhi, A. Ballesta, R. Tang and J.-P. Marie. 'Analysis of a New Model of Cell Population Dynamics in Acute Myeloid Leukemia'. In: *Delay Systems : From Theory to Numerics and Applications*. Ed. by T. Vyhlídal, J.-F. Lafay and R. Sipahi. Vol. 1. Advances in Delays and Dynamics. Springer, Jan. 2014, pp. 315–328. DOI: 10.1007/978-3-319-01695-5_23. URL: https://hal.inria.fr/hal-00932779.

[59] J. L. Avila Alonso, C. Bonnet, H. Ozbay, J. Clairambault and S.-I. Niculescu. 'A coupled model for healthy and cancer cells dynamics in Acute Myeloid Leukemia'. In: *The 19th World Congress of the International Federation of Automatic Control*. Cape Town, Souh Africa, Aug. 2014. URL: https://hal.inria.fr/hal-00940245.

[60] J. L. Avila Alonso, C. Bonnet, H. Ozbay, J. Clairambault and S.-I. Niculescu. 'A discrete-maturity Interconnected Model of Healthy and Cancer Cell Dynamics in Acute Myeloid Leukemia'. In: *Mathematical Theory of Networks and Systems*. Groningen, Netherlands, July 2014. URL: https://hal.inria.fr/hal-00940305.

[61] H. T. Banks, M. Doumic, C. Kruse, S. Prigent and H. Rezaei. 'Information Content in Data Sets for a Nucleated-Polymerization Model'. In: *Journal of Biological Dynamics* 9.1 (June 2015), p. 26. DOI: 10.1080/17513758.2015.1050465. URL: https://hal.inria.fr/hal-01123847.

[62] H. T. Banks, M. Doumic-Jauffret and C. Kruse. 'A numerical scheme for the early steps of nucleation-aggregation Models'. In: *Journal of Mathematical Biology* 74.1-2 (Jan. 2017), pp. 259–287. DOI: 10.1007/s00285-016-1026-0. URL: https://hal.inria.fr/hal-00954437.

[63] J. Barre, P. Degond, D. Peurichard and E. Zatorska. 'Modelling pattern formation through differential repulsion'. In: *Networks and Heterogeneous Media* 15.3 (2020), pp. 307–352. DOI: 10.3934/nhm.2020021. URL: https://hal.archives-ouvertes.fr/hal-02499520.

[64] F. Bekkal Brikci, J. Clairambault and B. Perthame. 'Analysis of a molecular structured population model with possible polynomial growth for the cell division cycle'. In: *Math. Comput. Modelling* 47.7-8 (2008), pp. 699–713.

[65] F. Bertaux, S. Stoma, D. Drasdo and G. Batt. 'Modeling Dynamics of Cell-to-Cell Variability in TRAIL-Induced Apoptosis Explains Fractional Killing and Predicts Reversible Resistance'. In: *PLoS Computational Biology* 10.10 (2014), p. 14. DOI: 10.1371/journal.pcbi.1003893.s016. URL: https://hal.inria.fr/hal-00942885.

[66] J. Bertoin and A. Watson. 'Probabilistic aspects of critical growth-fragmentation equations'. In: *Advances in Applied Probability* (Sept. 2015).

[67] P.-A. Bliman. 'A feedback control perspective on biological control of dengue vectors by Wolbachia infection'. In: *European Journal of Control* 59 (2021), pp. 188–206.

[68] P.-A. Bliman, M. S. Aronna, F. C. Coelho and M. A. H. B. da Silva. 'Ensuring successful introduction of Wolbachia in natural populations of Aedes aegypti by means of feedback control'. In: *Journal of Mathematical Biology* (Aug. 2017). DOI: 10.1007/s00285-017-1174-x. URL: https://hal.inria.fr/hal-01579477.

[69] P.-A. Bliman, D. Cardona-Salgado, Y. Dumont and O. Vasilieva. 'Implementation of control strategies for sterile insect techniques'. In: *Mathematical biosciences* 314 (2019), pp. 43–60.

[70] P.-A. Bliman, D. Cardona-Salgado, Y. Dumont and O. Vasilieva. 'Optimal control approach for implementation of sterile insect techniques'. In: *arXiv preprint arXiv:1911.00034* (2019).

