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Activity Report 2017

Project-Team MAMBA

Modelling and Analysis for Medical and Biological Applications

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

RESEARCH CENTER
Paris

THEME
Modeling and Control for Life Sciences

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

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1. Personnel

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2. Overall Objectives

2.1. Context and overall objectives of the project-team

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 two kinds of problems involving dynamics of Partial Differential Equations (PDEs).

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

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

3. Research Program

3.1. Introduction

Data and image analysis, statistical, ODEs, PDEs, and agent-based approaches are used either individually or in combination, with a strong focus on PDE analysis and agent-based approaches. Mamba was created in January 2014, as a continuation of the BANG project-team, that had been headed by Benoît Perthame from 2003-2013, and in the last years increasingly broaden its subjects as its individuals develop their own research agendas. It aims at developing models, simulations and numerical 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, multicelluar growth, wound healing and liver regeneration, cancer evolution, healthy and tumour growth control by pharmaceuticals, protein polymerisation occurring in neurodegenerative disorders, etc.

Another guideline of our project is to remain close to the most recent questions of experimental biology or medicine, to design models and problems under study as well as the related experiments to be carried out by our collaborators in biology or medicine. In this context, our ongoing collaborations with biologists and physicians: the collaboration with St Antoine Hospital in Paris within the Institut Universitaire de Cancérologie of UPMC (IUC, Luis Almeida, Jean Clairambault, Dirk Drasdo, Alexander Lorz, Benoît Perthame); Institut Jacques Monod (Luis Almeida); the INRA team headed by Human Rezaei and Wei-Feng Xue's team in the university of Canterbury through the ERC Starting Grant SKIPPER^{AD} (Marie Doumic); our collaborators within the HTE program (François Delhommeau at St Antoine, Thierry Jaffredo, and Delphine Salort at IBPS, UPMC, Paris; François Vallette at INSERM Nantes); Frédéric Thomas at CREEC, Montpellier; Hôpital Paul Brousse through ANR-IFlow and ANR-iLite; and the close experimental collaborations that emerged through the former associate team QUANTISS (Dirk Drasdo), particularly at the Leibniz Institute for Working Environment and Human Factors in Dortmund, Germany, are key points in our project.

Our main objective is the creation, investigation and transfer of new models, methods and algorithms. 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.

Taking advantage of the last 4-year evaluation of MAMBA (September 2017), we have re-organised the presentation of our research program in five main axes, three methodological, and two application-driven axes. In more details, these research axes are the following.

Axis 1 (methodological) is devoted to works in physiologically-based design, analysis and control of population dynamics. It encompasses populations of bacteria, 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 cell age, cell size, time elapsed since last firing (neurons).

Axis 2 (methodological) is devoted to reaction and motion equations for living systems. It aims at describing biological phenomena such as tumour growth, chemotaxis and wound healing.

Axis 3 (methodological) tackles the question of model and parameter identification, combining stochastic and deterministic approaches and inverse problem methods in nonlocal and multi-scale models.

Axis 4 (applicative) 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.

Axis 5 (applicative) is devoted to growth, evolution and regeneration in populations and tissues. It involves protein aggregation and fragmentation models for neurodegenerative diseases (prion, Alzheimer), organ modelling, mainly of the liver, its damages induced by toxic molecules, and its regeneration after toxic insult. Newcomers in this applicative field are epidemiological modelling of propagation of insect vector-borne diseases by reaction-diffusion equations and of their optimal control, bacterial growth and wound healing.

3.2. Research axis 1: analysis and control for population dynamics

Personnel

Pierre-Alexandre Bliman, Jean Clairambault, Marie Doumic, Alexander Lorz, Benoît Perthame

Project-team positioning

Population dynamics is a field with varied and wide applications, many of them being in the core of MAMBA interests - cancer, bacterial growth, protein aggregation. Their theoretical study also brings a qualitative understanding on the interplay between individual growth, propagation and reproduction in such populations. In the previous periods of evaluation, many results where obtained in the BANG team on the asymptotic and qualitative behaviour of such structured population equations, see e.g. [113], [59], [79], [68]. Other Inria teams interested by this domain are Mycenae, Numed and Dracula, with which we are in close contacts. Among the

leaders of the domain abroad, we can cite among others our colleagues Tom Banks (USA), Graeme Wake (New Zealand), Glenn Webb (USA), Jacek Banasiak (South Africa), Odo Diekmann (Netherlands), with whom we are also in regular contact. Most remarkably and recently, connections have also been made with probabilists working on Piecewise Deterministic Markov Processes (F. Malrieu at the university of Rennes, Jean Bertoin at the ETH in Zurich, Vincent Bansaye at Ecole Polytechnique, Julien Berestycki at Cambridge, Amaury Lambert at College de France, M. Hoffmann at Paris Dauphine), leading to a better understanding of the links between both types of results - see also axis 3.

Scientific achievements

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

Time asymptotics for nucleation, growth and division equations

Following the many results obtained in the BANG team on the asymptotic and qualitative behaviour 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 [65], the case of equal mitosis (division into two equally-sized offspring) with linear growth rate was studied, and strangely enough, it appeared that the general relative entropy method could also be adapted to such a non-dissipative case. Many discussions and common workshops with probabilists, especially through the ANR project PIECE coordinated by F. Malrieu, have led both communities to work closer.

In [77], the case of constant fragmentation rate and linear growth rate has been investigated in a deterministic approach, whereas similar questions were simultaneously raised but in a stochastic process approach in [62].

We also enriched the models by taking into account a nucleation term, modeling the spontaneous formation of large polymers out of monomers [122]. We investigated the interplay between four processes: nucleation, polymerization, depolymerization and fragmentation.

