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Activity Report 2016

Project-Team MAMBA

Modelling and Analysis for Medical and Biological Applications

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

RESEARCH CENTER
Paris

THEME
Modeling and Control for Life Sciences

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

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2. Overall Objectives

2.1. Overall objectives

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

Problems from life sciences (cell motion, early embryonic development, tissue growth and regeneration, cancer modelling, pharmacology,...) have been considered, and still constitute the core of MAMBA. Models for complex fluid flows (shallow water models, flows with a free surface) were studied until December 2012, when the scientists in charge of the "Géophysique" part left BANG to constitute the new Inria team ANGE (https://team.inria.fr/ange/), while the remaining ("Biophysique") part of the BANG team continue their research work within the new Inria team MAMBA, now headed by Marie Doumic.

The dynamics of complex physical or biophysical phenomena involving many agents, including proteins or cells - seen as *active* agents - can be represented efficiently either by explicitly considering the behaviour of each particle individually (e.g. through branching trees and piecewise deterministic Markov processes, or stochastic differential equations) or by Partial Differential Equations (PDEs) which, under certain hypotheses, represent local averages over a sufficiently large number of agents.

Biology and medicine currently face the difficulty to make sense out of data newly available by means of recent signal acquisition methods. Modelling through agent-based or continuous models is a unique way to explain (i.e., model) the observations and then compute, control and predict. These are the goals of MAMBA.

3. Research Program

3.1. Introduction

At small spatial scales, or at spatial scales of individual matter components, where heterogeneities in the medium occur, agent-based models are developed ([1], [76], Dirk Drasdo's former associate team QUANTISS). Another approach, that is considered in the project-team MAMBA consists in considering gene expression at the individual level by stochastic processes [2], by ordinary differential equations [3], or by a mixed representation of Markov processes and ordinary differential equations [4], the outputs of which quantify focused aspects of biological variability in a population of individuals (cells) under study.

Both these approaches complement the partial differential equation models considered on scales at which averages over the individual components behave sufficiently smoothly. Investigating the links between these models through scales is also part of our research [5]. Moreover, in order to quantitatively assess the adequacy between the biological phenomena we study and the mathematical models we use, we also develop inverse problem methods.

[1] Drasdo, Hoehme, Block, *J. Stat. Phys.*, 2007
[2] as in M. Sturrock et al., spatial stochastic modelling of the Hes1 gene regulatory network: intrinsic noise can explain heterogeneity in embryonic stem cell differentiation, *Journal of The Royal Society Interface*, 2013
[3] as in A. Friedman et al, Asymptotic limit in a cell differentiation model with consideration of transcription, *J. Diff. Eq.*, 2012
[4] as in R. Yvinec et al., Adiabatic reduction of stochastic gene expression with jump Markov processes, *J. Math. Biol.*, 2013.
[5] H. Byrne and D. Drasdo, Individual-based and continuum models of growing cell populations: a comparison, *J. Math. Biol*, 2009

3.2. PDE analysis and simulation

PDEs arise at several levels of our models. Parabolic equations [6] can be used for large cell populations and also for intracellular spatio-temporal dynamics of proteins and their messenger RNAs in gene regulatory networks, transport equations [7] are used for protein aggregation / fragmentation models and for the cell division cycle in age-structured models of proliferating cell populations. Existence, uniqueness and asymptotic behaviour of solutions have been studied [65], [62]. Other equations, of the integro-differential type, dedicated to describing the Darwinian evolution of a cell population according to a phenotypic trait, allowing exchanges with the environment, genetic mutations and reversible epigenetic modifications, are also used [81], [80], [79], [82], possibly enriched to classical PDEs by the adjunction of diffusion and advection terms [63]. Through multiscale analysis, they can be related to stochastic and free boundary models used in cancer modelling.

3.3. Inverse problems

When studying biological populations (usually cells or big molecules) using PDE models, identification of the functions and parameters that govern the dynamics of a model may be achieved to a certain extent by statistics performed on individuals to reconstruct the probability distribution of their relevant characteristics in the population they constitute, but quantitative observations at the individual level (e.g., fluorescence in single cells [60] or size/age tracking [87]) require sophisticated techniques and are most often difficult to obtain. Relying on the accuracy of a PDE model to describe the population dynamics, inverse problem methods offer a tractable alternative in model identification, and they are presently an active theme of research in MAMBA. Following previous studies [68], [69], some combining statistical and deterministic approaches [67] with application to raw experimental data [66], we plan to develop our methods to new structured-population models (or stochastic fragmentation processes as in [66]), useful for other types of data or populations (e.g. size/age tracking, polymer length distribution, fluorescence in single cells).

3.4. Stochastic and agent-based models

The link between stochastic processes and kinetic equations is a domain already present in our research [8] [67] and that we plan to develop further. They can be viewed either as complementary approaches, useful to take into account different scales (smaller scales for stochastic models, larger scales for mean-field limits), or even as two different viewpoints on the same problem [66], enriching each other. Neuroscience is a domain where this is particularly true because noise contributes significantly to the activity of neurons; this is the case of networks where mean field limits are derived from stochastic individual-based models and lead to fundamental questions on the well-posedness and behaviours of the system [9]. One strength and originality of our project is our close connection and collaboration not only with probability theorists but also with statisticians, who provide us with efficient help in the identification of our model parameters.

Agent-based systems consider each component individually. For example, in multi-cellular system modelling, the basic unit is the cell, and each cell is considered [70], [89]. This approach has advantages if the population of cells reveals heterogeneities on small spatial scales as it occurs if organ architecture is represented [76], or if the number of cells in a particular state is small. Different approaches have been used to model cellular agents in multi-cellular systems in space, roughly divided in lattice models (e.g. [85]) and in lattice-free (or off-lattice) models, in which the position [70], [73] or even the shape (e.g. [89]) of the cell can change gradually.

[6] B. Perthame, Parabolic equations in biology, Springer, 2015
[7] B. Perthame, Transport equations in biology, Springer, 2007
[8] H. Byrne and D. Drasdo, Individual-based and continuum models of growing cell populations: a comparison, *J. Math. Biol*, 2009
[9] Cáceres, Carrillo, Perthame *J. Math. Neurosci.* 2011; Pakdaman, Perthame, Salort *Nonlinearity* 2010

The dynamics of cells in lattice-based models is usually described by rules chosen to mimic the behaviour of a cell including its physical behavior. The advantage of this approach is that it is simpler and that simulation times for a given number of cells are shorter than in lattice-free models. In contrast, most lattice-free models attempt to parameterise cells by measurable values with a direct physical or biological meaning, hence allowing identification of physiologically meaningful parameter ranges. This improves model simulation feasibility, since parameter sensitivity analyses in simulations shows significant improvements when a high dimensional parameter space can be reduced. It also facilitates the development of systematic systems biology and systems medicine strategies to identify mechanisms underlying complex tissue organisation processes ([89], [71]).
Moreover, it is straightforward to include relevant signal transduction and metabolic pathways in each cell within the framework of agent-based models, which is a key advantage in the present times, as the interplay of components at many levels is more and more precisely studied [91].