[71] C. Bonnet, J. L. Avila Alonso, H. Ozbay, J. Clairambault, S.-I. Niculescu and P. Hirsch. 'A Discrete-Maturity Interconnected Model of Healthy and Cancer Cell Dynamics in Acute Myeloid Leukemia'. In: *The 10th AIMS Conference on Dynamical Systems,Differential Equations and Applications*. Madrid, Spain, July 2014. URL: https://hal.inria.fr/hal-01110309.

[72] T. Bourgeron, M. Doumic and M. Escobedo. 'Estimating the division rate of the growth-fragmentation equation with a self-similar kernel'. In: *Inverse Problems* 30.2 (Jan. 2014), p. 025007. DOI: 10.1088/0266-5611/30/2/025007. URL: http://dx.doi.org/10.1088/0266-5611/30/2/025007.

[73] T. Bourgeron, Z. Xu, M. Doumic and M. T. Teixeira. 'The asymmetry of telomere replication contributes to replicative senescence heterogeneity'. In: *Scientific Reports* 5 (Oct. 2015), p. 15326. DOI: 10.1038/srep15326. URL: http://hal.upmc.fr/hal-01272075.

[74] K. Bourtzis. '*Wolbachia*-Based Technologies for Insect Pest Population Control'. In: *Advances in Experimental Medicine and Biology*. Vol. 627. Springer, New York, NY, Feb. 2008.

[75] A. Brown. 'Insecticide resistance in mosquitoes: a pragmatic review.' In: *Journal of the American Mosquito Control Association* 2.2 (1986), pp. 123–140.

[76] F. Bubba, B. Perthame, C. Pouchol and M. Schmidtchen. 'Hele–shaw limit for a system of two reaction-(cross-) diffusion equations for living tissues'. In: *Archive for Rational Mechanics and Analysis* 236.2 (2020), pp. 735–766.

[77] M. J. Caceres and B. Perthame. 'Beyond blow-up in excitatory integrate and fire neuronal networks: refractory period and spontaneous activity'. In: *Journal of Theoretical Biology* 350 (2014), pp. 81–89. DOI: 10.1016/j.jtbi.2014.02.005. URL: http://hal.upmc.fr/hal-00874746.

[78] V. Calvez, M. Doumic and P. Gabriel. 'Self-similarity in a general aggregation–fragmentation problem. Application to fitness analysis'. In: *Journal de Mathématiques Pures et Appliquées* 98.1 (2012), pp. 1–27. DOI: 10.1016/j.matpur.2012.01.004. URL: http://www.sciencedirect.com/science/article/pii/S002178241200013X.

[79] V. Calvez, N. Lenuzza, M. Doumic, J.-P. Deslys, F. Mouthon and B. Perthame. 'Prion dynamic with size dependency - strain phenomena'. In: *J. of Biol. Dyn.* 4.1 (2010), pp. 28–42.

[80] J. A. Carrillo, F. James, F. Lagoutière and N. Vauchelet. 'The Filippov characteristic flow for the aggregation equation with mildly singular potentials'. In: *Journal of Differential Equations* 260.1 (2016). 33 pages, pp. 304–338. URL: https://hal.archives-ouvertes.fr/hal-01061991.

[81] G. Cellière. 'Multi-scale modeling of hepatic drug toxicity and its consequences on ammonia detoxification'. Theses. Université Paris 6 - Pierre et Marie Curie, July 2017.

[82] J. Chevallier, M. J. Caceres, M. Doumic and P. Reynaud-Bouret. 'Microscopic approach of a time elapsed neural model'. In: *Mathematical Models and Methods in Applied Sciences* (Dec. 2015), p. 2669. DOI: 10.1142/S021820251550058X. URL: http://hal.upmc.fr/hal-01159215.

[83] R. H. Chisholm, T. Lorenzi and J. Clairambault. 'Cell population heterogeneity and evolution towards drug resistance in cancer: Biological and mathematical assessment, theoretical treatment optimisation'. In: *BBA - General Subjects* 1860 (June 2016), pp. 2627–2645. DOI: 10.1016/j.bbagen.2016.06.009. URL: https://hal.inria.fr/hal-01321535.