The ERC Starting Grant SKIPPER^{AD} (Doumic) supported and was the guideline for the study of nucleation, growth and fragmentation equations.

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 axis 4, 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 behaviour 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 [109], [106], [105], [107]. Space may be added as a complementary structure variable provided that something is known of the (Cartesian) geometry of the population [108], which is seldom the case.

Mathematical models of infectious diseases
These models are made to understand and predict the dynamics of the spread of infectious diseases. We initiated studies with the aim to understand how to use epidemiological data (typically given through incidence rate) in order to estimate the state of the population as well as constants, characteristic of the epidemics such as the transmission rate. The methods rely on observation and identification techniques borrowed from control theory.

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 [116], followed by [112], [101], [117], [67]. This field also yields a beautiful illustration for the capacity of the team to combine and compare stochastic and PDE modelling (see axis 3), in [72].

Collaborations

- Nucleation, growth and fragmentation equations: **Juan Calvo**, university of Granada, came for two one-month visits, **Miguel Escobedo**, University of Bilbao (see also axis 3), **Pierre Gabriel**, University of Versailles-Saint Quentin, former B. Perthame and M. Doumic's Ph.D student, who now co-supervises Hugo Martin's Ph.D thesis.
- 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 axis 4). **Emmanuel Trélat**, UPMC professor, member of LJLL and of the CAGE Inria team, is the closest Mamba collaborator for optimal control.
- Estimation and identification of epidemiological models: **Maria Soledad Aronna**, Fundação Getulio Vargas, Brazil; **Alain Rapaport**, INRA-Montpellier; **Abderrahmane Iggidr**, Inria Nancy-Grand Est
- Neural networks: **Delphine Salort,** Professor UPMC, Laboratory for computations and quantification in biology, and **Patricia Reynaud**, University of Nice, **Maria Cáceres**, university of Granada.

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

Personnel

Luis Almeida, Casimir Emako-Kazianou, Alexander Lorz, Benoît Perthame, Nicolas Vauchelet.

Project-team positioning

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

Scientific achievements

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

Mathematical modelling for bacterial chemotaxis.
Chemotaxis is the phenomenon in which cells direct their motion in response to a chemical signal present in their environment. Our unique expertise is on mathematical aspects of the kinetic equations which describe the run and tumble motion of bacteria and their asymptotic analysis.

An interdisciplinary collaboration with biophysicists from Institut Curie has been successful on experimental observations concerning the interaction between two species of bacteria and emergence of travelling bands [86]. The mathematical models used in this work are derived in [51] thanks to a diffusive limit of a kinetic system with tumbling modulation along the path. A numerical investigation of this limit is provided in [87]. These works enter into the framework of the PhD of Casimir Emako-Kazianou [88]. Recently, we have been able to derive rigorously such kinetic models from a more sophisticated equation incorporating internal variable when cells adapt rapidly to changes in their environment [119].

Aggregation equation.
In the mathematical study of collective behaviour, an important class of models is given by the aggregation equation. In the presence of a non-smooth interaction potential, solutions of such systems may blow up in finite time. To overcome this difficulty, we have defined weak measure-valued solutions in the sense of duality and its equivalence with gradient flows and entropy solutions in one dimension [100]. The extension to higher dimensions has been studied in [70]. 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 behaviour of such weak measure-valued solutions [93], [99].

Free boundary problems for tumour growth.
Fluid dynamic equations are now commonly used to describe tumour growth with two main classes of models: those which describe tumour growth through the dynamics of the density of tumoral cells subjected to a mechanical stress; those describing the tumour 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 [115] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [102].

Since more realistic systems are used in the analysis of medical images, we have extended these studies to include active motion of cells in [114], viscosity in [120] and proved regularity results in [110]. 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 [118], see also 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 [103].

Collaborations

- Institut Curie, joint work with Axel Buguin on bacterial models for chemotaxis.
- Shanghai Jiao Tong University, joint publications with Min Tang on bacterial models for chemotaxis and free boundary problems for tumour growth.
- Imperial College London, joint works with José Antonio Carrillo on aggregation equation.
- University of Maryland at College Park, UCLA, Univ. of Chicago, Univ. Autónoma de Madrid, Univ. of St. Andrews (Scotland), joint works on mathematics of tumour growth models.

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

Personnel

Marie Doumic, Dirk Drasdo, Aurora Armiento, Thibault Bourgeron, Rebecca Chisholm, Tommaso Lorenzi

Project-team positioning

Mamba developed and addressed model and parameter identification methods and strategies in a number of mathematical and computational model applications including growth and fragmentation processes emerging in bacterial growth and protein misfolding, in liver regeneration [82], TRAIL treatment of HeLa cells [61], growth of multicellular spheroids [98], blood detoxification after drug-induced liver damage [124], [92].

This naturally led to increasingly combine methods from various fields: image analysis, statistics, probability, numerical analysis, PDEs, ODEs, agent-based modelling 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 variablity 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 Robert (Inria RAP) in probability, with Tom Banks (Raleigh, USA) and Philippe Moireau (Inria M3DISIM) in inverse problems and data assimilation, and with numerous experimentalists.

Scientific achievements

Direct parameter identification is a great challenge particularly in living systems in which part of parameters at a certain level are under control of processes at smaller scales.

Estimation methods for growing and dividing populations

In this domain, all originated in two papers in collaboration with J.P. Zubelli in 2007 [121], [81], 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 [65]. 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) [35]. 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 [80], a work which inspired also very recently other groups in statistics and probability [62], [95] and was the basis for Adélaïde Olivier's Ph.D thesis [111], [96] and of some of her more recent works [21] (see also axis 5).

