Evaluation of Inria theme Modelling and Control for the Life Sciences

Project-team MAMBA

12/10/2017

Project-team title: MAMBA

Scientific leader: Marie Doumic

Research centre: Inria de Paris

Common project-team with: University Pierre and Marie Curie (UPMC)

1 Personnel

Current composition of the project-team:

Research scientists and faculty members:

- Marie Doumic, head of the team, ingénieure en chef des Ponts et Chaussées
- Luís Lopes Neves de Almeida, CNRS DR
- Pierre-Alexandre Bliman, INRIA DR
- Jean Clairambault, INRIA DR
- Dirk Drasdo, INRIA DR
- Alexander Lorz, UPMC assistant professor
- Stéphane Mischler, professor at Paris-Dauphine university (in delegation for 1 year)
- Benoît Perthame, UPMC professor

Engineers:

- Paul Van Liedekerke
- Yi Yin
- Tim Johann (Leibniz Institute IfADo)

Post-docs:

- Cécile Carrère
- Ayham Zaza (Leibniz Institute IfADo)
- Jieling Zhao (Leibniz Institute IfADo)

Ph.D. students:

- Noémie Boissier (Inria until 30.6.2017, since then Leibniz Institute IfADo)
- Federica Bubba
- Julia Delacour
- Ghassen Haddad
- Shalla Hanson
- Hugo Martin
- Mathieu Mézache
- Camille Pouchol
- Antonin Prunet
- Andrada Quillas Maran
- Martin Strugarek
- Cécile Taing

Administrative assistant:

- Kevin Bonny

Personnel at the start of the evaluation period (01/01/2014)

	INRIA	CNRS	University	Other	**Total**
DR (1) / Professors	2	1	1	1	**5**
CR (2) / Assistant professors			2		**2**
ARP and SRP (3)					
Permanent engineers (4)					
Temporary engineers (5)	3				**3**
Post-docs	4		2		**6**
PhD Students			16		**16**
Total	**9**	**1**	**21**	**1**	**32**

(1) "Senior Research Scientist (Directeur de Recherche)"
(2) "Junior Research Scientist (Chargé de Recherche)"
(3) "Inria Advanced Research Position" and "Inria Starting Research Position"
(4) "Civil servant (CNRS, INRIA, ...)"
(5) "Associated with a contract (Ingénieur Expert, Ingénieur ADT, . . .)"

Personnel at the time of the evaluation (12/10/2017)

	INRIA	CNRS	University	Other	**Total**
DR / Professors	3	1	2	1	**7**
CR / Assistant professors			1		**1**
ARP and SRP					
Permanent engineers					
Temporary engineers	2			1	**3**
Post-docs				3	**3**
PhD Students			12		**12**
Total	**5**	**1**	**14**	**2**	**26**

Changes in the scientific staff

DR / Professors Present situation	INRIA 4	CNRS 1	University 1	Other 1	**Total** **7**
Arrivals	+1				**+1**
Departures					
CR / Assistant Professors Arrivals					
Departures			-1		**-1**

Comments: **Pierre-Alexandre Bliman**, Inria DR, previously in a detached position, joined MAMBA in January 2016. The retirement of **Jean Clairambault**, Inria DR, planned in 2018, is not accounted for in this table; nor is the recruitment of a new Inria CR2 at Fall 2017. **Alexander Lorz**, member of the team from start, has been for the last two years research visiting faculty at KAUST, maintaining a close contact with regular visits in Paris to the team. **Nicolas Vauchelet**, who was a UPMC assistant professor, member of MAMBA from start, left the team to take a full professor position at Paris XIII in Fall 2016. The research engineer Tim Johann, and the postdocs Ayham Zaza and Jieling Zhao, hired in the Leibniz Research Center for Working Environment and

human factors in Dortmund, are supervised by Dirk Drasdo and attached to the team. **Stéphane Mischler** is in delegation for one year in Mamba (from september 2017 to august 2018).

Current position of former project-team members

Assistant professors:

Nicolas Vauchelet, who was a UPMC assistant professor, member of MAMBA from start, left the team to take a full professor position at Paris XIII in Fall 2016.

Postdocs:

Ibrahim Cheddadi, postdoc 2012 - 2015, firstly took another postdoc position at INRA-INRIA in Montpellier; he is since October 2016 assistant professor at Grenoble University.

Rebecca Chisholm, Inria-funded postdoc December 2013 - January 2015, went back to Australia in February 2014, and is presently on a postdoc position in Melbourne.

Stefan Hoehme, research associate, is now a Emmy-Noether group leader at the University of Leipzig.

Nick Jagiella, PhD student 2007 - 2012, postdoc 2013 - 2015, Helmholtzzentrum, Munich is now a now software developer at ART, Munich.

Tim Johann, is now a software engineer at the Leibniz Research Center for Working Environment and human factors in Dortmund.

Carola Kruse, postdoc 2013-2014, left in 2014 to take a position in the industry, and is now a research engineer in Cerfacs, Toulouse.

Tommaso Lorenzi, postdoc 2013-2015, went away in September 2015 to take a 5-year tenure teaching and research position at the University of St Andrews (Scotland).

Margriet Palm, postdoc January 2014 - December 2015, has been since January 2016 a postdoc at the University of Leiden.

Stéphanie Prigent, postdoc 2013-2014, left in 2014 and is now a research engineer in Sanofi.

Magali Tournus, postdoc February-August 2015, has been hired on a permanent assistant professor position at the École Centrale de Marseille in September 2015.

PhD students:

Aurora Armiento, PhD student (UPMC, defence December 2016) is for one year a volunteer for progress in Peru.

François Bertaux, PhD student (UPMC, defence June 2016) is a postdoc at Imperial College in London.

Youssef Bourfia, PhD student (co-tutela UPMC and U. Cadi Ayyad Marrakech, defence December 2016) is now a postdoctoral fellow at the University of Marrakech.

Thibault Bourgeron, PhD student (UPMC, defence June 2015), has been since then (2015-2017) a postdoc at ENS-Lyon.

Géraldine Cellière, PhD student (defence 2015), is now CTO in the company Lixoft.

Adrian Friebel, PhD student (still ongoing), is now in the research group of Stefan Hoehme at University of Leipzig.

Ján Eliaš, PhD student (UPMC, defence September 2015), has been a Postdoc at University Paris-Sud (2015-2017), and has been hired in Fall 2017 on a 6-year tenure teaching and research position at the University of Graz, Austria.

Hadjer Wafaâ Haffaf, PhD student (UPMC, defence October 2014) has been since 2015 an associate professor at the university of Tlemcen (Algeria).

Casimir Emako Kazianou, PhD student (UPMC, defence March 2016), has been since 2015 with JPMorgan Chase & Co. in London.

Sarah Eugène, PhD student (UPMC, defence September 2016), is now with Goldman-Sachs in London.

Adélaïde Olivier, PhD student (ENSAE and Paris-Dauphine, defence November 2015) has been since September 2016 an associate professor at University Paris-Sud.

Cristóbal Quiñinao Montero, PhD student (UPMC, defence June 2015), previously Postdoc at the Pontificia Univ. Católica de Chile, Santiago and at University Paul Sabatier, Toulouse, has been hired in March 2017 as assistant professor at the University of O'Higgins, Chile.

Last INRIA enlistment

Pierre-Alexandre Bliman, DR2 INRIA, has joined the team in January 2016.

2 Research goals and results

2.1 Keywords

Multiscale Analysis, Population Dynamics, Darwinian Evolution, Control theory, Flow modelling, Numerical methods, Inverse Problems, Growth-fragmentation equation, Stochastic modelling, Data assimilation, Cancer, Pharmacokinetics and pharmacodynamics, Drug resistance, Neuroscience, Epidemiology, Ecology, Multiphysics modelling, Wound healing modelling, liver regeneration, amyloid diseases, protein polymerization.