[84] R. H. Chisholm, T. Lorenzi, A. Lorz, A. K. Larsen, L. N. de Almeida, A. Escargueil and J. Clairambault. 'Emergence of Drug Tolerance in Cancer Cell Populations: An Evolutionary Outcome of Selection, Nongenetic Instability, and Stress-Induced Adaptation'. In: *Cancer Research* 75.6 (Mar. 2015), pp. 930–939. DOI: 10.1158/0008-5472.CAN-14-2103. URL: https://hal.inria.fr/hal-01237893.

[85] J. Clairambault. 'Plasticity in Cancer Cell Populations: Biology, Mathematics and Philosophy of Cancer'. In: *Mathematical and Computational Oncology. ISMCO 2020*. Ed. by G. Bebis, M. Alekseyev, H. Cho, J. Gevertz and M. Rodriguez Martinez. Vol. 1258. Lecture Notes on Computer Science. Invited conference paper. International Symposium on Mathematical and Computational Oncology. Cham: Springer, Dec. 2020, pp. 3–9.

[86] J. Clairambault. 'An evolutionary perspective on cancer, with applications to anticancer drug resistance modelling and perspectives in therapeutic control'. In: *Journal of Mathematical Study* (2019), pp. 1–21. URL: https://hal.inria.fr/hal-02126730.

[87] J. Clairambault. 'Stepping From Modeling Cancer Plasticity to the Philosophy of Cancer'. In: *Frontiers in Genetics* (2020), 11:579738.

[88] J. Clairambault and C. Pouchol. 'A survey of adaptive cell population dynamics models of emergence of drug resistance in cancer, and open questions about evolution and cancer'. In: *BIOMATH*. BIOMATH 2019 8.1 (May 2019). Copyright: 2019 Clairambault et al. This article is distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited., p. 23. DOI: 10.11145/j.biomath.2019.05.147. URL: https://hal.inria.fr/hal-02132713.

[89] J. Delacour. 'Mathematical Modelling of p62-Ubiquitin aggregates involved in cellular autophagy'. Theses. Sorbonne Université ; Universität Wien, Dec. 2020. URL: https://tel.archives-ouvertes.fr/tel-03141004.

[90] C. Desjardins, Q. Salardaine, G. Vignoud and B. Degos. 'Movement disorders analysis using a deep learning approach'. In: *Movement Disorders*. Vol. 35. 2020. URL: https://www.mdsabstracts.org/abstract/movement-disorders-analysis-using-a-deep-learning-approach/.

[91] O. Diekmann, J. A. P. Heesterbeek and J. A. Metz. 'On the definition and the computation of the basic reproduction ratio R 0 in models for infectious diseases in heterogeneous populations'. In: *Journal of mathematical biology* 28.4 (1990), pp. 365–382.

[92] W. Djema, F. Mazenc, C. Bonnet, J. Clairambault, P. Hirsch and F. Delhommeau. 'Stability of a Delay System Coupled to a Differential-Difference System Describing the Coexistence of Ordinary and Mutated Hematopoietic Stem Cells'. In: *Conference on Decision and Control*. Las Vegas, United States, Dec. 2016. URL: https://hal.inria.fr/hal-01389870.

[93] M. Doumic, B. Perthame and J. Zubelli. 'Numerical Solution of an Inverse Problem in Size-Structured Population Dynamics'. In: *Inverse Problems* 25.4 (2009), p. 045008.

[94] M. Doumic, M. Escobedo and M. Tournus. 'Estimating the division rate and kernel in the fragmentation equation'. In: *Annales de l'Institut Henri Poincaré (C) Non Linear Analysis* (2018). https://arxiv.org/abs/1804.08945. DOI: 10.1016/j.anihpc.2018.03.004. URL: https://hal.archives-ouvertes.fr/hal-01501811.

[95] M. Doumic, S. Eugene and P. Robert. 'Asymptotics of Stochastic Protein Assembly Models'. In: *SIAM Journal on Applied Mathematics* 76.6 (Nov. 2016), p. 20. DOI: 10.1137/16M1066920. URL: https://hal.inria.fr/hal-01301266.

[96] M. Doumic, K. Fellner, M. Mezache and H. Rezaei. 'A bi-monomeric, nonlinear Becker–Döring-type system to capture oscillatory aggregation kinetics in prion dynamics'. In: *Journal of theoretical biology* 480 (2019), pp. 241–261.