3.5. Multi-level modelling

Multi-level modelling addresses models spanning many spatial scales composed of functional connected modules on each of these scales [64]. Typical representatives of multilevel systems are organs, that are composed of cells of different types coordinated in space, extracellular matrix, etc. Development, parameterisation, verification and validation of such models is challenging as it is usually not possible to simultaneously perform experimental measurements on each level simultaneously.

The fundamental strategy is composed of a multi-step strategy, parameterising sub-models individually before connecting them [71]. For this, models shall be parameterised by measurable quantities for which parameter ranges can be reliably estimated. Then simulated parameter sensitivity simulations are run, comparing results with experiments. If the best agreement between model and experiment is insufficient, the model is wrong or incomplete. If several models are able to explain the data, settings should be run with these models that lead to experimentally testable distinguishable outcomes.

4. Application Domains

4.1. Cancer modelling

Evolution of healthy or cancer cell populations under environmental pressure; drug resistance. Considering cancer as an *evolutionary disease*, evolution meaning here Darwinian evolution, but also Lamarckian instruction, of populations structured according to phenotypes relevant to describe their heterogeneity at stake in studies led in collaboration with our biologist partners within the Institut Universitaire de Cancérologie (IUC) of UPMC, we tackle the problem of understanding and limiting: a) the evolution from pre-malignancy to malignancy in cell populations (in particular we study early leukaemogenesis, leading to acute myeloid leukaemia), and b) in established cancer cell populations, the evolution towards drug-induced drug resistance. The environmental pressure guiding evolution has many sources, including signalling molecules induced by the peritumoral stroma (e.g., between a breast tumour and its adipocytic stroma), and anticancer drugs and their effects on both the tumour and its stromal environment. The models we use [63], [79], [80], [81] are close to models used in ecology for adaptive dynamics.

Drugs: pharmacokinetics-pharmacodynamics, therapy optimisation. We focus on multi-drug multi-targeted anticancer therapies aiming at finding combinations of drugs that theoretically minimise cancer cell population growth with the constraint of limiting unwanted toxic side effects under an absolute threshold (this is not L^2 nor L^1, but L^∞ optimisation, i.e. the constraints as well as the objective function are L^∞) in healthy cell populations and avoiding the emergence of resistant cell clones in cancer cell populations [59], [80], [60], [79]. Prior to using optimisation methods, we design models of the targeted cell populations (healthy and tumour, including molecular or functional drug targets [58]) by PDEs or agent-based models [56], and molecular pharmacological (pharmacokinetic-pharmacodynamic, PK-PD) models of the fate and effects in the organism of the drugs used, usually by ODE models. A special aspect of such modelling is the representation of multi-cellular spatio-temporal patterns emerging from therapies.

Multi-scale modelling of cancer invasion. The major step from a benign tumour to an invasive cancer is the development step at which cells detach from the tumour mass and invade individually the surrounding tissue [10]. We performed *in vitro* simulations of cancer cell invasion for breast cancer evaluating under which conditions the observed migration pattern occurs. (In collaboration with our biologist partners within the Institut Curie)

4.2. Modelling and control in epidemiology

The spread of certain strains of the intracellular parasitic bacterium *Wolbachia* in populations of mosquitoes *Aedes aegypti* drastically reduces their competence as vector of dengue and other severe mosquito-borne viral diseases known as arboviral infections (chikungunya, Zika, yellow fever...). In absence of vaccine, or of preventive or curative treatment, the release of mosquitoes infected 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. Therefore mathematical modeling is of great interest for the study of the feasibility of the control of dengue fever using this strategy.

Key questions about this method concern the efficacy of the strategies used to release Wolbachia-infected mosquitoes in the field that can be applied successfully and with limited cost.

4.3. Protein polymerisation

Self-assembly of proteins into amyloid aggregates is an important biological phenomenon associated with various human neurodegenerative diseases such as Alzheimer's, Parkinson's, Prion (in particular variant Creutzfeldt-Jakob disease, epidemically linked to bovine spongiform encephalopathy, or so-called "mad cow", disease), Huntington's disease. Amyloid fibrils also have potential applications in nano-engineering of biomaterials.

However, the mechanisms of polymerisation are far from being quantitatively understood by biologists. They can be modelled with the help of coagulation-fragmentation equations, a field of expertise of MAMBA [16], [36], or with stochastic models [20]. One difficulty of this application is that the reactions imply both very small and very large scales for the sizes of polymers [7], experimental data giving only access to the time evolution of size-averaged quantities [6]. Moreover, there exists an intrinsic variability among experiments, which has to be distinguished from a lack of reproducibility [20].

The European starting grant SKIPPER^{AD} involves a long-term collaboration with Human Rezaei's team, a biologist expert group in amyloid diseases at INRA Jouy-en-Josas. It allowed us to further develop new collaborations, in particular with Wei-Feng Xue's team in Canterbury, who is one of the rare biophysicists in this area who is able to measure not only size-averaged quantities, as for instance the time-evolution of the total polymerised mass, but also size distribution of polymers (at least over a certain threshold). Such measurements allow us to use much more powerful inverse problems and data assimilation methods [6].

Moreover, this field of applications to human neurogenerative diseases brings us new questions [17], which is a stimulation for our mathematical research and at the same time allows us to provide biologists with a new and efficient tool.

4.4. Cell motion

Several processes are employed by cells to communicate, regulate and control their movements, and generate collective motion. Among them, chemotaxis is the phenomenon by which cells direct their active motion in response to an external chemical (or physical) agent. In chemotaxis, cells not only respond but can also produce the chemical agent, leading to a feedback loop. Understanding this phenomenon is a major challenge for describing the collective behaviour of cells. Many mathematical models have been proposed at different scales, yielding a good description of cell aggregation. In particular, mathematical models at macroscopic scale may be derived departing from kinetic description at mesoscopic scale. An interesting study at the

[10] Weinberg, The biology of cancer, Garland, 2007

numerical level is to provide numerical schemes able to treat both scales. Then in [27], we have proposed an asymptotic preserving scheme for a model describing the formation of networks of cells in tissues. In collaboration with biophysicists at Institut Curie in Paris, we develop and study [11] mathematical models based on kinetic equations for bacterial travelling waves in a microchannel. These models have shown a remarkable quantitative agreement with experimental observations. In [18], we extend this approach to study the behavior of the interaction between two populations of E. Coli. We show that in certain cases populations that travel with its own speed in the channel when separated, may synchronise their movements when put together.