2.2 Context and overall goals of the project

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.

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 polymerization 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;Hopital 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.

We have organised the presentation of our research activity in five main axes, three methodological axes, and two application-driven axes. This diversity is meant so that we are in keeping with cutting-edge research both in development of mathematical methods and models and in the bio-medical application domains. We believe that this is a pre-requisite to ensure a real transfer of science between both domains. 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 tumor 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 pheno-type-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.

2.3 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. [Per07, BBCP08, DG09, CDG12]. 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), Graham Waake (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 [44], the case of constant fragmentation rate and linear growth rate has been investigated, whereas similar questions were simultaneously raised but in a stochastic process approach in [BW15]. In [26], 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 [PBC$^+$12]. We investigated the interplay between four processes: nucleation, polymerization, depolymerization and fragmentation. We revisited the well-known Lifshitz-Slyozov model, which takes into account only polymerization and depolymerization, and progressively enriched the model. Taking into account depolymerization and fragmentation reaction term may surprisingly stabilize the system, since a steady size-distribution of polymers may then emerge, so that " Ostwald ripening " does not happen [136].

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 [LLH$^+$13], [77, 76, 152], and for many in [160]. Space may be added as a complementary structure variable provided that something is known of the (Cartesian) geometry of the population [80], which is seldom the case. 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 [159], work led in common with E. Trélat (LJLL and Inria team CAGE) and accepted in the J. Maths. Pures Appl.

Mathematical models of infectious diseases

These models are made to understand and predict the dynamics of the spreading of infectious diseases. We initiated studies in the aim of understanding 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. First results in this subject (which is new for the team) have been obtained for elementary models including a model of vector-borne disease [127, 130].

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 [PS13], followed by [89, 71, 94, 31]. 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 [34].

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 Caceres**, university of Granada.

External support

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

Self assessment

The strong points of the team in this axis are its long-standing expertise in this field, together with collaborations with internationally-renowned experts in related fields of mathematics (E. Trélat in control, P. Reynaud in statistics) and biology, which brings original new problems and synergies for their solution.

Its main difficulty lies in the modeling itself: are the equations studied relevant for the biomedical problem they have been designed to? It is partially solved by the appplication-driven spirit of the team, and our collaborations with biology experts, see axis 4 and 5 and their links with this axis.

The team will continue to study this type of equations with new application focuses, following the development of axis 4 and 5, which continuously bring new and original mathematical questions.

2.4 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 developped 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 will benefit 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 organization 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 expertize is on mathematical aspects of the kinetic equations which describe the run and tumble motion of bacteria and their asymptotic analysis. For instance, a kinetic model of chemotaxis for angiogenesis may be found in [88]. An interdisciplinary collaboration with biophysicists from Institut Curie has been successful on new experimental observations concerning the interaction between two species of bacteria and emergence of travelling bands [53]. The mathematical models used in this work are derived in [11] thanks to a diffusive limit of a kinetic system with tumbling modulation along the path. A numerical investigation of this limit is provided in [147]. These works enter into the framework of the PhD of Casimir Emako-Kazianou [6]. 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 [98].

Aggregation equation.
In the mathematical study of collective behavior, an important class of models is given by the aggregation equation. In the presence of a non-smooth interaction potential, solutions of such system 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 [69]. Based on this approach an extension to a model for two species in interaction has been proposed in [54]. The extension to higher dimensions has been studied in [33]. 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 [62, 68].

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 the 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 [93] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [72]. Since more realistic systems are used in the analysis of medical images, we have extended this studies to include active motion of cells in [92], viscosity in [99] and proved regularity results in [153]. The limiting Hele-Shaw free boundary model has been used to describe mathematically the invasion capacity of a tumor by looking for traveling wave solutions, in [97], see also axis 3. Motivated by numerical observations from D. Drasdo using ABMs, the article [79] studies the interfaces between two cell populations described by continous models with different mobilities and recover interface instabilities. 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 [73].

Finally, we mention that part of these results have been presented by Benoît Perthame in a pleanary talk at the 2014 International Congress of Mathematicians [111].

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 tumor growth.
- Imperial College London, joint works with José Carrillo on aggregation equation.
- Universities of Maryland (College Park), UCLA, Univ. of Chicago and Univ. Autonoma de Madrid, Univ. of St-Andrews (Scottland), joint works on mathematics of tumor growth models.

External support

- ANR Blanc Kibord.
- Programme Hubert Curien Xu GuangQi with Shanghai Jiao Tong University.
- Institut Universitaire de France, Benoît Perthame Senior member

Self assessment

The departure of Nicolas Vauchelet after his promotion to full professorship in Paris-Nord will certainly affect the continuation of this research axis.

2.5 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 [49], TRAIL treatment of HeLa cells [16], growth of multicellular spheroids [67], blood detoxification after drug-induced liver damage [103, 59].

This naturally led to increasingly combine methods from various fields: image analysis, statistics, probability, numerical analysis, PDEs, ODEs, agent-based modeling methods, involving inverse methods as well as direct model and model parameter identification in biological and biomedical applications. Model types comprise agent-based simulations for which Mamba is among the leading international groups, and Pharmoco-kinetic (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 [PZ07, DPZ09], 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 [26]. 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) [141]. 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 [46], a work which inspired also very recently other groups in statistics and probability [BW15, Hoa16] and was the basis for Adélaïde Olivier's Ph.D thesis [9, 66, 87] (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 [67] [Jag12] (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 Criterions 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 [164].

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). Following Carola Kruse's post-doc [14], 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 [12], we settled a frame-

work 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 [7], was devoted to the stochastic modelling and analysis of protein aggregation, compared both with the deterministic approach traditionnally developed in Mamba [PBC$^+$12] 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 modeling can inform liver disease pathogenesis. [49]. Liver has a complex micro-architecture ensuring its function (axis 5). Hence many clinical questions require quantitative characterization of micro-architecture in normal liver and during degeneration or regeneration processes which has been performed using the software TiQuant ([57] 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 characterizing 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 parameterized 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 [HBB$^+$10]. 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 unrecognized mechanisms could be identified (axis 5).

Statistical methods decide on subsequently validated mechanism of ammonia detoxification

To identify the mechanisms involved in ammonia detoxification [59], 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.

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

In [110] we developed in close collaboration with University and DKFZ Heidelberg and I. Vignon-Clementel (Inria, Reo) a procedure to estimate tumor heterogeneity and cellularity from Diffusion-Weighted Imaging by calibration with 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 tumor 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 tumor heterogeneity. The

biopsies have to be taken in regions of largely different diffusion values.

Collaborations

- **Philippe Robert**, Inria Rap, for the stochastic process modelling [56]
- **Marc Hoffmann,** Université Paris-Dauphine, for the statistical approach to growth and division processes [46], **M. Escobedo**, Bilbao and **M. Tournus**, Marseille, for the deterministic approach [141]
- **Tom Banks**, North Carolina State University, and **Philippe Moireau,** Inria M3DISIM, for the inverse problem and data assimilation aspects [14, 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

External support

The ERC Starting Grant SKIPPER^{AD} supported and was the guideline for the inverse problem and data assimilation methods developed for growth, aggregation and division processes.

The work on liver and tumor growth was supported by ANR iLite, BMBF MS-DILI, BMBF LiSyM, BMBF LiverSimulator, ANR IFlow, INSERM INVADE (Drasdo, $\sim$ 150kEuro/3yrs) and BMBF VLN (Drasdo $\sim$ 1Mio Euro/5yrs; 2010-2015).