[97] M. Doumic and P. Gabriel. 'Eigenelements of a General Aggregation-Fragmentation Model'. In: *Mathematical Models and Methods in Applied Sciences* 20 (5 May 2010), pp. 757–783. URL: https://hal.archives-ouvertes.fr/hal-00408088.

[98] 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. DOI: 10.3934/mbe.2020356. URL: https://hal.archives-ouvertes.fr/hal-02865566.

[99] M. Doumic, M. Hoffmann, N. Krell and L. Robert. 'Statistical estimation of a growth-fragmentation model observed on a genealogical tree'. 46 pages, 4 figures. Oct. 2012. URL: https://hal.archives-ouvertes.fr/hal-00763601.

[100] M. Doumic, A. Olivier and L. Robert. 'Estimating the division rate from indirect measurements of single cells'. In: *Discrete and Continuous Dynamical Systems - Series B* 25.10 (Oct. 2020), pp. 3931–3961. DOI: 10.3934/dcdsb.2020078. URL: https://hal.archives-ouvertes.fr/hal-02175633.

[101] D. Drasdo, A. Buttenschön and P. Van Liedekerke. 'Agent-Based Lattice Models of Multicellular Systems'. In: *Numerical Methods and Advanced Simulation in Biomechanics and Biological Processes*. Elsevier, 2018, pp. 223–238. DOI: 10.1016/B978-0-12-811718-7.00012-5. URL: https://hal.inria.fr/hal-01968847.

[102] D. Drasdo, S. Hoehme and J. G. Hengstler. 'How predictive quantitative modeling of tissue organization can inform liver disease pathogenesis'. In: *Journal of Hepatology* 61.4 (Oct. 2014), pp. 951–956. DOI: 10.1016/j.jhep.2014.06.013. URL: https://hal.inria.fr/hal-01110644.

[103] V. A. Dyck, J. Hendrichs and A. S. Robinson. *The Sterile Insect Technique, Principles and Practice in Area-Wide Integrated Pest Management*. Springer, Dordrecht, 2006, p. 787.

[104] S. Eugene. 'Stochastic modelling in molecular biology: a probabilistic analysis of protein polymerisation and telomere shortening'. Theses. UPMC LJLL, Sept. 2016. URL: https://hal.inria.fr/tel-01377561.

[105] S. Eugene, W.-F. Xue, P. Robert and M. Doumic-Jauffret. 'Insights into the variability of nucleated amyloid polymerization by a minimalistic model of stochastic protein assembly'. In: *Journal of Chemical Physics* 144.17 (May 2016), p. 12. DOI: 10.1063/1.4947472. URL: https://hal.inria.fr/hal-01205549.

[106] A. Ghallab, G. Cellière, S. Henkel, D. Driesch, S. Hoehme, U. Hofmann, S. Zellmer, P. Godoy, A. Sachinidis, M. Blaszkewicz, R. Reif, R. Marchan, L. Kuepfer, D. Häussinger, D. Drasdo, G. Gebhardt and J. G. Hengstler. 'Model-guided identification of a therapeutic strategy to reduce hyperammonemia in liver diseases'. In: *Journal of Hepatology* 64.4 (Nov. 2015), pp. 860–871. DOI: 10.1016/j.jhep.2015.11.018. URL: https://hal.archives-ouvertes.fr/hal-01257127.

[107] A. Ghallab, U. Hofmann, S. Sezgin, N. Vartak, R. Hassan, A. Zaza, P. Godoy, K. M. Schneider, G. Guenther, Y. A. Ahmed, A. Abbas, V. Keitel, L. Kuepfer, S. Dooley, F. Lammert, C. Trautwein, M. Spiteller, D. Drasdo, A. Hofmann, P. L. Jansen, J. Hengstler and R. Reif. 'Bile Microinfarcts in Cholestasis Are Initiated by Rupture of the Apical Hepatocyte Membrane and Cause Shunting of Bile to Sinusoidal Blood'. In: *Hepatology* (Aug. 2018). URL: https://hal.inria.fr/hal-01968843.

[108] A. Ghallab, M. Myllys, C. H Holland, A. Zaza, W. Murad, R. Hassan, Y. A Ahmed, T. Abbas, E. A Abdelrahim, K. M. Schneider et al. 'Influence of liver fibrosis on lobular zonation'. In: *Cells* 8.12 (2019), p. 1556.