Model identification for growing multicellular spheroids

For multicellular spheroids growing under different conditions, first an agent-based model on an unstructured lattice for one condition has been developed and then stepwise extended for each additional condition which could not be captured by the present model state [98] [97] (axis 5). The multicellular dynamics has been mimicked by a master equation, intracellular processes by ODEs, and extracellular molecular transport processes by partial differential equations. The model development was based almost completely on bright field image sequences, whereby image segmentation parameter identification was performed by investigation of sensitivity and specificity of the segmentation with a biologist expert serving as gold standard. The Akaike and Bayesian Information Criteria were used to evaluate whether parameters introduced due to the model extension led to a significant increase of the information. It turned out that the final model could predict the outcome of growth conditions not considered in model development.
A similar stepwise strategy has been recently performed to identify the pressure and strain constraints of growing multicellular cell populations subject to mechanical stress. Here, a novel deformable cell model has been used that permits to display cell shape changes explicitly [127].

Data assimilation and stochastic modelling 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 [52], 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 [89], was devoted to the stochastic modelling and analysis of protein aggregation, compared both with the deterministic approach traditionnally developed in Mamba [122] and with experiments.

Model identification in liver regeneration

Based on successful model predictions for models addressing different aspects of liver regeneration, we extracted a general workflow on how modelling can inform liver disease pathogenesis [82]. Liver has a complex micro-architecture ensuring its function (axis 5). Hence many clinical questions require quantitative characterisation of micro-architecture in normal liver and during degeneration or regeneration processes which has been performed using the software TiQuant ([91] see software) or other tools we generated. Disease specific and personal information can be used to build a list of hypotheses on the question of interest, which then can be systematically implemented in mathematical models and in simulation runs tested against the data. As confocal micrographs only display part of lobules, statistically representative lobules were constructed to permit definition of boundary conditions for flow and transport.

In order to compare data and model results quantitatively, quantitative measures characterising the processes under study have to be defined, and measured in both experiment and model. Models in a context where micro-architecture is important were based on agent-based models representing each hepatocyte as well as blood vessels explicitly. They were parameterised by measurable parameters as for those physiologically relevant ranges can be identified, and systematic simulated parameter sensitivity analyses can be performed. Movement of each cell was then mimicked by an equation of motion, describing the change of position as a function of all forces on that cell including active migration. If the best model disagreed with the data, the underlying

hypotheses were considered incomplete or wrong and were modified or complemented. Models quantitatively reproducing data were either used to predict so far unknown situations, or the key mechanisms were directly challenged by our experimental partners. Along this line, two unrecognised mechanisms could be identified (axis 5).

Statistical methods decide on subsequently validated mechanism of ammonia detoxification

To identify the mechanisms involved in ammonia detoxification [92], 8 candidate models representing the combination of three possible mechanisms were developed (axis 5). First, the ability of each model to capture the experimental data was assessed by statistically testing the null hypothesis that the data have been generated by the model, leading to exclusion of one of the 8 models. The 7 remaining models were compared among each other by the likelihood ratio. The by far best models were those containing a particular ammonia sink mechanism, later validated experimentally (axis 5). For each of the statistical tests, the corresponding test statistics has been calculated empirically and turned out to be not chi2-distributed in opposition to the usual assumption stressing the importance of calculating the empirical distribution, especially when some parameters are unidentifiable.

Collaborations

- **Philippe Robert**, Inria Rap, for the stochastic process modelling [90]
- **Marc Hoffmann,** Université Paris-Dauphine, for the statistical approach to growth and division processes [80], **M. Escobedo**, Bilbao and **M. Tournus**, Marseille, for the deterministic approach.
- **Tom Banks**, North Carolina State University, and **Philippe Moireau,** Inria M3DISIM, for the inverse problem and data assimilation aspects [57],[1]
- **Jan G. Henstler group**, IfADo, Dortmund (Germany), **Irene Vignon-Clementel** (Inria, REO), others for Liver regeneration, ammonia detoxification.
- **Kai Breuhahn group**, DKFZ Heidelberg (Germany), **Pierre Nassoy**, Univ. Bordeaux, for multicellular tumor growth

3.5. Research axis 4: Focus on cancer

Personnel

Luis Almeida, Thibault Bourgeron, Cécile Carrère, Rebecca Chisholm, Jean Clairambault, Marie Doumic, Dirk Drasdo, Sarah Eugène, Paul Van Liedekerke, Tommaso Lorenzi, Alexander Lorz, Benoît Perthame, Yi Yin

Project-team positioning

The MAMBA team designs and analyses mathematical models of tumour growth and therapy, at the cell population level, using agent-based or partial differential equations, with special interest in methodologies for therapeutic optimisation using combined anticancer drug treatments. Rather than, or not only, modelling 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 antagonising 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 analysing models of cell populations structured in continuous phenotypes, relevant for the description of the behaviour 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 modelling 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 tumour environmental pressure (drugs, cytokines or metabolic conditions, mechanical stress and spatial conditions), in particular from drug sensitivity to resistance. This position is original on the international scene of teams dealing with drug resistance in cancer.

Scientific achievements

Molecular modelling towards theoretical optimisation of anticancer drug delivery
The protein p53, guardian of the genome and tumour suppressor, has been the object of Ján Eliaš's PhD thesis [85], defended in September 2015, and of articles in 2014 and 2017 [83], [84], [11]. Based on an original intracellular spatial PDE model of the protein dynamics, it allows for the prediction of biologically observed oscillations of p53 nuclear concentrations in case of (e.g. radiotherapy- or anticancer drug-induced) damage to the DNA. In parallel, in [75], that for us concluded works initiated by a fruitful collaboration with Francis Lévi (retired from CNRS 2014), we associate pharmacokinetics-pharmacodynamics of anticancer drugs, their action on the cell cycle at the cell population level, and optimisation algorithms to maximise their combined action under the constraint of preserving healthy tissue integrity.