Self assessment

Strengths: collaborations with excellent specialists in probability and statistics, which allow us a deep understanding of the mechanisms studied, and also inspired other researchers; collaborators with internationally recognized well equipped experimental laboratories willing and capable of validating model results and parameter estimated. Projects in France and Germany permitted to combine advantages of research environments and structures in both countries.

Difficulties: data assimilation and stochastic modelling for protein aggregation is very difficult due to the poor quality of the data. Much remains to be done to establish our models on reliable grounds. Generally, multi-level, multi-scale models including molecular, cell, histological, organ and body scale are difficult to validate, and scientific procedures and workflow on experimental and modeling side are time consuming, partially longer than PhD thesis durations.

Future: the field remains relatively new and still needs many developments, especially to generalise our methods to other models like the "incremental" model [TABS$^+$15] (see also axis 5). Continued development of image analysis and modeling software helps to increasingly speed up procedures on the computational side. We will continue our recently chosen path to develop methods, models and tools for toxicology, clinical applications, and biotechnology, progressing beyond biological knowledge alone as an end product.

2.6 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 [5], defended in September 2015, and of articles in 2014 and 2017 [50, 51, 52]. 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 [37], that for us concludes 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 [113, 114, 115, 125, 120, 126]. 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 [35, 36, 76, 77, 80].

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 below). 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 [27, 55].

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 modeling 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 [107, 164].

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 [16, 132].

Radiotherapy

In close cooperation with M. Herrero (U. Complutense, Madrid) we 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 tumor center and lower doses at the tumor periphery should outperform homogeneous irradiation [75]. 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 tumor 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).
- INSERM HTE laureate project MoGlImaging: **François Vallette**, CRCNA and INSERM Nantes

- Adaptive dynamics to model drug resistance: **Alexandre Escargueil** (2 articles in common [36, 80]), **Michèle Sabbah** (2 PhD theses in common) at Annette Larsen's lab, St Antoine hospital, Paris.
  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 Sarclay and Inst. Pasteur (France)

External support

INSERM HTE call: 2 funded projects, MoGlImaging and EcoAML. Inria PRE: 1 funded project. INSERM INVADE (Drasdo), INSERM PHYSCANCER (Drasdo), ANR Sine2Arti (Drasdo) Teresa Teixeira's ANR grant InTelo (2017-2020).

Self-assessment

Drug resistance.
Strengths: Original modelling by PDEs.Collaborations with biological and medical teams following our publications [36, 35].
Weaknesses: Insufficient identification from actual biological measurements (so far) of the models designed and analysed.
Opportunities: Ongoing collaborations with teams working on the biology of cancer with dynamic measurements of the expression of genes (INSERM Nantes, François Vallette). Ongoing collaboration with a team of evolutionary biologists of cancer in Montpellier (CREEC, Frédéric Thomas). Perspectives of applications to therapeutic optimisation in the clinic of cancers.
Threats: Sparse collaborations with teams of biocomputer scientists and statisticians working on cancer may limit the identification of the models designed and analysed. We are working towards establishing cooperations with colleagues at LSTA and LPMA, UPMC.

Telomere shortening
Strengths: an excellent collaboration with an internationally-renowned biological team (Teresa Teixeira and Wei-Feng Xue), convinced of the interest of mathematical modelling.
Difficulties: rare and difficult data acquisition; a relatively new subject, with very few existing mathematical approaches, and a strong need of interaction between probability and estimation methods, partially solved by the collaboration with P. Robert (to join Mamba in Jan. 2018).

2.7 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 spans 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 modeling 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. Works by Schliess [103, 59] 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 (USA) in control, and Susanne 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 [CLD$^+$10], 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 [45, 55, 56], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [7].

In collaboration with Tom Banks first [15, 14] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [12], we proposed new models and mechanisms and most recently we predicted the existence of several coexisting species of protein fibrils [13].

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 absence of vaccine, or of 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 traveling wave. We proposed in [105] a mathematical model to study such phenomena and have simplified it to recover a well-know 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 [163], and [154] 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 [22, 117].

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 [101, 108] 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 [103]. Hyperammoniae 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 [HBB$^+$10]. This model had previously predicted the subsequently validated orientation of dividing hepatocytes along the liver capillaries as order mechanism. It 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 [59] 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 model that include molecular HGF control of cell cycle progression (unpubl.) and ammonia detoxification (Celliere, PhD thesis, 2016; Boissier, PhD thesis, 2017). In these models, the intracellular models were executed in each individual hepatocyte, and transport of molecules with the blood were simulated. Blood flow was modelled by Poiseuille law in the entire capilary network. Further conditions could be identified, under which standard pharmaco-dynamics pharmaco-kinetics (PDPK) models fail to predict the correct dynamics and need to be replaced by spatial temporal models representing organ microarchitecture. The model has further be 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-multiscale 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 metabolizing enzymes in vitro are measured, and micro-architecture is determined [4]. 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 [102], 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 Monod's thesis. Of special interest is the "adder" model [TABS$^+$15], for which we are currently developing new estimation methods.

External support

CAPES/COFECUB project "Modelling innovative control methods for dengue fever" (Bliman); SU-FAPERJ project "Control and Identification for Mathematical Models of Dengue Epidemics"

(2016) (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); ERC Starting Grant SKIPPER^{AD} (Doumic); EU-Notox (Drasdo, 2010-2015), BMBF-Virtual Liver Network (Drasdo, 2010-2015), ANR IFLOW (Drasdo), BMBF LiverSimulator (Drasdo, 2014 - 2017). (Follow ups: ANR-iLite (Drasdo); BMBF-LiSym (Drasdo); BMBF-MS-DILI (Drasdo)).

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); others.
- Wound healing: **Patrizia Bagnerini** (Genova, Numerical methods), **Benoit Ladoux** (Institut Jacques Monod et Mechanobiology Institure Singapore, Biophysics) and **Antonio Jacinto** (CEDOC, Lisbon, Biology and Medicine).

Self assessment

- Strengths:
  Liver: excellent networks with experimentalists and clinicians in follow up projects, clear direction towards clinical and toxicological applications. Persistence through image analysis and modeling software tools.
  Bacterial growth, protein aggregation: expertise on the non-parametric estimation methods we developed, which can be adapted to many situations and are more powerful than the standard methods used by biologists.
  Dengue: Strong connection between modeling and applications which is asserted by the dynamism in developing new collaborations with various applicative teams and entomologists.
  Wound healing : strong collaboration with biophysicists working on in vitro cell monolayers and biologists working on in vivo models in drosophila and zebrafish. The mathematical model turned out to be sufficiently general to be pertinent in a great diversity of biological contexts.
- Weaknesses:
  Liver: A weakness was the spatial separation between experiments and models, which has been removed by moving the German part of the team from University of Leipzig to IfADo.
  Bacterial growth, protein aggregation: transfer to biologists needs to be amplified, e.g. through user-friendly software development, to spread our methods.
  Dengue: data are not always available nor usable because of confidentiality constraints. Due to the geographical dispersion of the participants, it is necessary to have sustainable financing.
  Wound healing: To develop more precise models we need to understand better the details of the mechanisms of acto-myosin cable formation and contraction which is very complex and experimentally delicate to characterize in detail.

2.8 Evolution of research directions during the evaluation period

When we proposed the creation of the Mamba team in 2014, we defined our guidelines as follows:

"The research undertaken in the framework of MAMBA are expected to lead to academic results, accompanied with software development for some of them. The main criterion of assessment for the academic results will be the publications of the original results in highstandard journals of applied mathematics, mathematical biology, physical biology, systems biology, systems medicine and/or biological/medical journals. The organisation of international conferences, international collaborations are also important criteria.