[109] L. Gosse and N. Vauchelet. 'Hydrodynamic singular regimes in 1+1 kinetic models and spectral numerical methods'. In: *Journal of Mathematical Analysis and Applications* (2016). DOI: 10.1016/j.jmaa.2016.07.059. URL: https://hal.archives-ouvertes.fr/hal-01354980.

[110] J. Hemingway and H. Ranson. 'Insecticide resistance in insect vectors of human disease'. In: *Annual review of entomology* 45.1 (2000), pp. 371–391.

[111] M. Hertig and S. B. Wolbach. 'Studies on rickettsia-like micro-organisms in insects'. In: *The Journal of medical research* 44.3 (1924), p. 329.

[112] V. H. Hoang. 'Adaptive estimation for inverse problems with applications to cell divisions'. Theses. Université de Lille 1 – Sciences et Technologies, Nov. 2016. URL: https://tel.archives-ouvertes.fr/tel-01417780.

[113] S. Hoehme, M. Brulport, A. Bauer, E. Bedawy, W. Schormann, M. Hermes, V. Puppe, R. Gebhardt, S. Zellmer, M. Schwarz, E. Bockamp, T. Timmel, J. G. Hengstler and D. Drasdo. 'Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration'. In: *Proceedings of the National Academy of Sciences* 107.23 (2010), pp. 10371–10376.

[114] M. Hoffmann and A. Olivier. 'Nonparametric estimation of the division rate of an age dependent branching process'. In: *Stochastic Processes and their Applications* (Dec. 2015). DOI: 10.1016/j.spa.2015.11.009. URL: https://hal.archives-ouvertes.fr/hal-01254203.

[115] N. Jagiella, B. Müller, M. Müller, I. E. Vignon-Clementel and D. Drasdo. 'Inferring Growth Control Mechanisms in Growing Multi-cellular Spheroids of NSCLC Cells from Spatial-Temporal Image Data'. In: *PLoS Computational Biology* 12.2 (2016), e1004412. DOI: 10.1371/journal.pcbi.1004412. URL: http://hal.upmc.fr/hal-01244593.

[116] F. James and N. Vauchelet. 'Equivalence between duality and gradient flow solutions for one-dimensional aggregation equations'. In: *Discrete and Continuous Dynamical Systems - Series A* 36.3 (2016), pp. 1355–1382. URL: https://hal.archives-ouvertes.fr/hal-00803709.

[117] F. James and N. Vauchelet. 'Numerical methods for one-dimensional aggregation equations'. In: *SIAM Journal on Numerical Analysis* 53.2 (2015), pp. 895–916. DOI: 10.1137/140959997. URL: https://hal.archives-ouvertes.fr/hal-00955971.

[118] G. Jankowiak, D. Peurichard, A. Reversat, C. Schmeiser and M. Sixt. 'Modelling adhesion-independent cell migration'. In: *Mathematical Models and Methods in Applied Sciences* (2020). DOI: 10.1142/S021820252050013X. URL: https://hal.archives-ouvertes.fr/hal-02076901.

[119] M.-J. Kang, B. Perthame and D. Salort. 'Dynamics of time elapsed inhomogeneous neuron network model'. In: *Comptes Rendus Mathématique* 353 (Sept. 2015), pp. 1111–1115. DOI: 10.1016/j.crma.2015.09.029. URL: http://hal.upmc.fr/hal-01241300.

[120] J. Kean, S. Rainey, M. McFarlane, C. Donald, E. Schnettler, A. Kohl and E. Pondeville. 'Fighting arbovirus transmission: natural and engineered control of vector competence in Aedes mosquitoes'. In: *Insects* 6.1 (2015), pp. 236–278.

[121] I. C. Kim, B. Perthame and P. E. Souganidis. 'Free boundary problems for tumor growth: a viscosity solutions approach'. In: *Nonlinear Analysis: Theory, Methods and Applications* 138 (2016), pp. 207–228. DOI: 10.1016/j.na.2016.01.019. URL: http://hal.upmc.fr/hal-01155696.

[122] M. Kolwalczyk, B. Perthame and N. Vauchelet. 'Transversal instability for the thermodiffusive reaction-diffusion system'. In: *Chinese Annals of Mathematics - Series B* 36.5 (2015). 13 pages, pp. 871–882. URL: https://hal.archives-ouvertes.fr/hal-00939013.