Modelling Acute Myeloid Leukaemia (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 [54], [55], [56], [64], [76], [53]. These works study the stability of the haematopoietic system and its possible restabilisation 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 modelling with a evolutionary perspective on tumour heterogeneity, is documented in a series of articles [73], [74], [105], [106], [108]. 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)

Senescence modelling 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 [66].

Biomechanically mediated growth control of cancer cells

Mechanical feedback has been identified as a key regulator of tissue growth, by which external signals are transduced into a complex intracellular molecular machinery. Using multi-scale computational modelling of multicellular growth in two largely different experimental settings with the same tumour cell line we were able to show that the cellular growth response on external mechanical stress is surprisingly quantitatively predictable. For this purpose, the mechanical parameters of a center-based agent-based model were calibrated with a deformable agent-based cell model, which displays cell shape and hence can deal with high cell compressions. The cell cycle progression function was calibrated with findings of population growth in an

elastic capsule. The emerging model was able to correctly predict the growth response both for modified stresses in a capsule as well as the growth response in a different experimental setting [128], [127].

Model identification for TRAIL treatment

Repetitive administration of TRAIL (TNF-Related Apoptosis Induced-Ligand) on HeLa cells produces characteristic resistance pattern in time that can be explained by cell-to-cell variability in the protein composition. The TRAIL signal transduction pathway is one of the best-studied apoptosis pathways and hence permits detailed comparisons with data. Within a stochastic model of gene expression coupled to transcription and translation to the pathway members, we were able to quantitatively explain the resistance pattern. An important challenge was in parameter identification at each of the level for numerous proteins, whereby the most sensitive parameter was to correctly capture short-lived proteins in the TRAIL toxicity pathway as those mainly determine the regeneration of protein distribution in the cell population and thereby may generate strong stochastic fluctuations [61], [60].

Radiotherapy

In close cooperation with M. Herrero (U. Complutense, Madrid) we have explored by extensive computer simulations using an agent-based model the consequences of spatially inhomogeneous x-ray irradiation in cancer treatment. The model predicted that in the case of different competing sub-populations, namely cancer stem cells with unlimited division capacity, and cancer cells with limited division capacity, inhomogeneous radiation focusing higher doses at the tumour center and lower doses at the tumour periphery should outperform homogeneous irradiation [104]. Cancer stem cells are believed to have a longer cell cycle duration than cancer cells, and are less radiosensitive than cancer cells, which is why they often survive radiation and lead to tumour relapse.

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 (2 articles in common [74], [108]), **Michèle Sabbah** (2 PhD theses in common) at Annette Larsen's lab, 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: one funded Inria PRE project in common.
- Telomere shortening: **Teresa Teixeira** and **Zhou Xu** (IBCP, Paris), **Philippe Robert** (Inria RAP).
- TRAIL treatment: **Gregory Batt,** Inria Saclay and Inst. Pasteur (France)

3.6. Research axis 5: Growth, evolution and regeneration in populations and tissues

Personnel

Luis Almeida, Pierre-Alexandre Bliman, Marie Doumic, Dirk Drasdo, Benoît Perthame, Nicolas Vauchelet

Project-team positioning

The applications in this category span very different subjects from amyloid diseases, dengue fever, wound healing, liver regeneration and toxicity, up to bacterial growth. 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 modelling on the histological scale, integration of molecular processes in each individual cell, and single-cell (agent) based models. Works by Schliess [124], [92] have been highlighted in editorials.

Mathematical modelling 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 (UPMC) and Monique Chyba (Hawaii, USA) in control, and Suzanne Sindi (USA) for the modelling of the yeast prion. We have interactions with all these groups and organised a workshop in June 2017, gathering both the biophysics and applied mathematics communities.

Scientific achievements

Amyloid disease

Application to protein aggregation in amyloid diseases is a long-standing interest of Mamba, dating back to 2010 [69], and developed through the collaboration with Human Rezaei's team at Inra. More recently, with Wei-Feng Xue in Canterbury, we investigated the intrinsic variability among identical experiments of nucleation [78], [90], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [89].

In collaboration with Tom Banks first [58], [57] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [52], we proposed new models and mechanisms.

Dengue fever

The spread of certain strains of the intracellular parasitic bacterium Wolbachia in populations of mosquitoes Aedes aegypti drastically reduces their competence as vector of dengue and other severe mosquito-borne viral diseases. In the absence of a vaccine, or of any preventive or curative treatment, the release of mosquitoes deliberately infected in laboratory by this bacterium has been recently considered a promising tool to control these diseases. Technically the situation can be described by a bistable model, and the issue consists in moving from a Wolbachia-free equilibrium to a fully contaminated equilibrium.

When implementing such a method, an important issue concerns the spatial propagation of the mosquitoes: on releasing infected mosquitoes in a given domain (which can be part of a city), the hope is to invade the whole area. The study of this propagation phenomena falls into the study of existence of travelling waves.

Wound healing

We studied cell motion in epithelial gap closure, a form of collective cell migration that is a very widespread phenomenon both during development and adult life - it is essential for both the formation and for the maintenance of epithelial layers. Due to their importance, *in vivo* wound healing and morphogenetic movements involving closure of holes in epithelia have been the object of many studies. In our works [1] we considered wound healing and epithelial gap closure in both in vivo (in particular drosophila pupa) and in vitro (MDCK cell and human keratinocytes). We found some similarities in the geometry dependence of the wound closure strategies between these two situations, indicating the existence of conserved mechanisms that should be widespread across living beings.