However, the accordance between theoretical results of a mathematical nature and observation of the output of experimental is of course of the utmost importance for us. This concern is managed in our interactive collaborations with our biologist partners, with whom we are careful to undertake projects in which interest of the work led by either side (modellers and experimentalists), as well as its expected results, is clear for both.

These guidelines have been fully followed, as can be assessed by a number of publications in high-level biological as well as mathematical journals.

In 2014, we had defined expected results in four directions, and this research program has been fully fulfilled: cancer modelling (axis 4 above), cell motion (axis 2), protein polymerisation (axis 1, 3 and 4), tissue organization and systems biology of liver (axis 3 and 4).

New subjects have also emerged or have developed beyond our expectancies.

- The theme of drug-induced drug resistance in cancer cell populations, that was beginning, has known interesting achievements in terms of publications, thriving from the *Chisholm et al.* article of 2015 in Cancer Research, that attracted to us requests for collaboration from teams of cancer biologists, and further gave rise to theoretical developments stepping from this article. In parallel, the optimal control theme for anticancer drug delivery (PhD thesis of Camille Pouchol, co-supervised by Emmanuel Trélat) has also been successfully rewarded by a publication in the *J. Maths. Pures Appl.*, to appear in 2017. Drug resistance is a major issue in the clinic of cancers, and the Mamba team is presently working towards setting an international interdisciplinary (mathematics and biology of cancer) working network based on the principle on Darwinian evolution in cancer cell populations.
- The dengue project, involving teams of biologists and mathematicians in France and South America, is very promising. Despite N. Vauchelet's departure, he will continue to develop it in collaboration with Mamba (P.-A. Bliman and B. Perthame).
- New collaborations with biologists have developed, for protein polymerisation with Wei-Feng Xue (Canterbury), for yeast senescence with Teresa Teixeira (IBCP, Paris), for cancer with François Vallette (Inserm, Nantes) and F. Delhommeau (Saint-Antoine Hospital, Paris).
- A need for probabilistic models has also emerged, leading to a close collaborations with Philippe Robert (Inria Rap). Of note, interactions between probability and PDE is a general trend not only of the team but of the mathematical community; the major article [74] is a beautiful illustration.

3 Knowledge dissemination

3.1 Publications

	2014	2015	2016	2017
PhD Theses	1	4	6	2
H.D.R. (*)	1			
Journals	22	26	27	20
Conference proceedings (**)	5	6	4	
Book chapters	1		1	1
Books (written)		1		
Books (edited)				
Patents				
General audience papers	1	1		
Technical reports	1	4	10	11

(*) HDR Habilitation à diriger des Recherches
(**) Conferences with an international program committee

5 major publications (available on the evaluation seminar website):

1. [36], published in Cancer Research (Impact Factor: 9.8).
   This work, co-authored by 5 members of the team and where J. Clairambault is the senior author, was inspired by biological observations showing reversible resistance in an aggressive cancer line, proposes a reaction-advection-diffusion model of a phenotype-structured cell population, able to numerically fit the observed behaviour of the cell population. To our best knowledge it is the first article able to take such observations into account.
2. [46]. This highly cited article (60 google scholar) combines probabilistic, deterministic and statistical methods to estimate the division rate on a growing and dividing population from sampling observations on a piecewise deterministic Markov process (PDMP) underlying the growth-fragmentation equation.
3. [74] This major mathematical article written by B. Perthame in collaboration with P.E. Souganidis (Chicago) and P.L. Lions (Collège de France) analyses scalar conservation laws with stochastic fluxes, following ideas which were first used for Hamilton-Jacobi equations. This also illustrates the growing interaction between PDE and probability, inside Mamba and more generally in the mathematical communities.
4. [101], published in Nature Communications (Impact Factor: 13)
   In this work, where L. Almeida was a co-senior author, a mathematical model helps clarifying the roles of the two main wound closure mechanisms. Moreover, it enables the identification of a universal mechanism explaining how epithelial tissues restore their integrity in a great variety of biological systems.
5. [103], published in the Journal of Hepatology (Impact Factor: 11)
   This article provides the model prediction of the later found chemical reaction in ammonia detoxification [59]. D. Drasdo was co-corresponding author and coordinator of modeling efforts. It also had an editorial.

Other major publications (available on https://team.inria.fr/mamba/publications/):

1. [59], published in the Journal of Hepatology (IF: 13.26). In this article, where D. Drasdo was the senior modeler, a new, in a previous communication [103] predicted ammonia sink mechanism was experimentally identified and validated. Modeling has predicted, and in this paper by statistically testing numerous models verified the mechanism, that provides a new potential therapy option in hyperammonemia. This paper had an editorial.

2. [93]. This paper deals with the incompressible (also called Hele-Shaw) asymptotics for mechanical models of tumor growth and has already a big impact with several subsequent contributions. Co-authored by F. Quirós and J.L. Vázquez (Madrid), it has been the main subject of B. Perthame's plenary talk at the ICM 2014.
3. [102], published in BMC Biology (Impact Factor: 7.5).
   In this highly cited paper (58 google scholar), where M. Doumic is the senior author, all the methodology developed in statistical and deterministic inverse problem - see [46, 26] - is used to answer the seminal question of which mechanism triggers bacterial growth.
4. [108], published in Nature Communications (Impact Factor: 13)
5. [159], accepted in the Journal de Mathématiques Pures et Appliquées
   In this article, we studied the asymptotic behaviour of 2 phenotype-structured PDEs representing a healthy and a cancer cell population density, interacting in a nonlocal Lotka-Volterra way, and then added a two-way control standing for a combined cytotoxic and cytostatic pharmacotherapy.

Due to the broad scientific spectrum of the team, the major journals are many, and consequently the number of publications in each of them relatively small. This shows how the team has an impact in a wide variety of scientific communities. We list the main ones below.

Major journals at the interface between biology and mathematics/informatics:

- Bioinformatics (Impact Factor: 8) **1 article [57]**
- PLoS Computational Biology (Impact Factor: 5). **3 articles [16, 67, 53]**
- Scientific Reports (Impact Factor: 4.8) **1 article [27]**
- PLoS One (Impact Factor: 3.4) **3 articles [75, 42, 13]**

Major journals in the applicative domain:

- Nature Communications (Impact Factor: 13) **2 articles [108, 101]**
- Hepatology (Impact Factor: 13.2) **1 article [103]**
- Journal of Hepatology (Impact Factor: 12.5) **2 articles [59, 49]**
- Cancer Research (Impact Factor: 9.8) **1 article [36]**
- Annals of Surgery (Impact Factor: 9.4, 1st journal in surgery) **1 article [28]**
- BMC Biology (Impact Factor: 7.5) **1 article [102]**
- Journal of Pathology (Impact Factor: 6.8) **1 article [86]**
- Archives of Toxicology (Impact Factor: 5.9) **2 articles [63, 48]**

Major journals in mathematics applied to biology:

- Journal of Theoretical Biology (Impact Factor: 2.2) **5 articles [55, 52, 12, 77, 31]**
- Journal of Mathematical Biology (Impact Factor: 1.9) **3 articles [21, 15, 98]**

Major journals in mathematics and applied mathematics:

- Mathematical Models and Methods in Applied Sciences (IF: 2.9) **4 articles [91, 88, 97, 34]**
- Archive for Rational Mechanics and Analysis (Impact Factor: 2.8) **2 articles [93, 81]**
- Journal of Differential Equations (Impact Factor: 2.2) **1 article [33]**
- Nonlinear Analysis: Real World Applications (Impact Factor: 2.2) **1 article [64]**
- Philosoph. Trans. of the Royal Society of London Series A (IF: 2.2) **1 article [99]**
- Inverse Problems (Impact Factor: 1.9) **1 article [26]**
- Journal de Mathématiques Pures et Appliquées (Impact Factor: 1.9) **2 articles [84, 159]**
- SIAM Appl. Math (Impact Factor: 1.9) **3 articles [45, 105, 29]**
- SIAM Num. Anal. (Impact Factor: 2.5) **2 articles [58, 68]**
- Comm. PDE (Impact Factor: 1.8) **1 article [65]**

3.2 Software

TiQuant We developed a novel software for tissue image analysis (**Ti**ssue **Quant**ifier) and simulation (**Ti**ssue **Sim**ulator). TiQuant [63, 57] is implemented in portable object-oriented JSO C++. The GUI is based on QT and supports real-time visualization 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.