[123] P. V. Liedekerke, J. Neitsch, T. Johann, E. Warmt, I. Gonzàlez-Valverde, S. Hoehme, S. Grosser, J. Kaes and D. Drasdo. 'A quantitative high resolution computational mechanics cell model for growing and regenerating tissues'. working paper or preprint. Dec. 2018. URL: https://hal.inria.fr/hal-01956023.

[124] T. Lorenzi, R. H. Chisholm and J. Clairambault. 'Tracking the evolution of cancer cell populations through the mathematical lens of phenotype-structured equations'. In: *Biology Direct* 11.1 (Dec. 2016), p. 43. DOI: 10.1186/s13062-016-0143-4. URL: https://hal.inria.fr/hal-01355314.

[125] T. Lorenzi, R. H. Chisholm, L. Desvillettes and B. D. Hughes. 'Dissecting the dynamics of epigenetic changes in phenotype-structured populations exposed to fluctuating environments'. In: *Journal of Theoretical Biology* 386 (Sept. 2015), pp. 166–176. DOI: 10.1016/j.jtbi.2015.08.031. URL: https://hal.inria.fr/hal-01237890.

[126] T. Lorenzi, R. H. Chisholm and A. Lorz. *Effects of an advection term in nonlocal Lotka-Volterra equations*. Dec. 2015. URL: https://hal.archives-ouvertes.fr/hal-01237529.

[127] A. Lorz, T. Lorenzi, J. Clairambault, A. Escargueil and B. Perthame. 'Modeling the effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors'. In: *Bulletin of Mathematical Biology* 77.1 (Jan. 2015), pp. 1–22. DOI: 10.1007/s11538-014-0046-4. URL: http://hal.upmc.fr/hal-00921266.

[128] A. Lorz, T. Lorenzi, M. E. Hochberg, J. Clairambault and B. Perthame. 'Populational adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies'. In: *ESAIM: Mathematical Modelling and Numerical Analysis* (Mar. 2013), p. 23. DOI: 10.1051/m2an/2012031. URL: https://hal.archives-ouvertes.fr/hal-00714274.

[129] A. Mellet, B. Perthame and F. Quiros. 'A Hele-Shaw Problem for Tumor Growth'. working paper or preprint. Dec. 2015. URL: http://hal.upmc.fr/hal-01241309.

[130] L. A. Moreira, I. Iturbe-Ormaetxe, J. A. Jeffery, G. Lu, A. T. Pyke, L. M. Hedges, B. C. Rocha, S. Hall-Mendelin, A. Day, M. Riegler, L. E. Hugo, K. N. Johnson, B. H. Kay, E. A. McGraw, A. F. van den Hurk, P. A. Ryan and S. L. O'Neill. 'A *Wolbachia* Symbiont in *Aedes aegypti* Limits Infection with Dengue, Chikungunya, and Plasmodium'. In: *Cell* 139.7 (2009), pp. 1268–1278.

[131] T. N. Nguyen, J. Clairambault, T. Jaffredo, B. Perthame and D. Salort. 'Adaptive dynamics of hematopoietic stem cells and their supporting stroma: A model and mathematical analysis'. In: *Mathematical Biosciences and Engineering* 16.05 (May 2019), pp. 4818–4845. DOI: 10.3934/mbe.2019243.. URL: https://hal.archives-ouvertes.fr/hal-01963820.

[132] A. Olivier. 'How does variability in cells aging and growth rates influence the malthus parameter?' In: *Kinetic and Related Models* 10.2 (June 2017), pp. 481–512. DOI: 10.3934/krm.2017019. URL: https://hal.archives-ouvertes.fr/hal-01274529.

[133] A. Olivier. 'Statistical analysis of growth-fragmentation models'. Theses. Université Paris Dauphine - Paris IX, Nov. 2015. URL: https://hal.archives-ouvertes.fr/tel-01235239.

[134] K. Pakdaman, B. Perthame and D. Salort. 'Adaptation and Fatigue Model for Neuron Networks and Large Time Asymptotics in a Nonlinear Fragmentation Equation'. In: *Journal of Mathematical Neuroscience* 4.1 (2014), p. 14. DOI: 10.1186/2190-8567-4-14. URL: https://hal.inria.fr/hal-01054561.