Cell motion arises also in the growth of solid tumours, which can be described through cell population models or multiphase flows [12]. This is a very active subject because several bio-chemico-physical mechanisms are at work; for instance motion can arise from pressure forces resulting from cell divisions and from active cell motility. At the smaller scale stochastic agent-based models of tumour cells invading the tumour environment or blood vessels are considered [13], and allow to represent detailed behaviours and interactions. At a larger scale, free boundary problems are widely used, e.g., for image-based prediction because of the reduced number of parameters [14]. Asymptotic analysis makes a link between these different mechanistic models [88]. One other setting where we will study cell motion is 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 [86], [90] 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 settings, indicating the existence of conserved mechanisms that should be widespread across living beings. In the 01365414 thesis of Telmo Pereira, some differences between the two settings are also studied.

4.5. Physics of tissue organisation

Many new insights in the last years indicate that migration, growth and division of cells are largely impacted by cell and tissue mechanics [15], [16], [17]. Centre-based growth models already account for many of the observed phenomena [18], [19]. They furthermore allow calculation of the stress tensor in the tissue. A critical shortcoming of centre-based models is that forces between cells are calculated based on pairwise interactions hence multi-cellular interactions leading to true cell compression cannot be taken into account.
In order to scope with this shortcoming we (1.) developed a strategy in which forces are calibrated with a high resolution agent based model (so called deformable cell model), so that stress in tissue can then be calculated also at high cell density [54]; (2.) integrated cell division in deformable cell models to permit direct simulations of phenomena with this model type; (3.) developed hybrid models permitting to simulate centre-based and deformable cell models in the same simulations to be able to reach sufficiently high cell numbers.
Deformable cell models [20] resolve cell surface at reasonable resolution, and allow to calculate cell deformation as function of stress emerging in the tissue, hence the stress tensor cannot only be resolved at the position of the cell centre, as in the case of centre-based models, but in this case at any point on the cell surface or inside the cell. The higher resolution causes much longer simulation times which is why currently simulation of large multi-cellular systems with deformable cell models on standard computers is not feasible.

[11] N. Bournaveas, V. Calvez, S. Gutiérrez and B. Perthame, Global existence for a kinetic model of chemotaxis via dispersion and Strichartz estimates, *Comm. PDE*, 2008
[12] J. Ranft et al, Fluidisation of tissues by cell division and apoptosis, *PNAS*, 2010 and L. Preziosi and A. Tosin, Multiphase modelling of tumour growth and extracellular matrix interaction: mathematical tools and applications, *J. Math. Biol.*, 2009.
[13] I. Ramis-Conde et al., J. Phys. Biol., 2009
[14] Works by O. Saut, T. Colin, A. Iollo, N. Ayache, J. Lowengrub
[15] Ingber, Proc. Natl. Acad. Sci (USA), 2005
[16] Trepat et. al., Nat. Phys. 2009
[17] Alessandri et. al., Proc. Natl. Acad. Sci. (USA) 2013
[18] Drasdo and Hoehme, Phys. Biol. 2005
[19] Drasdo and Hoehme, New Journal of Physics 2012
[20] Odenthal, Smeets, van Liedekerke, et. al., PloS Comput Biol. 2013

4.6. Liver modelling

Liver is the main detoxifying organ of the human body and can regenerate up to about 70% of its mass. It performs its task by using a complex tissue architecture, with hepatocytes aligning along micro-capillaries and forming a dense network. The incidence rate of liver diseases is steadily increasing, liver cancer ranking 6th among all cancers. About one person in 12, otherwise said 500 million people worldwide, will suffer from viral hepatitis. Hepatitis B and C as well as misuse of drugs or alcohol are major causes of liver cancer. Notwithstanding the importance of this public health problem, disease pathogenesis and regeneration in liver are still not well understood.
So far systems biology approaches addressing the tissue scale are rare. Most of those which do so base on compartment models (e.g. [21]); only recently are approaches addressing the tissue scale being developed [76] [22], [23], [24], [25]. We have developed a multi-scale model of liver regeneration representing the tissue architecture, the different cell types, the flow systems, hepatocyte metabolism and signal transduction controlling cell cycle entrance in the regeneration processes, taking into account extrahepatic compartments when relevant. Applications are regeneration after drug-induced damage and after partial hepatectomy, drug pharmacodynamics and pharmacokinetics in liver and liver cancer, and model-based prediction of in-vivo drug toxicity from in-vitro measurements [26].

5. Highlights of the Year

5.1. Highlights of the Year

5.1.1. Personnel

Marie Doumic has moved in September 2015 for a 1-year sabbatical to the Wolfgang Pauli Institute in Vienna. Stefan Hoehme left in July 2015 to start a prestigious “Emmy Noether” junior research group at University of Leipzig, faculty for computer sciences. Of note, this is the first Emmy Noether research group in Leipzig, and he was the only one accepted this year (out of 20 presented).

Nicolas Vauchelet left the team in September 2015, becoming a full professor at University Paris XIII.

5.1.2. THE ITMO Cancer national call.

The team has been successful in simultaneously participating in 2 different funded projects of the ITMO Cancer THE (“Tumour Heterogeneity in its Ecosystem”, a programme managed by INSERM) national call for 2016: one, EcoAML (4 teams), on early leukaemogenesis in Acute Myelogenous Leukaemia (AML), headed by François Delhommeau (CDR St Antoine, Paris), with whom we have a long-lasting collaboration, and the other, MoGlImaging (8 teams), on treatment-induced treatment resistance and heterogeneity in glioblastoma, headed by Elizabeth Moyal (INSERM, Toulouse), a project inside which we have recently developed a work collaboration with the team of François Vallette (INSERM, Nantes) on the in-vitro resistance of glioblastoma to temozolomide. In both these collaborative projects, begun in November 2016 and to be integrated in 2017 in the future THE consortium (gathering the 6 projects laureates to the national call), we propose to develop our phenotype-structured models for both the cancer and the supporting stromal cell populations, with representation of mutualistic interactions between them.