Liver regeneration

An integrated model, coupling a spatial-temporal model of liver regeneration after drug-induced damage to a compartment model of detoxification blood from ammonia, identified the lack of an ammonia detoxifying reaction in the biochemical consensus scheme [124]. Hyperammonia is the most frequent reason for death due to acute liver failure in UK and USA. The spatial model represents liver micro-architecture in a group of liver lobules, the repetitive anatomical and functional units of liver, mimicking each hepatocyte as single agent and blood vessels as a network of chains of spherical objects. This model had previously predicted the subsequently validated orientation of dividing hepatocytes along the liver capillaries as order mechanism. It

[1] ravasio:hal-01245750, vedula:hal-01298859

was here coupled to ODEs for metabolites participating in the zonated ammonia metabolism by calculating the volume of each liver lobule zone with time during regeneration after drug induced damage, which is an input parameter for the detoxification compartment model. Experiments triggered by the model predictions could identify later a candidate ammonia sink mechanism which in a follow-up work [92] could be shown to be the most likely mechanism compared with alternative explanations (see axis 3). This mechanism could be validated, and led to a possible therapy option in treatment of hyperammonemia.
The models have been further expanded towards true multilevel-multiscale models that include molecular HGF control of cell cycle progression (unpublished) and ammonia detoxification (Géraldine Cellière's PhD thesis, 2016; Noémie Boissier's PhD thesis, 2018). In these models, the intracellular models were executed in each individual hepatocyte, and transport of molecules with blood were simulated. Blood flow was modelled by Poiseuille law in the entire capillary network. Further conditions could be identified, under which standard pharmacokinetics-pharmacodynamics (PKPD) models fail to predict the correct dynamics and need to be replaced by spatial temporal models representing organ microarchitecture. The model has further been extended towards bile flow.

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. The multilevel-multi scale approach outlined above has been used to explore a strategy to predict the in vivo damage of paracetamol (acetaminophen) from in vitro experimental data. Model simulations and data obtained so far strongly suggest that the prediction is quantitative, if the time development of the toxicity in vitro is displayed (this is so far not common), differences in the concentration kinetics of drug metabolising enzymes in vitro are measured, and micro-architecture is determined (Géraldine Cellière's PhD thesis [71]). Common strategies in toxicology based on relating the maximum drug concentration or area under the drug concentration - time curve between in vitro and in vivo damage could be shown to fail.

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 [123], 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.

Collaborations

- Dengue control by releasing Wolbachia infected mosquitoes **Maria Soleda Aronna, F.C. Coelho** (Fundação Getulio Vargas, Brazil); **D. Villela, C. Struchiner** (Fiocruz, Brazil); **Jorge Zubelli** (IMPA, Brazil); **Alain Rapaport** (INRA-Montpellier), **Y. Dumont** (CIRAD-Montpellier); **Ch. Schaerer** (UNA, Paraguay).
- Protein aggregation in amyloid diseases: **Human Rezaei**'s team at Inra Jouy-en-Josas (France) and **W-F Xue**'s team in at university of Kent (Great Britain); **Tom Banks** at the North Carolina State University (USA), **Philippe Moireau** (M3DISIM) and **Philippe Robert** (Rap) in Inria
- bacterial growth and division: **Lydia Robert**, UPMC (France)
- Liver research & toxicology: **JG. Hengstler** group (IfADo, Dortmund, Germany); **R. Gebhardt** (Univ. Leipzig); **U. Klingmueller** (DKFZ, Heidelberg); **Irène Vignon-Clementel** (Inria, REO)
- Wound healing: **Patrizia Bagnerini** (Genova, Numerical methods), **Benoît Ladoux** (Institut Jacques Monod et Mechanobiology Institute Singapore, Biophysics) and **Antonio Jacinto** (CEDOC, Lisbon, Biology and Medicine).

4. Highlights of the Year

4.1. Highlights of the Year

4.1.1. Awards

Benoît Perthame has been elected member of the Académie des Sciences, in the section "Physique, mécanique, informatique".

4.1.2. Personnel

Marie Doumic has prolonged for one more year her sabbatical at WPI (Vienna, Austria, 2016-2018).

Diane Peurichard has been hired as Chargée de Recherche classe normale in Mamba, beginning in October 2017.

5. New Software and Platforms

5.1. TiQuant

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

- Author: Dirk Drasdo
- Contact: Dirk Drasdo

5.2. TiSim

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

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

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

5.3. Platforms

TiQuant and TiSim The software for tissue image analysis (**Ti**ssue **Quant**ifier) and simulation (**Ti**ssue **Sim**ulator) has been enriched. In more details,

5.3.1. TiQuant

TiQuant [94], [91] is implemented in portable object-oriented JSO C++. The GUI is based on QT and supports real-time visualisation using OpenGL. TiQuant is embedded in the tissue modelling framework CellSys and thus is tightly linked with TiSim, a versatile and efficient simulation environment for tissue models. TiQuant provides an interface to VolView and further complements its functionality by linking to the open-source libraries ITK and VTK (itk/vtk.org). The image/volume processing chains currently implemented in TiQuant for example include techniques to segment conduit and cell segmentation from 3D confocal micrographs of liver tissue based on the Adaptive Otsu Thresholding method and a number of morphological operators. TiQuant was currently extended by a machine-learning component, largely replacing the manual image-processing pipeline.

5.3.2. TiSim

TiSim permits agent-based simulations of multicellular systems. It is modular, in object-oriented ISO C++, the GUI based on Qt and OpenGL, while also allowing for batch mode runs. The software permits multi-scale simulations by integration of molecular pathways (for signalling, metabolisms, drug) into each individual cell. Applications so far are monolayer growth, multicellular spheroids, liver regeneration, TRAIL-treatment simulations. It has an SBML interface. In a largely finished follow-up version it will integrate a deformable cell model by triangulation of cell surface, deformable rod models, extracellular matrix and vascular flow and transport. TiSim can be directly fed by structures synthesised from processed image data from TiQuant.