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 signaling, 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 synthezised 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 organized a workshop on benchmarking and comparing agent-based models and tools (workshop Leipzig, volet 5).

Curr. stat: TiQuant/TiSim (ambition): A-4/3(5), SO-4/4, SM-3/3, EM-2/2(3), SDL-1/1(2up), OC-TPM; (2/4, concepts, models)).

- Audience: A-3 (ambitious software, usable by people outside the team). A-4 (large audience, used by people outside the team). A-5 (wide audience, large user's community).
- Software originality: SO-4 (original software implementing a fair number of original ideas).
- Software maturity: SM-3 (well-developed software, good documentation, reasonable software engineering).
- Evolution and maintenance: EM-2 (basic maintenance to keep the software alive).
- Software distribution and licensing: SDL-1 (none). SDL-2 (privately distributed within the close community).

TiQuant and TiSim have the ambition to become community tools equally used and extended by modellers and developers, as by users from biology / medicine.

3.3 Technology transfer and socio-economic impact

The socio-economic impact of our work and its transfer to medical doctors or biologists can be related to the number of papers written in medicine and biology journals, many of them clearly having a therapeutic ultimate aim [59, 49, 103, 60, 61, 156, 86].

It would be false however to say that our work is meant as directly usable by MDs. Our main contributions are to help them to decipher new mechanisms, understand or discover new reactions, thus guiding toward possible new therapies. Illustrations may be found in several places in axis 4 and 5, see e.g. [86, 67, 36, 103, 59].

3.4 Teaching

We indicate here only the courses given by scientific staff members who do not have a teaching position. Nicolas Vauchelet and Benoît Perthame give courses in UPMC.

Luis Ameida is in charge of the Major MathBio of the speciality "Mathematics of modelling", M2 level, UPMC.
Nicolas Vauchelet gave a course "An Introduction to mathematical modeling of biophysical phenomena" at IMPA, Rio de Janeiro, **30h/yr** in 2014, 2015 and 2016.

- *Luis Almeida*
  2017: Tissue growth (with Delphine Salort, IBPS). UPMC M2 course, Paris **20 h**
  2016: Reaction-Diffusion Equations Arising in the Mathematical Modelling of Population Dynamics (with Tommaso Lorenzi). International M1 course, Verona **24 h**
  and Tissue growth (with Benoît Perthame). UPMC M2 course, Paris **20 h**
  2015: Mathematical models of biology (with Tommaso Lorenzi). International M1 course, Verona **24 h**
  2014: Mathematical models of tumor growth. International M1 course, Verona **15 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**
  2016: Analysis, Graduate cycle, School of Applied Mathematics, Fundação Getulio Vargas, Rio de Janeiro, Brazil **60 h**
  and Introduction to Control theory, Graduate cycle, School of Applied Mathematics, Fundação Getulio Vargas, Rio de Janeiro, Brazil **60 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**
  2016: Winter school, Shanghai Jiaotong University (China), December 2016 **4 h**
  and International course on stem cells, UPMC, September 2016 **2 h**
  and Mathbio summer school, Santiago (Cuba), June 2016 **4 h 30**
  and BIOMAT Summer school, Granada (Spain), June 2016 **3 h**
  and Mathbio Winter school, Bedlewo (Poland), January 2016 **2 h**
  2015: Courses, University of Tlemcen (Algeria), April 2015 **3 h**
  and Fall courses, U. Federal Fluminense, Niteroi, Rio de Janeiro, February 2015 **3 h**
  2014: Winter school BIOMAT, La Falda (Córdoba, Argentina), August 2014 **3 h**
  and M2 Pharmacology, Rennes (remote from Villejuif) **4 h**
  and DESC Oncology, UPMC (J.-P. Lotz, Tenon Hospital, Paris), February 2014 **2 h**
  and Beginning-of-year "fitness" courses in biological mathematics, M2 UPMC (at Laboratoire Jacques-Louis Lions), September 2014 **6 h**
- *Marie Doumic*
  2014 to 2017: Direct and inverse problems in population dynamics (with P. Moireau, Inria M3DISIM). UPMC M2 course, Paris **24 h / yr**
  2016: CIMPA school, Mauritius, **4,5 h**
  and BIOMAT Summer school, Granada (Spain), **4 h 30**
  2014: PDE-Proba, Institut Henri Poincaré, **2 h**
- *Dirk Drasdo*

2012 to 2017:: Agent-based models of tissue organization, UPMC M2 course, Paris **24 h / yr**
2017: University of Rome: Tutorial, 2h: TiSim: A modeling tool for multicellular simulations.

3.5 General audience actions

- *Pierre-Alexandre Bliman* was a keynote speaker at the International conference on Digital Sciences and Technologies for Health, Paris, France.
- *Jean Clairambault:* Articles [38, 39]; conference "Science and Society", Nancy, October 2015
- *Marie Doumic:* Conference "Science and Society" Nancy, May 2016; participation to the video for the launching of the H2020 program by the french government; participation to the event (conference, interview and video) "10 years of the ERC, 50 years of Inria"
- *Dirk Drasdo:* article on liver regeneration modeling in "Physik Journal (11/2013) (Picture on cover page); Interview on modeling drug toxicity by ACM, Nov. 2013; Interview on modeling liver regeneration & toxicity by journalist for "Cite de Science"; Interview for German ministry of research report for politicians (not scientific report) (2015/2016).
- *Nicolas Vauchelet:* 2 talks in highschools about mathematics applied to biology

3.6 Visibility

Organisation of workshops and Conferences

- **2018** *(already announced and financed workshops)*:
  January 22-24 Transport phenomena in mathematical biology, Banach Center, Warsaw, Poland (Piotr Gwiazda, Pierre-Emmanuel Jabin, Benoit Perthame, Agnieszka Swierczewska-Gwiazda)
  January 31-February 2: CMM-Fields-INRIA workshop on "Mathematics for Medicine", Fields institute, Toronto, Canada (Jean Clairambault, Jean-Frédéric Gerbeau, Huaxiong Huang, Benoît Perthame and Sivabal Sivaloganathan);
  July 9-13: Workshop on "Mathematical Perspectives in the Biology and Therapeutics of Cancer", CIRM, Luminy, France (Guillemette Chapuisat, Jean Clairambault, Florence Hubert, Urszula Ledzewicz and Vitaly Volpert);
  November 25-30: Workshop on "Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy", Casa Matemática Oaxaca (CMO-BIRS), Oaxaca, Mexico (Tomás Alarcón, Jean Clairambault and Thomas Hillen).
- **2017**
  March 23-24: Workshop on "Coagulation and Fragmentation Equations", Wolfgang Pauli Institute, Vienna, Austria (Marie Doumic and Christian Schmeiser)
  March 27-29: Current Topics in Kinetic Theory, Banach Center, Warsaw, Poland (José Carrillo, Piotr Gwiazda, Benoît Perthame and Agnieszka Świerczewska-Gwiazda)
  May 10-12: Workshop on "Cross-diffusion systems and kinetic equations for biology", Wolfgang Pauli Institute, Vienna, Austria (Ayman Moussa, Ansgar Jüngel, Marie Doumic, Christian Schmeiser)
  June 6-9: Workshop on "Protein aggregation: Biophysics and Mathematics", Wolfgang Pauli Institute, Vienna, Austria (Marie Doumic, Human Rezaei, Christian Schmeiser, W-F. Xue)
  July 28-29: Workshop on "Mathematical Methods in Biology and Medecine", Wolfgang Pauli Institute, Vienna, Austria (Walter Berger, Marie Doumic, Doron Levy, Anna Obenauf, Christian Schmeiser)