[21] Diaz-Ochoa et. al. Frontiers in Pharmacology, 2013
[22] Ricken, Dahmen, Dirsch, Biomech. Model. Mechanobiol. 2010
[23] Debbaut et. al., J. Biomech. Eng. 2014
[24] Siggers, Leungchavphongse, Ho, Repetto, Biomech. Model. Mechanobiol. 2014
[25] Schwen et. al., PLoS Comput. Biol. 2014
[26] Godoy et al., *Arch Toxicol. 2013* Aug;87(8):1315-1530

6. New Software and Platforms

6.1. TiQuant

Tissue Quantifier
KEYWORDS: Systems Biology - Bioinformatics - Biology - Physiology
Systems biology and medicine on histological scales require quantification of images from histological image modalities such as confocal laser scanning or bright field microscopy. The latter can be used to calibrate the initial state of a mathematical model, and to evaluate its explanatory value, which hitherto has been little recognised. We generated a software for image analysis of histological material and demonstrated its use in analysing liver confocal micrografts, called TiQuant (Tissue Quantifier). The software is part of an analysis chain detailing protocols of imaging, image processing and analysis in liver tissue, permitting 3D reconstructions of liver lobules down to a resolution of less than a micrometer [72]. It is implemented in portable object-oriented ANSI C++. The GUI is based on QT and supports real-time visualisation using OpenGL. TiQuant is embedded in the tissue modelling framework CellSys and thus is tightly linked with TiSim, a versatile and efficient simulation environment for tissue models. TiQuant provides an interface to VolView and further complements its functionality by linking to the open-source libraries ITK and VTK (itk/vtk.org). The image/volume processing chains currently implemented in TiQuant for example include techniques to segment conduit and cell segmentation from 3D confocal micrographs of liver tissue based on the Adaptive Otsu Thresholding method and a number of morphological operators [75]. TiQuant is currently extended by a machine learning component.

FUNCTIONAL DESCRIPTION

We generated a software for image analysis of histological material and demonstrated its use in analysing liver confocal micrografts, called TiQuant (Tissue Quantifier). The software is part of an analysis chain detailing protocols of imaging, image processing and analysis in liver tissue, permitting 3D reconstructions of liver lobules down to a resolution of less than a micrometer.

- Contact: Dirk Drasdo
- URL: http://www.msysbio.com

6.2. TiSim

Tissue Simulator
KEYWORDS: Systems Biology - Bioinformatics - Biology - Physiology
FUNCTIONAL DESCRIPTION

TiSim (Tissue Simulator) is a software for agent-based models of multicellular systems. It permits model development with centre-based models and deformable cell models; it contains modules for monolayer and multicellular spheroid simulations as well as for simulations of liver lobules. Besides agent-based simulations, the flow of blood and the transport of molecules can be modelled in the extracellular space; intracellular processes such as signal transduction and metabolism can be simulated, for example over an interface permitting integration of SBML-formulated ODE models.
TiSim is written in modern C++, keeping central model constituents in modules to be able to reuse them as building blocks for new models. For user interaction, the GUI Framework Qt is used in combination with OpenGL for visualisation. A non-interactive mode to use the software also exists, accepting a combination of XML and HDF5 (hierarchical data format v5) as input, which produces output data in VTP (VTK) and HDF5 format. SBML, SBML_ODESolver and sundials are deployed for the creation and solution of the differential equations of metabolic networks and signalling pathways presented in SBML data format. TiSim permits agent-based simulations of multicellular systems and can be directly fed by processed image data from TiQuant.

- Contact: Dirk Drasdo
- URL: (No url yet)

7. New Results

7.1. Cancer

Participants: Luis Lopes Neves de Almeida, Group Emmanuel Barillot [Institut Curie], Catherine Bonnet [DISCO team, Saclay], Thibault Bourgeron, Group Kai Breuhahn [Hospital of University of Heidelberg, Pathology], Rebecca Chisholm, Jean Clairambault, François Delhommeau [Haematology department, St Antoine Hospital, Paris], Marie Doumic, Dirk Drasdo, Walid Djema [DISCO team, Saclay], Julie Favre [EPFL, Lausanne], Olivier Fercoq [Télécom ParisTech], Ghassen Haddad [ENIT, Tunis], Shalla Hanson [Department of mathematics, Duke University, Durham, NC], Pierre Hirsch [Haematology department, St Antoine Hospital, Paris], Groups Invade, Lungsysii, Hicham Janati [ENSAE, Paris], Tim Johann, Group Klingmueller [German Cancer Center, Heidelberg], Michal Kowalczyk [Univ. Santiago de Chile], Annette Larsen [Cancer biology and therapeutics lab, St Antoine Hospital, Paris], Tommaso Lorenzi [University of St Andrews, Scotland], Alexander Lorz, Frédéric Mazenc [DISCO team, Saclay], Benoît Perthame, Camille Pouchol, Andrada Quillas Maran, Fernando Quirós [Univ. Autónoma de Madrid], Michèle Sabbah [Cancer biology and therapeutics lab, St Antoine Hospital, Paris], Min Tang [Jiaotong University, Shanghai], Teresa Teixeira [IBCP], Emmanuel Trélat [LJLL, UPMC], Paul Van Liedekerke, Oliver Sedlaczek [German Cancer Center (DKFZ) and Hospital of University of Heidelberg, Germany], François Vallette [INSERM, CRCNA, Nantes], Nicolas Vauchelet, Irène Vignon-Clementel [REO], Zhou Xu [IBCP], Yi Yin.

7.1.1. Senescence and telomere shortening

In many animals, aging tissues accumulate senescent cells, a process which underlies the loss of regeneration capacity of organs and is ultimately detrimental to the organism. Senescence is also required to protect organisms from unlimited proliferation that may arise from numerous stimuli or deregulations. Due to these opposing effects in aging and cancer, senescence is considered antagonistic pleiotropic; senescence is beneficial to protect from cancer in the young organism, but becomes detrimental late in life. Therefore, understanding the mechanisms of cellular senescence may lead to the development of global therapies to debilities specific for the aged, as well age-associated diseases and cancer. These are major public health issues in France, and other western aging countries.

Replicative senescence, induced by telomere shortening, exhibits considerable asynchrony and heterogeneity, the origins of which remain unclear. In [19], following [61], we formally study how telomere shortening mechanisms impact on senescence kinetics and define two regimes of senescence, depending on the initial telomere length variance. We provide analytical solutions to the model, highlighting a non-linear relationship between senescence onset and initial telomere length distribution. This study reveals the complexity of the collective behaviour of telomeres as they shorten, leading to senescence heterogeneity.