[135] P. E. Pérez-Estigarribia, P.-A. Bliman and C. E. Schaerer. 'A class of fast–slow models for adaptive resistance evolution'. In: *Theoretical Population Biology* 135 (2020), pp. 32–48.

[136] B. Perthame. *Transport equations in biology*. Frontiers in Mathematics. Basel: Birkhäuser Verlag, 2007, pp. x+198.

[137] B. Perthame and J. Zubelli. 'On the inverse problem for a size-structured population model'. In: *Inverse Problems* 23.3 (2007), pp. 1037–1052.

[138] B. Perthame, F. Quirós, M. Tang and N. Vauchelet. 'Derivation of a Hele-Shaw type system from a cell model with active motion'. July 2013. URL: http://hal.upmc.fr/hal-00906168.

[139] B. Perthame, F. Quirós and J.-L. Vázquez. 'The Hele-Shaw asymptotics for mechanical models of tumor growth'. In: *Archive for Rational Mechanics and Analysis* 212 (2014), pp. 93–127. DOI: 10.1007/s00205-013-0704-y. URL: http://hal.upmc.fr/hal-00831932.

[140] B. Perthame and D. Salort. 'On a voltage-conductance kinetic system for integrate and fire neural networks'. In: *Kinetic and Related Models* 6.4 (Dec. 2013), pp. 841–864. DOI: 10.3934/krm.2013.6.841. URL: http://hal.upmc.fr/hal-00871609.

[141] B. Perthame, D. Salort and G. Wainrib. 'Distributed synaptic weights in a LIF neural network and learning rules'. In: *Physica D: Nonlinear Phenomena* 353-354 (2017), pp. 20–30. DOI: 10.1016/j.physd.2017.05.005. URL: http://hal.upmc.fr/hal-01541093.

[142] B. Perthame, M. Tang and N. Vauchelet. 'Traveling wave solution of the Hele-Shaw model of tumor growth with nutrient'. In: *Mathematical Models and Methods in Applied Sciences* 24.13 (2014). 25 pages, pp. 2601–2626. URL: https://hal.archives-ouvertes.fr/hal-00931399.

[143] B. Perthame and N. Vauchelet. 'Incompressible limit of mechanical model of tumor growth with viscosity'. In: *Philosophical Transactions of the Royal Society of London. Series A, Mathematical and Physical Sciences (1934–1990)* 373 (2015). 16 pages, p. 20140283. DOI: 10.1098/rsta.2014.0283. URL: https://hal.archives-ouvertes.fr/hal-01066494.

[144] D. e. a. Peurichard. ' Extra-cellular matrix rigidity may dictate the fate of injury outcome'. In: *J. Theor Biol* 469 (2019), pp. 127–136.

[145] D. e. a. Peurichard. 'Simple mechanical cues could explain adipose tissue morphology'. In: *J. Theor Biol* (2017). URL: https://doi.org/10.1016/j.jtbi.2017.06.030.

[146] C. Pouchol, J. Clairambault, A. Lorz and E. Trélat. 'Asymptotic analysis and optimal control of an integro-differential system modelling healthy and cancer cells exposed to chemotherapy'. accepted in the J. Math. Pures et App. Dec. 2016. URL: https://hal.archives-ouvertes.fr/hal-01416594.

[147] S. Prigent, A. Ballesta, F. Charles, N. Lenuzza, P. Gabriel, L. M. Tine, H. Rezaei and M. Doumic. 'An efficient kinetic model for assemblies of amyloid fibrils and its application to polyglutamine aggregation.' In: *PLoS ONE* 7.11 (2012), e43273. DOI: 10.1371/journal.pone.0043273. URL: https://hal.archives-ouvertes.fr/hal-00778052.

[148] M. Rabé, S. Dumont, A. Álvarez-Arenas, H. Janati, J. Belmonte-Beitia, G. F. Calvo, C. Thibault-Carpentier, Q. Séry, C. Chauvin, N. Joalland, F. Briand, S. Blandin, E. Scotet, C. Pecqueur, J. Clairambault, L. Oliver, V. Pérez-García, A. M. Nadaradjane, P.-F. Cartron, C. Gratas and F. Vallette. 'Identification of a transient state during the acquisition of temozolomide resistance in glioblastoma'. In: *Cell Death and Disease* 11.1 (Jan. 2020). DOI: 10.1038/s41419-019-2200-2. URL: https://hal.archives-ouvertes.fr/hal-02429194.