Impact: The tool is used by our collaborators in liver biology, medicine and toxicology. We recently trained a PhD student from P. Segers (Ghent Univ.) on TiQuant and from T. Hillen (Univ. Alberta, Ca) on TiSim and organised a workshop on benchmarking and comparing agent-based models and tools (workshop Leipzig, volet 5).

6. New Results

6.1. Analysis and control for population dynamics

Time asymptotics for nucleation, growth and division equations

We revisited the well-known Lifshitz-Slyozov model, which takes into account only polymerisation and depolymerisation, and progressively enriched the model. Taking into account depolymerisation and fragmentation reaction term may surprisingly stabilisde the system, since a steady size-distribution of polymers may then emerge, so that "Ostwald ripening" does not happen [33].

Cell population dynamics and its control

The question of optimal control of the population dynamics, that naturally arises when dealing with anticancer drug delivery optimisation, has been specifically the object of [24], work led in common with E. Trélat (LJLL and Inria team CAGE) and published in the *J. Maths. Pures Appl*.

The asymptotic behaviour of interacting populations in a nonlocal Lotka-Volterra way is also, independently of any control, studied for two populations in this article, and for many in [49].

Mathematical models of infectious diseases

First results in this subject (which is new for the team) have been obtained for elementary models including a model of vector-borne disease [31], [29].

6.2. Reaction and motion equations for living systems

Mathematical modelling for chemotaxis

A new kinetic model of chemotaxis for angiogenesis has been developed [22].

Aggregation equation.

Based on the approach relying on weak measure-valued solutions [100], an extension to a model for two species in interaction has been proposed in [12].

Free boundary problems for tumour growth.

Motivated by numerical observations from D. Drasdo using agent-based modelling, the article [17] studies the interfaces between two cell populations described by continuous models with different motilities and recovers interface instabilities.

6.3. Model and parameter identification combining stochastic and deterministic approaches in nonlocal and multi-scale models

Data assimilation and stochastic modelling for protein aggregation

Following Carola Kruse's post-doc [57], in collaboration with Tom Banks, Aurora Armiento's Ph.D [1], co-supervised with Philippe Moireau, was devoted to the question of adapting data assimilation strategies to the specific context and difficulties of protein aggregation.

In parallel with the statistical approach to growth and division processes, the deterministic approach has been continued in collaboration with Magali Tournus [35].

Estimating cellularity and tumour heterogeneity from Diffusion-Weighted MRI based on histological data

In [25] we developed, in close collaboration with the University of Heidelberg and DKFZ, together with I. Vignon-Clementel (Inria team REO), a procedure to estimate tumour heterogeneity and cellularity from Diffusion-Weighted Imaging (DWI) with calibration using histological data. The estimate is based on the intravoxel incoherent motion (IVIM) model that relates the DWI signal to water diffusion within each image voxel, as well as on an image processing and analysis procedure we developed for automated cell counting in large histological samples after tumour removal. We recently showed that biopsies routinely taken are likely to be sufficient to construct a calibration curve to relate DWI diffusion coefficient to cell density, and thus to infer the whole tumour heterogeneity. The biopsies have to be taken in regions of largely different diffusion values.

6.4. Focus on cancer

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

The collaboration with the DISCO team at Inria-Saclay has been continued in conference papers [26], [27]. In one of these papers, the concept of *dormancy* in cancer as a state of coexistence between tumour and healthy stem cell populations is studied using a new model.

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

This topic, main subject in Camille Pouchol's ongoing PhD thesis, has already been mentioned about Axis 1. It has led to the publication [24].

The general question of drug resistance in cancer, from biological observations to mathematical modelling and optimal control, has been reviewed in [14], [15] and presented in various international conferences and workshops.

Senescence modelling by telomere shortening

This work, following Sarah Eugène's PhD thesis, has been continued in collaboration with Zhou Xu at IBPC [13].

6.5. Growth, evolution and regeneration in populations and tissues

Amyloid disease
With Wei-Feng Xue in Canterbury, we continued to investigate the intrinsic variability among identical experiments of nucleation [78], [90], with recent results in [13].

Making use of data assimilation and statistical methods [52], we proposed new models and mechanisms and most recently we predicted the existence of several coexisting species of protein fibrils [2].

Dengue fever
The release of Wolbachia-infected mosquitoes in Dengue infested zones and the study of their propagation may be represented by spatial reaction-diffusion models. When implementing such a method, an important issue concerns the spatial propagation of the mosquitoes: on releasing infected mosquitoes in a given domain (which can be part of a city), the hope is to invade the whole area. The study of this propagation phenomena falls into the study of existence of travelling waves. We proposed in [125] a mathematical model to study such phenomena and have simplified it to recover a well-known simple bistable system for which existence of traveling wave is known. The study of the probability of success of spatial invasiveness has been performed in [126], and [41] is devoted to the blocking of the propagation in heterogeneous environment presenting strong enough population gradient. In the previous works, the invasion is installed by large enough impulsive deliveries. Another approach, consisting in igniting the propagation by feedback control, has been studied in [63], [6].

Toxicity extrapolation from in vitro to in vivo
The investigation of this field has been continued by Géraldine Cellière, leading to her PhD defense in June 2017 [71].