7.1.2. Stability analysis of a delay differential model of healthy and leukaemic haematopoiesis

The collaboration with the DISCO team (Inria Saclay, C. Bonnet, F. Mazenc and their PhD student W. Djema), supported by the collaboration with the team of haematologists led by F. Delhommeau at St. Antoine Hospital in Paris, has been continued, with common research work underway. A new model describing the coexistence between ordinary and mutated haematopoietic stem cells was introduced and analysed in [32]. Interpreting theoretical conditions found to guarantee the survival of healthy cells while eradicating unhealthy ones leads us to propose possibly innovative therapies obtained by combining the infusion of different drugs (Flt-3 inhibitors such as quizartinib, cytosine arabinoside, anthracyclines).

7.1.3. Interactions between tumour cell populations and their cellular micro-environments

This is the main object of study, together with the consideration of phenotype and genotype heterogeneity in cancer cell populations (see *Highlights of the Year*), of the *THE ITMO Cancer* national call 2016, to which two (out of three) of the submitted projects involving our team, which themselves were two out of the six laureate projects at the national level, have been successfully funded. The two projects, EcoAML and MoGlImaging have been launched in November 2016.

7.1.4. Evolution and cancer; drug resistance in cancer cell populations

We have continued to develop our phenotypically based models of drug-induced drug resistance in cancer cell populations, representing their Darwinian or Lamarckian evolution under drug pressure by integro-differential equations. The properties of phenotype-structured PDEs are explored in theoretical articles with examples [25], [78]. We will also use them in the two projects laureates to the THE (*Tumour Heterogeneity in its Ecosystem*) ITMO Cancer call of 2016 (see *Highlights of the Year*), EcoAML and MoGlImaging, to help predict early evolution towards leukaemogenesis (EcoAML, leader F. Delhommeau, St. Antoine Hospital, Paris) and emergence of resistance to temozolomide in glioblastoma cell populations (MoGlImaging, leader E. Moyal, Toulouse, F. Vallette, Nantes, being our main work correspondent). In this version, mutualistic exchanges between the cancer cell population and its supporting stroma will be represented as impinging on the phenotypic variables that describe the relevant heterogeneity at stake in the two cell populations.

With F. Vallette, we have co-supervised Hicham Janati's ENSAE 2nd year (M1) internship on the investigation of cancer resistance in a Glioblastoma cell line [46] with gene expression data coming from F. Vallette's lab in Nantes. This internship represents for us a first step in the quest for relevant (most likely multidimensional) phenotypes, based on bioinformatic and biostatistic methods to process experimental dynamic gene expression data, to interactively identify our physiologically structured models of heterogeneity and its evolution in cancer cell populations. The task ahead is immense, but our commitment in the THE consortium (see *Highlights of the Year*) with biologists providing us with such data (F. Vallette, F. Delhommeau) gives us good expectations to be successful with it in a close future. Following Hicham Janati's internship [46], Julie Favre (M1 student at EPFL) has been hired in a new internship to set the practical grounds for the interactive collaboration (begun with the THE program in November 2016) between our team and F. Delhommeau's team on model-based processing of gene expression data produced by a heterogeneous leukaemic cell population and by its surrounding stromal cell population.

The evolution towards drug-induced drug resistance in cancer cell populations may be described by methods of adaptive dynamics for continuous phenotype-structured populations, as such cell populations are fundamentally phenotypically, if not genetically, heterogeneous. In [11], [40], we review the bases of heterogeneity and drug resistance in cancer, its assessment by biological experiments and by mathematical modelling and methods of optimal control that may be applied to represent and optimise combined delivery of cytotoxic and cytostatic drugs, see below "Optimal control and drug resistance" [52].

7.1.5. Therapy optimisation

PK-PD: optimisation with respect to unwanted side effects. A previous pharmacokinetics-pharmacodynamics (PK-PD) model for the action of anticancer drugs at the molecular level, coupled with an age-structured linear model of the cell division cycle, has been updated in [12] (introduced in a special issue on PK-PD [9]) with optimisation of the combined delivery of 3 different drugs (5-fluorouracil, oxaliplatin, leucovorin). This is joint work with Olivier Fercoq, Télécom ParisTech. It represents the coalescence of two distinct types of models, both studied in previous years in our team: molecular ODE-based models of the action of anticancer drugs, and optimisation (using a Uzawa-like algorithm applied to the first eigenvalues of the two growing populations, minimising the cancer eigenvalue - objective - while maintaining the healthy eigenvalue above a reference threshold - constraint -, supposed to be linked to the state of health of the patient) of the control of linear growth models based on age-structured transport equations for the cell division cycle in the two populations separately.

Optimal control and drug resistance. In the framework of Camille Pouchol's PhD thesis, co-supervised at LJLL by E. Trélat and J. Clairambault, analysing the behaviour of healthy and cancer cell populations structured in a continuous resistance phenotype to a cytotoxic drug, and exposed to cytostatic and cytotoxic chemotherapies, we have firstly established, in an asymptotic analysis using a Lyapunov functional inspired from works by P.-E. Jabin and G. Raoul [77], results of convergence and concentration for constant drug concentrations [52] (following [84]). In a second part of this work, we have derived from them analytical conditions of optimality for the delivery of the drugs in a general class of controls. A numerical example of the optimal strategy is illustrated on Figure 1, where the phenotype x continuously ranges from totally

sensitive ($x = 0$) to totally resistant ($x = 1$), and healthy and cancer cells are represented by densities of cells $n_H(t, x)$, $n_C(t, x)$. The simulations confirm that the optimal strategy consists of letting the cancer cell population become more and more homogeneous around a sensitive phenotype, and then to use the maximal amount of drugs. This proposed strategy may be related with the "drug holiday" practiced in the clinic of cancers. We also show *en passant* the clearly detrimental effect of delivering cytotoxic drugs at high *constant* doses, as they inevitably induce the emergence of a thriving resistant subpopulation, which is illustrated on Figure 2.