[149] L. Robert, M. Hoffmann, N. Krell, S. Aymerich, J. Robert and M. Doumic. 'Division in Escherichia coli is triggered by a size-sensing rather than a timing mechanism'. In: *BMC Biology* 12.1 (2014), p. 17. DOI: 10.1186/1741-7007-12-17. URL: https://hal.inria.fr/hal-00981312.

[150] F. Schliess, S. Hoehme, S. Henkel, A. Ghallab, D. Driesch, J. Böttger, R. Guthke, M. Pfaff, J. Hengstler, R. Gebhardt, D. Häussinger, D. Drasdo and S. Zellmer. 'Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration'. In: *Hepatology* 60.6 (Dec. 2014), pp. 2040–2051. DOI: 10.1002/hep.27136. URL: https://hal.inria.fr/hal-01110646.

[151] N. Sfakianakis, D. Peurichard, A. Brunk and C. Schmeiser. 'Modelling cell-cell collision and adhesion with the Filament Based Lamellipodium Model'. In: *BIOMATH* (2019). URL: http://dx.doi.org/10.11145/j.biomath.2018.11.097.

[152] S. Shen and J. Clairambault. 'Cell plasticity in cancer cell populations'. In: *F1000Research* (2020), 9:635.

[153] S. P. Sinkins. '*Wolbachia* and cytoplasmic incompatibility in mosquitoes'. In: *Insect Biochemistry and Molecular Biology* 34.7 (2004). Molecular and population biology of mosquitoes, pp. 723–729.

[154] M. Strugarek. 'Mathematical modeling of population dynamics, applications to vector control of Aedes spp. (Diptera:Culicidae)'. Theses. Sorbonne Université , UPMC, Sept. 2018. URL: https://hal.archives-ouvertes.fr/tel-01879201.

[155] M. Strugarek, H. Bossin and Y. Dumont. 'On the use of the sterile insect technique or the incompatible insect technique to reduce or eliminate mosquito populations'. https://arxiv.org/abs/1805.10150 - working paper or preprint. May 2018. URL: https://hal.archives-ouvertes.fr/hal-01799954.

[156] M. Strugarek, L. Dufour, N. Vauchelet, L. Almeida, B. Perthame and D. A. M. Villela. 'Oscillatory regimes in a mosquito population model with larval feedback on egg hatching'. https://arxiv.org/abs/1801.03701 - working paper or preprint. Jan. 2018. URL: https://hal.archives-ouvertes.fr/hal-01674280.

[157] M. Strugarek and H. Ji. 'Sharp seasonal threshold property for cooperative population dynamics with concave nonlinearities'. https://arxiv.org/abs/1804.07641 - working paper or preprint. Apr. 2018. URL: https://hal.archives-ouvertes.fr/hal-01772628.

[158] S. Taheri-Araghi, S. Bradde, J. T. Sauls, N. S. Hill, P. A. Levin, J. Paulsson, M. Vergassola and S. Jun. 'Cell-Size Control and Homeostasis in Bacteria'. In: *Current Biology* 11679.1-7 (2015).

[159] G. Vignoud, J. Touboul and L. Venance. 'A synaptic theory for procedural and sequence learning in the striatum'. Preprint. 2022.

[160] T. Walker and S. P. Sinkins. 'Biological control of arbovirus vectors'. In: *Arboviruses: Molecular Biology, Evolution and Control. Caister Academic Press, Norfolk, UK* (2016), pp. 291–302.

[161] Y. Yin, O. Sedlaczek, B. Müller, A. Warth, M. González-Vallinas, B. Lahrmann, N. Grabe, H.-U. Kauczor, K. Breuhahn, I. Vignon-Clementel and D. Drasdo. 'Tumor cell load and heterogeneity estimation from diffusion-weighted MRI calibrated with histological data: an example from lung cancer'. In: *IEEE Transactions on Medical Imaging* (2017). DOI: 10.1109/TMI.2017.2698525. URL: https://hal.inria.fr/hal-01421398.