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

Industrial contract with SANOFI on the modelling of employees population dynamics and turnover.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

8.1.1.1. ANR Blanc 2014-2018 "Kibord"

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

8.1.1.2. ANR 2014-2017 IFLOW

Eric Vibert, Hopital Paul Brousse (coordinator). Partners: Inria REO, Hopital Toulouse, Dirk Drasdo. Objectives are simulation of liver perfusion after partial hepatectomy with and without therapeutic manipulations to improve patients survival after PHx.

8.1.1.3. ANR iLITE 2016 - 2020

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

8.1.1.4. ANR InTelo 2017-2020

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

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

8.1.2.1. ITMO Cancer EcoAML

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

8.1.2.2. ITMO Cancer MoGlImaging

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

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

Research axis 1 (population dynamics): The ERC Starting Grant SKIPPER^{AD} (Marie Doumic, 2014-2018) supported and was the guideline for the study of nucleation, growth and fragmentation equations.

Benoît Perthame has obtained in April 2017 the ERC Advanced Grant ADORA (Asymptotic approach to spatial and dynamical organisations)

8.2.2. Collaborations with Major European Organisdations

German BMBF: LiverSimulator (Dirk Drasdo, 2014 - 2017)

8.3. International Initiatives

8.3.1. Participation in International Programs

CAPES/COFECUB project "Modelling innovative control methods for dengue fever" (Bliman)
STIC AmSud project "MOSTICAW- MOdelling the Spread and (opTImal) Control of Arboviroses by Wolbachia" (2016-2017) (Bliman)..

ECOS-Nord project "New methods for controlling epidemics of dengue fever and arboviroses" (2017-2019) (Bliman)

(See below)

8.3.1.1. International Initiatives

MOSTICAW

Title: MOdelling the Spread and (opTImal) Control of Arboviroses by Wolbachia

International Partners (Institution - Laboratory - Researcher):

Universidad de Buenos Aires (Argentina) - Hernán G. Solari

Universidad de Chile (Chile) - Carlos Conca

Universidade Federal Fluminense (Brazil) - Max Souza

Duration: 2016 - 2017

Start year: 2016

The spread of certain strains of the intracellular parasitic bacterium Wolbachia in populations of mosquitoes Aedes aegypti drastically reduces their competence as vector of dengue and other severe mosquito-borne viral diseases known as arboviral infections. In absence of vaccine, or of preventive or curative treatment, the release of mosquitoes infected by the bacterium has been recently considered a promising tool to control these diseases, and experimental introductions in wild populations are currently under way in Brazil and Colombia. A key question about this method concerns the effective strategies of release of the infected mosquitoes in the field that can be applied with limited cost to reach the desired state of complete exclusion of Wolbachia-free mosquitoes. The mathematical study of central topics is the core of this project. The scientific questions to be addressed during this project are related to the study of the dynamic and control of the key invasion mechanism on finite-dimensional compartmental models; and to specific focus on the spatial aspects, achieved through more elaborate models (PDE, models on interaction graphs, stochastic models). We further propose to elaborate on the risks involved in the spreading of Wolbachia, implementing in mathematical models critical analysis, complex systems (R. García) and a complexity aware epistemology (E. Morin) in contrast with the instrumental reason (Horkheimer).

8.3.1.2. International Initiatives

C17M01

Title: New methods for the control of epidemics of dengue and arboviroses

International Partner (Institution - Laboratory - Researcher):

Universidad del Valle (Colombia) - Olga Vasilieva

Duration: 2017 - 2019

Start year: 2017

8.4. International Research Visitors

8.4.1. Internships

September 2016-January 2017: Julie Favre, M1 student at EPFL (Zürich), research internship report [39]

8.4.2. Visits to International Teams

8.4.2.1. Sabbatical programme

Doumic Marie

Date: Sep 2016 - Jul 2018

Institution: Wolfgang Pauli Institute, Vienna (Austria)

8.4.2.2. Research Stays Abroad

P.-A. Bliman is still a professor at Funadação Getulio Vargas, Rio de Janeiro, Brazil, and makes frequent stays there.

9. Dissemination

9.1. Promoting Scientific Activities

Editorial activities, scientific boards, research administration

P.-A. Bliman is member of the Scientific committee of the ANR program “Environnement, pathogènes et maladies émergentes ou ré-émergentes - One health".

J. Clairambault is member of the expert group of ITMO Cancer, representative of Inria (since 2008) and member of the bureau of the interdisciplinary doctoral programme “Interfaces pour le Vivant” (IPV) at Sorbonne Université.

M. Doumic is member of the expert group of ITMO BMSV, representative of Inria (since 2014).

D. Drasdo is head of a research team, until June 2017 co-localised at Interdisciplinary Center for Bioinformatics, Univ. Leipzig, and since July 2017 co-localised at Leibniz Institute for Work-environment IfADo, Dortmund. He is member of the boards of TheScientificWorldJOURNAL and Royal Society open science (UK), J. Theor. Biol. and member of CaSyM expert committee for EU Horizon 2020.

B. Perthame is Chief Editor of Acta ApplicandæMathematicæ(Springer-Nature) (since october 2017), Editor of De Gruyter Series in Mathematics and Life Sciences and of Frontiers in Mathematical Sciences (Birkhaüser), and member of the scientific board for the ECMTB Conference 2018.

9.2. Teaching - Supervision - PhD and HDR defence committees

9.2.1. Teaching

We indicate here only the courses given by scientific staff members who do not have a teaching position. Benoît Perthame gives courses at UPMC.

Luis Ameida is in charge of the Major MathBio of the speciality “Mathematics of modelling”, M2 level, UPMC.