October 10-15: 2nd workshop of the STIC AmSud project MOSTICAW, Porquerolles, France (Pierre-Alexandre Bliman)

November 26-December 1 Minisymposium "New control methods for dengue and other related arboviruses" in the framework of the International Conference on Applied Mathematics and Informatics (ICAMI), San Andres, Colombia

- **2016**:

  January 11-14: Conference on Mathematical Modeling and Control of Communicable Diseases, Fundaçã o Getulio Vargas, Rio de Janeiro, Brazil (Pierre-Alexandre Bliman, Benoît Perthame)

  March 14-16: International Workshop on agent-based models, tools and markup languages, Leipzig ("Towards a unified framework for benchmarking multi-cellular models and modeling /simulation software", co-coords.: S. Hoehme, T. Johann, M. Loeffler, R. Gebhardt). *All top groups on agent-based modeling incl. USA were represented. Funded from VLN grant.*

  June 5-10: Minisymposium on "Multiscale & Multilevel modeling in detoxifying organs and organs of the digestive tract ", European Congress on Computational Methods in Applied Sciences and Engineering (ECCOMAS) (Dirk Drasdo, Irène Vignon-Clémentel)

  July 1-2: Workshop on "Models in Cancer Therapy", Wolfgang Pauli Institute, Vienna, Austria (Walter Berger, Marie Doumic, Doron Levy, Norbert Mauser, Christian Schmeiser)

  July 11-15: 2 Mini-symposia on the ECMTB conference, Nottingham, England:
  MS-12-AM-04 on heterogeneity, evolution and drug resistance in cancer (Jean Clairambault and Angela Oliveira Pisco),
  MS-13-AM-01 on asymptotic behaviour and inverse problem for discrete and continuous population dynamics (Luis Almeida and Marie Doumic)

  October 5-9: 1st workshop of the STIC AmSud project MOSTICAW, Asunción, Paraguay (Pierre-Alexandre Bliman)

- **2015**

  March 16-18 : ANR International Workshop on hybrid and multiscale modelling in cell and cell population biology, Paris, France (Jean Clairambault and Vitaly Volpert)

  June 1-8: "Mathematical modeling and new methods for dengue control" meeting in Rio de Janeiro (Brazil), (Luis Almeida)

  June 8-12: Minisymposium on "Coagulation/Fragmentation : stochastic and deterministic approaches" (M. Tournus)

  June: Mathematical modeling and control in epidemic spread, Laboratoire Jacques-Louis Lions, June 2015 (Luis Almeida, Benoît Perthame, Nicolas Vauchelet).

  September 23-29 : Session focused on heterogeneity in cell populations in the ICNAAM conference, Rhodes, Greece (Jean Clairambault)

- **2014**

  July: LJLL/Shanghai meeting, Laboratoire Jacques-Louis Lions (Benoît Perthame, Nicolas Vauchelet).

Selected invitations as plenary or keynote speaker

We choose here to select drastically the most prestigious among the numerous invitations. Most importantly, not only for Mamba but for our whole community, Benoit Perthame was a plenary speaker at the International Congress of Mathematicians ICM 2014 in Seoul. This was the first time that a mathematician working in mathematics applied to biology was invited at ICM.

- **June 2015:** Dirk Drasdo was a plenary speaker at the congress Cyto2015 (congress of the international society for advancement of Cytometry), Glasgow, United Kingdom.
- **August 2014:** Benoit Perthame was plenary speaker at the international congress of mathematicians, ICM 2014, Seoul.

- **June 2014:** Marie Doumic was a plenary speaker at the ECMTB (European Conference of Mathematical and Theoretical Biology), Gothenburg, Sweden.

Other invitations may be found, on a yearly basis, on our annual reports, e/g.
http://raweb.inria.fr/rapportsactivite/RA2016/mamba/uid142.html
http://raweb.inria.fr/rapportsactivite/RA2015/mamba/uid113.html
http://raweb.inria.fr/rapportsactivite/RA2014/mamba/uid118.html

3.6.1 Editorial activities, scientific boards, research administration

L. Almeida is member of the bureau of CID 51 of the Comité National de la Recherche Scientifique.

P.-A. Bliman is member of the Scientific committee of the ANR program "Environnement, pathogènes et maladies émergentes ou ré-émergentes - One health", and was member of the Conference Editorial Board of European Control Association (EUCA), actuating for 15th European Control Conference, Aalborg, Denmark, June-July 2016.

J. Clairambault is member of the expert group of ITMO Cancer, representative of Inria (since 2008), and M. Doumic of the expert group of ITMO BMSV, representative of Inria (since 2014).

D. Drasdo is head of a research team until 6/2017 co-localized at Interdisciplinary Center for Bioinformatics, Univ. Leipzig; since 7/2017 co-localized 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 was guest editor for PloS Comput. Biol. (2016), CaSyM expert committee for EU Horizon 2020 and member of the program committee for GCG2012 and SBMC 2016.

B. Perthame is Chief Editor of Acta Applicandae Mathematicae (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.

4 Funding

National initiatives

ANR 2011-2015 Bimod.

ANR Blanc 2014-2018 "Kibord", 221 k€.

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.

ANR IFLOW 2014–2017, $\sim$ 100kEuro / 3yrs.

Prediction of modifications of architecture, flow, transport and function of liver after partial hepatectomy; model animal: mouse, pig.

PI: Eric Vibert (Hopital Paul Brousse, DHU Hepatinov), partners: I Vigon-Clementel (Inria, REO), J. Hengstler, IfADo, Companies Fluoptics, MID.

ANR iLite 2017–2021 (Innovations for Liver Tissue Engineering): $\sim$ 550 k€/ 5yrs

Modeling accompanied and guided liver tissue engineering with the objective to engineer liver replacement tissue or devices that can be implanted into patients requiring liver transplantation. PI: Jean-Charles Duclos-Vallee, Hopital Paul Brousse, numerious companies in France. (Co-PI of modeling work package: D. Drasdo).

ANR InTelo 2016-219, 431.574 €.

Yeast senescence and telomere shortening. PI: Teresa Teixeira (IBCP). Inria: M. Doumic.

INCA PCNSL, 2017, 75k€.

Mathematical modelling treatment of primary central nervous system lymphomas at micro- and macro level (PCNSL). PI: Group Hoang-Xuan Khê (Neurology, Univ. Hospital La Pitié Salpêtrière), Colin (Inria Bordeaux), Soussain (Inst. Curie).

INSERM 2014 - 2016, INVADE. A model for a better understanding of breast cancer invasion. PI: Emmanuel Barillot, Institut Curie. Partners: Groups from Institut Curie, Dirk Drasdo.

ITMO Cancer EcoAML 2016-2020, 137 961 €for LCQB-LJLL, and 750 k€for the whole project. Early leukaemogenesis in Acute Myelogenous Leukaemia (AML), headed by François Delhommeau (CDR St Antoine, Paris), with whom we have a long-lasting collaboration. Two other teams:Thierry Jaffredo, IBPS, Paris and Fawzia Louache, IGR, Villejuif..