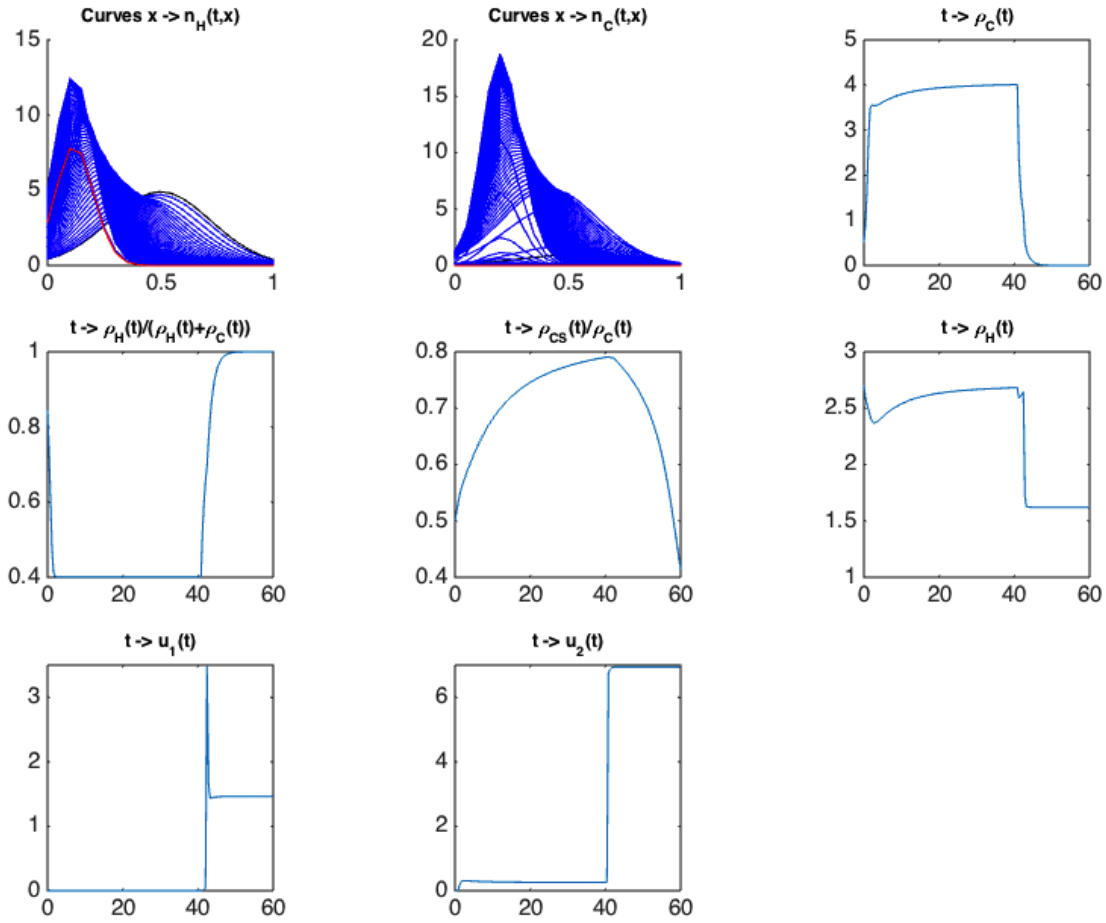

Figure 1. Simulation of the optimal control problem in time horizon $T = 60$. Top, left and middle: time evolution of $x \mapsto n_H(t, x)$, number of healthy cells with drug resistance expression phenotype x, and of $x \mapsto n_C(t, x)$, number of cancer cells with the same phenotype x. The initial conditions are in black, the final ones in red. Top right (resp., centre right): evolution with time of the total number of cancer cells $\rho_C(t) = \int_0^1 n_C(t, x)dx$ (resp., of healthy cells $\rho_H(t) = \int_0^1 n_H(t, x)dx$). Centre left (resp., centre middle), evolution with time of the ratio of healthy cells to total cells (resp., of sensitive cancer cells defined by the weighted integral $\rho_{CS}(t) = \int_0^1 (1 - x)n_C(t, x)dx$ to the total cancer cell population). Bottom, left and middle: evolution with time of the optimal drug infusions of cytotoxic (u_1) and cytostatic (u_2) drugs. One can check on this simulation the quasi-bang-bang character of the optimal control.

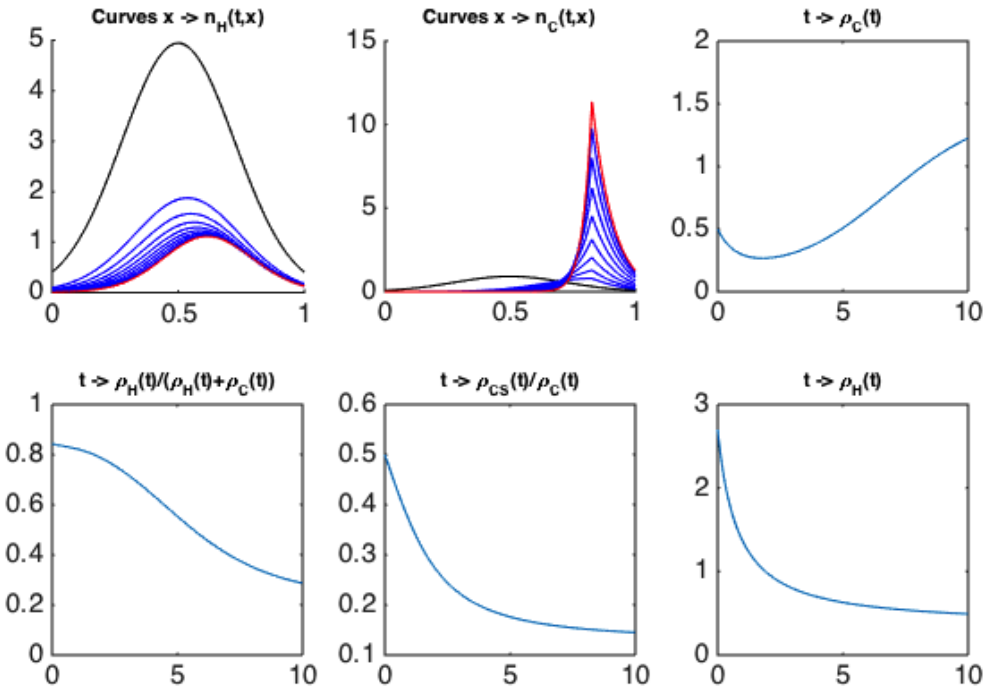

Figure 2. Comparative evolution with constant high drug doses. Catastrophic deleterious effects of the treatment on the concentration of the drug resistance phenotype x in the cancer cell population (top middle), and on the cell population numbers $\rho_C, \rho_H, \rho_{CS}$. Simulation with $u_1(t) = \mathrm{Cst} = 3.5$, $u_2(t) = \mathrm{Cst} = 2$, in time horizon $T = 10$.