- *Luis Almeida, 2017*

  Tissue growth (with Delphine Salort, IBPS). UPMC M2 course, Paris **20 h**

- *Pierre-Alexandre Bliman, 2017*

  Analysis, Graduate cycle, School of Applied Mathematics, Fundação Getulio Vargas, Rio de Janeiro, Brazil **60 h**

  and Calculus III, Graduate cycle, School of Applied Mathematics, Fundação Getulio Vargas, Rio de Janeiro, Brazil **30 h**

  and Control theory, Graduate cycle, School of Industrial Management, Université Mohamed 6 Polytechnique, Ben Guerir, Morocco **6 h**

- *Jean Clairambault, 2017*

  International course on stem cells, UPMC, September 2017 **2 h**

  and Spring school on systems biology, Instituto Gulbenkian de Ciência, Lisbon, May 2017 **6 h**

- *Marie Doumic, 2017*

  Direct and inverse problems in population dynamics (with P. Moireau, Inria M3DISIM). UPMC M2 course, Paris **24 h / yr**

- *Dirk Drasdo, 2017*

  Agent-based models of tissue organisation, UPMC M2 course, Paris **24 h / yr**

  University of Rome: Tutorial, 2h: TiSim: A modelling tool for multicellular simulations

9.2.2. Supervision

9.2.2.1. PhD defences in 2017

- Aurora Armiento, “Inverse problems and data assimilation methods applied on protein polymerisation”, UPMC, begun September 2013, supervision by M. Doumic and Ph. Moireau (Inria Saclay, M3DISIM team), PhD defence January 2017, UPMC
- Giulia Fabrini “Numerical methods for optimal control problems with biological applications”, supervision by L. Almeida and P. Bagnerini (University of Genova, Italy), PhD defence April 2017, Univ. Genova
- Walid Djema, “Understanding Cell Dynamics in Cancer from Control and Mathematical Biology Standpoints: Particular Insights into the Modelling and Analysis Aspects in Hematopoietic Systems and Leukemia”, supervision by C. Bonnet (DISCO, Saclay), J. Clairambault, and F. Mazenc (DISCO, Saclay), PhD defence November 2017, L2S, Gif/Yvette

9.2.2.2. Ongoing PhD theses

- PhD in progress: Noémie Boissier (since November 2013, PhD defence in February 2018), supervision by D. Drasdo and I. Vignon-Clementel
- PhD in progress: Julia Delacour (since September 2017), supervision by Marie Doumic and Christian Schmeiser (WPI, Vienna)
- PhD in progress: Adrian Friebel, “Software of image processing and analysis of liver tissue at histological scales”, supervision by D. Drasdo and S. Hoehme
- PhD in progress: Ghassen Haddad, “Optimisation of cancer treatments”, UPMC in co-tutela with ENIT Tunis, begun October 2015, supervision by J. Clairambault and S. Ben Miled (Tunis)
- PhD in progress: Hugo Martin, “New structured population models for bacterial growth", begun October 2016, supervision by M. Doumic in co-tutela with Pierre Gabriel (Versailles)
- PhD in progress: Mathieu Mézache, begun October 2016, “Oscillatory dynamics in protein aggregation", supervision by M. Doumic in co-tutela with Human Rezaei (INRA)
- PhD in progress: Johannes Neitsch, “Growth and regeneration modelling based on an agent-based model with deformable cells”, (since June 2011), supervision by D. Drasdo and P. Van Liedekerke
- PhD in progress: Pastor Pérez-Estigarribia, Universidad Nacional de Asunción, Paraguay, supervision by C. Schaerer and P.-A. Bliman
- PhD in progress: Camille Pouchol, “Modelling interactions between tumour cells and adipocytes in breast cancer”, UPMC, begun September 2015, supervision by J. Clairambault, M. Sabbah, and E. Trélat
- PhD in progress: Antonin Prunet, UPMC, begun October 2014, supervision by L. Almeida and M. Sabbah
- PhD in progress: Andrada Quillas Maran, “Modelling early leukaemogenesis”, UPMC, begun March 2014, supervision by J. Clairambault, F. Delhommeau and B. Perthame
- PhD in progress: Martin Strugarek, “Structured population dynamics for transmissible diseases”, UPMC, begun October 2015, supervision by N. Vauchelet and B. Perthame
- PhD in progress: Cécile Taing, UPMC, begun October 2014, supervision by A. Lorz and B. Perthame

9.2.3. PhD and HDR defence committees

- Luis Almeida: Giulia Fabrini, “Numerical methods for optimal control problems with biological applications”, PhD defence April 26, 2017, Genova (Italy)
- Jean Clairambault: Cécile Carrère, “Prise en compte de l’hétérogénéité tumorale dans l’optimisation d’une chimiothérapie : contrôle optimal, analyse théorique et numérique”, PhD defence October 6, 2017, Marseille

- Jean Clairambault: Sébastien Benzekry (HDR), “Contributions in Mathematical Oncology: When Theory Meets Reality”, HDR defence November 13, 2017, Bordeaux
- Jean Clairambault: Walid Djema, “Understanding Cell Dynamics in Cancer from Control and Mathematical Biology Standpoints: Particular Insights into the Modelling and Analysis Aspects in Hematopoietic Systems and Leukemia”, PhD defence November 21, 2017, Gif/Yvette
- Marie Doumic: Aurora Armiento, “Inverse problems and data assimilation methods applied on protein polymerisation”, UPMC, PhD defence January 13, 2017, UPMC
- Marie Doumic: Apollos Besse, “Modélisation mathématique de la leucémie myéloïde chronique", PhD defence July 6, University Lyon 1
- Marie Doumic: Aline Marguet, “Processus de branchement pour des populations structurées et estimateurs pour la division cellulaire”, PhD defence November 27, 2017, Ecole Polytechnique
- Benoît Perthame: Giulia Fabrini, “Numerical methods for optimal control problems with biological applications”, PhD defence April 26, 2017, Genova (Italy)

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