ITMO Cancer MoGlImaging 2016-2020, $\sim$ 1.2 M€in total, 95k€for our team
subject: treatment-induced treatment resistance and heterogeneity in glioblastoma, headed by Elizabeth Moyal (INSERM, Toulouse). 8 teams, including O. Saut (Inria Monc) and F. Vallette, INSERM, Nantes.

Peps PTI CNRS in 2012 in collaboration with Institut Curie in Paris : "Concentration waves of bacteria". Headed by Nicolas Vauchelet.

European projects

NOTOX, January 2011 - December 2015 (Inria partner: Dirk Drasdo), $\sim$ 790k€for Inria
Predicting long-term toxic effects using computer models based on systems characterization of organ-otypic cultures. Toxic effect of drugs on multi-cellular assemblies in the bioreactor. (this program was 50% financed by cosmetic industry)
Webpage: http://notox-sb.eu/fp7-cosmetics-europe/
Partners: DKFZ (German Cancer Center), Department for Systemsbiology (Germany), University Hospital of Heidelberg, Pathology (Germany), Leibniz Center, IfADo (Germany), University of Leipzig, Interdisciplinary center for bioinformatics (Germany)

LungSysII (2012-2016) (Inria partner: Dirk Drasdo), 180k€/3 yrs
German Bundesministerium für Bildung und Forschung (BMBF) initiative. The project coordinator is Ursula Klingmueller, German Cancer Research Centre (DKFZ), Heidelberg (http://www.lungsys.de/lungsys2/mission.php)

SKIPPER^{AD}, ERC Starting Grant (2012-2017)
Subject: mathematical analysis, inverse problem and data assimilation methods, and confrontation to experimental data for protein polymerization models.
Principal Investigator: M. Doumic. Total amount: 1.2M€. Partner: H. Rezaei's team (INRA, Jouy-en-Josas).

BMBF Lebersimulator, 2014–2017, 263kEuro / 3yrs
Software tool to simulate regeneration in liver. Integration of our models of liver regeneration, multiscale, into a software (TiSim) to make it available. Planned: 2017, we hold already a tutorial (section 3.4). Partners: Hengstler, IfADo, Dortmund.

BMBF: LiSyM, 2016–2020, $\sim$ 1 M€/ 5yrs
Liver Systems Medicine. Focus on fibrosis development and acute on chronic liver disease. D. Drasdo: modeling coordinator & co-coordinator (w. Klingmueller, DKFZ, HB, Lammert, Univ. Clinics Homburg) in one of 3 subprojects. About 20 partners. Our main collaborators: Hengstler, Ghallab, Vartikat (IfADo), Dooley (Univ. Hosp. Mannheim).

BMBF MS-DILI: 2016–2019, 229 k€/ 3yrs
Multiscale Modeling of drug-induced liver injury, focus on acetaminophen (paracetamol). main coordinator: Klingmueller (German Cancer Center (DKFZ), Heidelberg (HB)), project modeling coordinator: Dirk Drasdo, partners: Timmer (Univ Freiburg), Hengstler (IfADo), Dooley, Hepatology (Univ. Mannheim), Schirmacher (Pathology, Univ. HB), Grabe (Univ. HB), Mueller (HITS HB), Apic (Cambridge Cell Networks Ltd.).

Associated teams and other international projects

Programme Hubert Curien "PDE models for cell self-organization in biology", $\sim$ 10k€
Xu GuangQi with Shanghai Jiao Tong University, China. French part headed by Nicolas Vauchelet. Chinese part headed by Min Tang.

Project SU/FAPERJ in 2015-2016: "Control and identication for mathematical models of dengue epidemics". In collaboration with IMPA and FGV in Rio de Janeiro. French part headed by Benoît Perthame. Brazilian part headed by Jorge Zubelli.

CAPES-COFECUB
Modelling innovative control methods for dengue fever
Brazilian part headed by Claudio Struchiner
French part headed by Benoît Perthame

MOSTICAW , 2016-2017, STIC AmSud project
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, Universidad Tecnica Federico Santa Maria (Chile) - Pablo Aguirre, EMAp (Brazil) - Pierre-Alexandre Bliman, CIRAD (France) - Yves Dumont

ECOS-NORD project "New methods for the control of epidemics of dengue and arboviroses"
coordinator: Pierre-Alexandre Bliman.
Duration 2017-2019.
Partner: Universidad del Valle, Cali, Colombia.

PICS St-Andrews, Royaume-Uni (L. Almeida)

Euro-Med 3+3 'Mathematical Models and Methods in Cell Dynamics' (J. Clairambault)

DarEvCan, Darwinian evolution of Cancer, 8 teams (Inria: B. Perthame)

5 Follow up to the previous evaluation

During the previous evaluation, a general recommendation done by the panel was to intensify the links between the Inria teams. We followed this suggestion in several ways: common workshop organisations (e.g. in 2018 Reo and Mamba organize a conference with the Fields Institute, and with Dracula in the CIRM), common participation in national and international projects or networks (most notably the ITMO Cancer project MoGlImaging with Monc), or collaboration (D. Drasdo and Irène Vignon-Clémentel in REO [110], M. Doumic and Philippe Moireau in M3DISIM [12], D. Drasdo and G. Batt in Lifeware [16], M. Doumic and Philippe Robert in RAP [56], J. Clairambault with Thomas Lepoutre and Vitaly Volpert in Dracula [19, 23]).

Concerning specifically MAMBA, the evaluators had done three recommendations:

1. *to establish at least one more full time position in this area to strengthen the team and provide adequate resources to build on the obvious strengths*
   This will be finally done in october 2017, by the recruitement of Diane Peurichard. Her expertise falls in the very heart of Mamba, and by her previous work both on individual-based models and on PDE she will be able to collaborate with all the team members. However, this solves only partially the under-staffing problem, since Jean Clairambault will leave in 2018, and Nicolas Vauchelet left the team in 2016. Specifically, the liver project continues to need to recruit.
2. *We have noticed that several INRIA groups work on cancer modeling. We recommend a focused conference or workshop to bring these groups together and to invite international*

guests as participants.
A collaboration between Inria teams Mamba (J. Clairambault) and Disco (Catherine Bonnet) on haemato-poiesis modelling and therapeutic optimisation for AML exists, in particular resulting in PhD thesis supervisions (José Luis Avila Alonso, Walid Djema) and common conference proceedings. The recently emerged INRIA project CAGE is a partner of collaboration for Mamba (J. Clairambault and Emmanuel Trélat co-supervising Camille Pouchol's ongoing PhD thesis). Teams Monc and Mamba are associated within the MoGlImaging HTE ITMO Cancer program. Teams Reo (J.-F. Gerbeau) and Mamba (J. Clairambault, B. Perthame) are associated in the co-organisation of a joint Inria-CMM-Fields Institute workshop on mathematical medicine at the Fields Institute, Toronto, in Jan-Feb 2018, in which Monc will also participate. Team Dracula has been involved with Mamba in an ANR project that was concluded by an international workshop in March 2015 in Paris.

3. *The virtual liver project has an astonishing potential for rapid growth with proper support, which includes staffing and an investment in high performance computational hardware.*
The Evaluation Committee has highlighted the liver projects and the link to the University of Leipzig, which permitted execution of the large-scale liver projects. Consequently, Dirk Drasdo has maintained his association with Univ. Leipzig until June 2017. In 2017 he settled all his German grant projects at IfADo (Dortmund) to improve and permit at-site interactions with his main experimental collaborator J. Hengstler. This part of the group has now four members. His former scientific associate S. Hoehme started to establish end of 2015 his own research group (the first prestigious Emmy Noether group at Univ. Leipzig).
The evaluation committee had recommended support by an additional permanent scientist of liver research. This has unfortunately not yet been possible and a new junior research position to work fully in the liver projects with expertise in agent-based modeling would still be more than ever highly wished by Mamba.