7.1.6. Lung and breast cancer

Diffusion-weighted magnetic resonance imaging (DWI) is a key non-invasive imaging technique for cancer diagnosis and tumour treatment assessment, reflecting Brownian movement of water molecules in tissues. Since densely packed cells restrict molecule mobility, tumour tissues produce less attenuated DWI signals than normal tissues. However, no general quantitative relation between DWI data and the cell density has been established. In order to link low-resolution clinical cross-sectional data with high-resolution histological information, we have developed an image processing and analysis chain, which was used to study the correlation between the diffusion coefficient (D value) estimated from DWI and tumour cellularity from serial histological slides of a resected non-small cell lung cancer (NSCLC) tumour. Colour deconvolution followed by cell nuclei segmentation was performed on digitised histological images to determine local and cell-type specific 2D (two-dimensional) densities. From these the 3D (three-dimensional) cell density was inferred by a model-based sampling technique, which is necessary for the calculation of local and global 3D tumour cell count. Next, DWI sequence information was overlaid with high-resolution CT data and the resected histology using prominent anatomical hallmarks for co-registration of histology tissue blocks and non-invasive imaging modalities for data. The integration of cell numbers information and DWI data derived from different tumour areas revealed a clear negative correlation between cell density and D value. Importantly, spatial tumour density can be quantitatively calculated based on DWI data to estimate tumour heterogeneity [55].
In a followup we currently study to what extent the relation between cellularity and DWI - diffusion coefficient can be inferred from biopsies instead of tumour serial sections. Moreover, we are studying the relation between DWI and tumour microvasculature [33].

7.1.7. 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 multiscale computational modeling of multicellular growth in two largely different experimental settings with the same tumour cell line we demonstrated that the cellular growth response on external mechanical stress may nevertheless be surprisingly quantitatively predictable. Our computational model represents each cell as an individual unit capable of migration, growth, division, and death and is parameterised by measurable biophysical and bio-kinetic parameters. A cell cycle progression function depending on cell compression was established by comparisons of computer simulations with experiments of spheroids growing in an alginate elastic capsule. After a calibration step with free growing spheroids growing in a liquid suspension to capture the different growth conditions, the model using the same cell cycle progression function can predict the mechanical stress response of spheroid growth in a completely different experimental technique using Dextran, where stress is exerted by osmotic pressure. Our findings suggest that the stress response of cell growth may be highly reproducible even in otherwise different environments. This encourages the idea that robust functional modules may be identified, thus helping us to understand complex cell behaviours such as cell growth and division in relation to mechanical stress. The model analysis further elucidates the relation between applied pressure, cell compressibility and cell density. Moreover, the model developments within this paper points a way of how to handle the so far open issue of high compression within the popular so-called Centre-Based Models, in which force between cells is modelled as forces between cell centres [54].

7.2. Epidemiology

Participants: Luis Lopes Neves de Almeida, M. Soledad Aronna [FGV, Rio de Janeiro], Pierre-Alexandre Bliman, Flávio C. Coelho [FGV, Rio de Janeiro], Martin Strugarek, Nicolas Vauchelet, Jorge Zubelli [IMPA, Rio de Janeiro].

7.2.1. Establishing Wolbachia by feedback

The releases of *Wolbachia*-positive mosquitoes are usually completed on an open-loop approach, that is, with a schedule computed once for all before the beginning of the experiment. Using the fact that measurements are achieved and available during the whole release process, we applied feedback control technique to devise an introduction protocol which is proved to guarantee that the population converges to a stable equilibrium where

the totality of mosquitoes carry *Wolbachia*. A major advantage of feedback compared to open-loop approaches is its ability to cope with the uncertainties in the model dynamics (typically in the modelling of the life stages and the population structure), in the parameters (population size, mortality, reproductive rates, etc.), and in the size of the population to be treated.

7.2.2. Travelling waves in the problem of infestation by Wolbachia

As described above, a new method of control of dengue fever consists in releasing Wolbachia-infected mosquitos in the field, in the aim to replace the whole existing population by a population unable to transmit Dengue fever. In the study of the feasibility of such a strategy, an important issue concerns the spacial propagation of the mosquitoes. More precisely, releasing infected mosquitoes in a given domain (which can be a part of the city of Rio de Janeiro), the hope is to invade the whole area. The study of this propagation phenomena falls into the study of existence of traveling wave. In a recent paper [30], the authors have proposed a mathematical model to study such phenomena and they 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 spacial invasiveness has been performed in [53].

7.3. Aggregation Kinetics

Participants: Aurora Armiento, Tom Banks [CRSC, NCSU, Raleigh, USA], Etienne Bernard, Thibault Bourgeron, José Antonio Carrillo [Imperial College, London, United Kingdom], Marie Doumic, Dirk Drasdo, Miguel Escobedo [Universidad del País Vasco, Bilbao, Spain], Sarah Eugène, Pierre Gabriel [Université Paris-Dauphine], Marc Hoffmann [Ceremade, Université Paris-Dauphine], François James [MAPMO, Université d'Orléans], Nathalie Krell [Université de Rennes 1], Frédéric Lagoutière [Département de mathématiques d'Orsay], Philippe Moireau [Inria Paris Saclay, M3DISIM project-team], Benoît Perthame, Stéphanie Prigent, Human Rezaei [VIM, INRA Jouy-en-Josas], Lydia Robert [Laboratoire Jean Perrin, UPMC], Philippe Robert [Inria Paris, RAP project-team], Maria Teresa Teixeira [IBCP, Paris], Joan Torrent [INRA, Jouy-en-josas], Magali Tournus [Ecole Centrale de Marseille], Nicolas Vauchelet, Min Tang [Jiaotong University, Shanghai], Zhou Xu [IBCP, Paris], Wei-Feng Xue [University of Kent, United Kingdom], Yi Yin.

7.3.1. Heterogeneity as an intrinsic feature in biological dynamics

Variability in nucleated polymerisation The kinetics of amyloid assembly show an exponential growth phase preceded by a lag phase, variable in duration as seen in bulk experiments and experiments that mimic the small volumes of cells. Sarah Eugène's Ph.D, defended in September 2016, was devoted to the study of the origins and the properties of the observed variability in the lag phase of amyloid assembly currently not accounted for by deterministic nucleation dependent mechanisms. In [20], we formulated a new stochastic minimal model that is capable of describing the characteristics of amyloid growth curves despite its simplicity. We then solve the stochastic differential equations of our model and give mathematical proof of a central limit theorem for the sample growth trajectories of the nucleated aggregation process. These results give an asymptotic description for our simple model, from which closed form analytical results capable of describing and predicting the variability of nucleated amyloid assembly were derived. We also demonstrate the application of our results to inform experiments in a conceptually friendly and clear fashion. Our model offers a new perspective and paves the way for a new and efficient approach on extracting vital information regarding the key initial events of amyloid formation.