6 Objectives for the next four years

We shall keep our double general objective of cutting-edge mathematical research together with strong collaborations with biologists, whose questions guide all our research activities. These diverse collaborations also explain why the scientific goals may appear very broad: our main purpose is to develop our research questions across disciplines and methodological borders, even in cases where this may require to move into domains dominated by other scientific sub-communities.

Discrete agent-based models and continuous (by partial differential equations) models, either in parallel or, when possible, from the former to the latter by averaging among agents, will be concurrently used to represent, predict and control biological phenomena. Interactive physiologically based model design in collaboration with biologists partners and, as much as possible, experimental validation of the models will be pursued and intensified.

Staff evolution and link with our objectives

To present our main objectives in a condensed way - they have already been fully detailed for each of the five axes in the paragraphs entitled "Scientific achievements" (Sections 2.3 to 2.7) - we here detail the changes in the staff, which are closely related both to the new directions we want to impulse and, less fortunately, to the directions which might be under thread.

- **Pierre-Alexandre Bliman**, formerly control scientist in the team SISYPHE, joined MAMBA in 2016 after thematic mobility towards mathematical epidemiology. He will especially participate to the research on vector-borne diseases (including aspects related to Darwinian evolution and optimal control).

- **Diane Peurichard** has just been hired as Inria CR2, beginning on November 1st, 2017. Her skills in both PDE and agent-based modelling, together with exploiting biological data from experimentalists partners, will undoubtebly strengthen the team and reinforce the interaction between all Mamba team members. She will also bring new collaborations, in particular with the university of Vienna. The collaboration with Christian Schmeiser's group from the university of Vienna has indeed already begun during M. Doumic's sabbatical stay (a co-supervision of a Ph.D student, Julia Delacour, on the modelling of autophagy, begins in September 2017); Diane Peurichard's arrival is an excellent opportunity to intensify it, maybe through an Inria "associated team".
- **Nicolas Vauchelet**, now full professor at Paris XIII University, will continue to work in close collaboration with Mamba team members, in particular supervising Martin Strugarek's ongoing PhD thesis. The dengue project will thus continue, with the continuing implication of P.A. Bliman and B. Perthame.
- **Jean Clairambault**, whose retirement is planned in 2018, is willing to continue with Mamba as emeritus Inria DR1. He will coordinate an interdisciplinary European COST project on drug resistance in cancer (submission planned in April 2018), and to organise international events focused on interdisciplinary research on cancer (3 funded in 2018). He will also supervise Cécile Carrère who has been hired as *Math'Innov* postdoc, beginning on September 1st, 2017, to work in Mamba on *tumour bet hedging*, that appears to be a major evolutionary mode of drug resistance in cancer, using the theoretical framework of phenotype-structured shape optimisation (in collaboration with Grégoire Nadin at LJLL). Diane Peurichard will also be involved in the continuation of the ITMO Cancer projects, together with L. Almeida and M. Doumic.
- **Philippe Robert**, from the Inria team RAP, is also to join the team before 2018. This will allow us to intensify the "merging of competences" between stochastic and deterministic views, since he will bring to Mamba is expertise in stochastic processes (and the collaboration has already begun, with the co-supervision of S. Eugène's Ph.D [7]).

To tighten the link to IfADo (Dortmund), were a significant part of grant money pays currently 2 postdocs (Zaza, Zhao), the research engineer and program administrator of TiSim, Tim Johann, and a PhD student (Noemie Boissier), and to facilitate traveling between IfADo and INRIA, an associate team would be of great help. At time, Boissier and Zhao paid by IfADo work at INRIA. This associate team could also be linked with the Wolfgang Pauli Institute in Vienna, already evoked.

Some specific objectives

The main application directions will continue to develop and evolve, as detailed in the "Scientific achievement" section: liver modelling, cancer modelling, protein polymerization, wound healing.

Liver modelling

- A major objective for the next four years are to carry the modeling (1) into the clinical environment, (2) into evaluation pipelines of drug or food toxins, and (3) into biotechnology. For (1) this includes generation and assessing of clinical hypotheses, assistance in decision making both for diagnostics and therapy, for (2) establishment of integrated spatial-temporal PB-PDPK models bridging between in vitro experiments and in vivo toxicity, for (3) model-guided planning of optimal experimental design. A focus will be on liver-related projects, but the choice of projects will also follow raised funding.
- The tissue analysis and simulation tools TiQuant and TiSim should be established within the community of modelers and of biologists, biotechnologists and clinicians as standard tools.

- The relation between macro-scale information such as obtained by non-invasive imaging modalities and biomarkers with histology, and of models at macro and micro scales should be studied.

Protein polymerisation project

The ERC SKIPPER^{AD} has been the main guideline both to methodological and to application aspects around nucleation, growth and fragmentation models. This project coming to an end shortly, the research directions have now evolved.

In collaboration with Christian Schmeiser (who co-supervises J. Delacour's Ph.D), polymerisation occuring in autophagosome formation is a new application domain, which opens also new mathematical questions, such as the aggregation of two different species - this also rejoining the most recent conclusions of studies done with H. Rezaei [13], and continued with M. Mézache's Ph.D thesis.

The estimation of the division rate in the growth-fragmentation equation having been successfully applied to bacterial growth can now be extend to new applications: molecule tracking in life cells (work in progress with H. Berry, Inria Beagle), yeast senescence (with Teresa Teixeira and Zhou Xu), the "incremental model" (Hugo Martin's Ph.D thesis), and can go up to a software development.

Mechanical models of tissue growth and cancer So far, the mathematical theory is limited to very elementary models and, in consequence, the numerical methods are also poorly validated in theoretical terms. A target will be to better understand systems of equations where interactions (non competitive, non cooperative) needs new methodologies because comparison principles do not hold. These are the cases of interest when considering nutrients, types of cells with different motilities and many other classical models used in the field.

Dengue fever control Work on several aspects of the control of dengue fever and other arboviruses will go on, with a focus on questions related to the releases of Wolbachia infected mosquitoes. The practical implementation of the release yields interesting questions. On the one hand, questions of optimal control (minimizing the total number of released mosquitoes) and of optimal spatial location of the releases are quite important in practice. This question, that concerns cost and efficiency of the method, is more complex than it looks, with the possibility of releasing a prescribed proportion of male and female mosquitoes, or to release in parallel sterile insects, or finally of use of different strains of Wolbachia (superinfection). On the other hand, the issue of resistance to insecticides recently gained importance, with the finding that the vulnerability to insecticide of the released mosquitoes constitutes a supplementary disadvantage in urban environments where the local mosquitoes have became resistant.

Evolution models for cancer cell populations Modelling phenotype evolution in cancer cell populations, using physiologically structured PDEs and their control by anti-cancer drugs will be continued, in particular with the help of optimal control methods. Shape optimisation is one of the new tracks that will be followed to represent resistance phenotype bet hedging in cancer cell populations and therapeutic ways to overcome it by combinations of drugs. The representation by physiologically structured cell population dynamic models of the interactions (in particular mutualistic) between a tumour and its surrounding stroma, with possible applications in therapeutic control, is one of the objectives that will be pursued within the HTE interdisciplinary consortium to which we belong through two collaborative projects. Modelling the immune response in cancer and how to boost it, keeping it under control, is a more distant - nevertheless highly challenging and timely - objective that we will favour in collaboration with cancer immunologists and therapists.

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