However, this first model does not explain completely the variability observed in the experiments. In [17], we thus investigated extensions to take into account other mechanisms of the polymerisation process that may have an impact on fluctuations.The first variant consists in introducing a preliminary conformation step to take into account the biological fact that, before being polymerised, a monomer has two states, regular or misfolded. Only misfolded monomers can be polymerised so that the fluctuations of the number of misfolded monomers can be also a source of variability of the number of polymerised monomers. The second variant represents the reaction rate of spontaneous formation of a polymer as of the order of α, with α some positive constant. First and second order results for the starting instant of nucleation are derived from these limit theorems. The proofs of the results rely on a study of a stochastic averaging principle for a model related to an Ehrenfest urn model, and also on a scaling analysis of a population model.

Image and statistical analysis of protein fibrils Protein fibrils present an important structural diversity, not only their length, but also their width, whether they present branches or not, etc. These structures may reveal the presence of different types of aggregates, possibly formed out of different polymerisation pathways. To analyse this diversity of shapes and structures, we developed an image analysis software, based on the expertise acquired by Y. Yin during her PhD for the image analysis of vessels. This software is able to track fibrils and measure their length, number of branches, and variable widths, even with poor quality images and crossing fibrils. This done, it allows us to perform a statistical analysis of the fibrils, to elucidate the main structuring features (Figure 3).

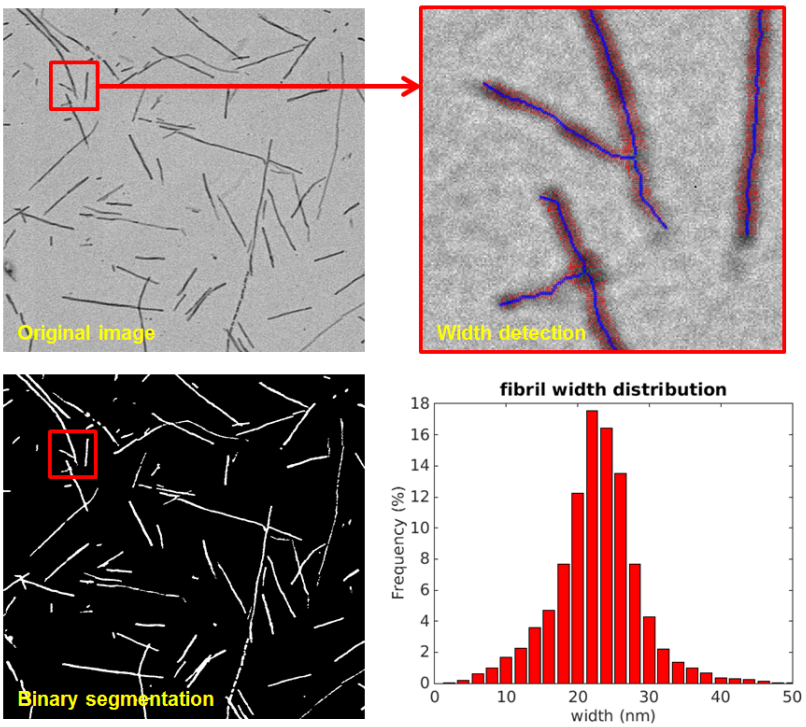

Figure 3. Fibril analysis yielding from original data via segmentation and analysis to the fibril length distribution.

7.3.2. Inverse Problems and Data Assimilation Applied to Protein Aggregation and other settings

Estimating reaction rates and size distributions of protein polymers is an important step for understanding the mechanisms of protein misfolding and aggregation, a key feature for amyloid diseases. A. Armiento's Ph.D was devoted to the question of adapting data assimilation strategies to the specific context and difficulties of protein aggregation. In [6], we settled a framework problem when the experimental measurements consist in the time-dynamics of a moment of the population (*i.e.*, for instance the total polymerised mass, as in Thioflavine T measurements, or the second moment measured by Static Light Scattering). We propose a general methodology, and we solve the problem theoretically and numerically in the case of a depolymerising system. We then apply our method to experimental data of degrading oligomers, and conclude that smaller aggregates of ovPrP protein should be more stable than larger ones. This has an important biological implication, since it is commonly admitted that small oligomers constitute the most cytotoxic species during prion misfolding process.

7.3.3. Time asymptotics for growth-fragmentation equations

The long-term dynamics of fragmentation and growth-fragmentation equations has constantly been for the MAMBA (and for the ex-BANG) team an important research field. Thanks to these common efforts, these equations are now well understood. However, there remain some interesting open questions. In particular, if the generic long-time behaviour for the linear equation is known - given by a (generally exponential) trend towards a steady exponential growth described by the positive eigenvector linked to the dominant eigenvalue, see [83] for most recent results - critical cases are not yet fully understood.

With Miguel Escobedo, we focused on an important critical case, when the fragmentation is constant and the growth rate is either null or linear [16]. Using the Mellin transform of the equation, we determine the long time behaviour of the solutions and the speed of convergence, which may be either exponential or at most polynomial according to the subdomain of $(t, x) \in \mathbb{R}_+^2$ which is considered. Our results show in particular the strong dependence of this asymptotic behaviour with respect to the initial data, in contrast to the generic results. Following our study, J. Bertoin and A. Watson proposed a complementary probabilistic analysis of related models [57]. These results exemplify the continuing need for further analysis of these interesting equations.

With E. Bernard and P. Gabriel, in [36], we investigated the "idealised" mitotic case, when the growth is exponential and the division results in two exactly equal parts. This case exhibits a lack of dissipativity, and the solutions appear to have a periodic limit cycle. We were nonetheless able to prove an entropy inequality, and to express the limit as an explicit oscillatory function, analytically given by the projection of the initial state on the space generated by the countable set of the dominant eigenvectors of the operator.

7.3.4. Cell aggregation by chemotaxis

Bacterial chemotaxis is now a well-known phenomenon. In particular, it has been established that the motion of bacteria is due to the alternation of straight swims in a given direction with tumble phases. More precisely, when bacteria notice that they do not go in a favorable direction, they may change their direction. Well established models are now available. In particular, the use of such systems allows to recover successfully the behaviour observed in biological experiments (see e.g. [18]). The bacterial response to changes in their environment can be described by an internal variable. In a recent work [29], it has been established that a well-known kinetic model can be obtained from such a model incorporating an internal variable.

When, the frequency of tumbling is high, the motion is mainly driven by tumbling and models reduce to describe aggregation phenomena. From a mathematical point of view, the study of such model is challenging since classical solution may not exist for any time. Then a notion of weak measure solution should be introduced [10]. Numerical investigation of such solutions has been performed in [21], [48].

7.4. Modelling of the liver

Participants: François Bertaux [Imperial College, London], Noémie Boissier, Dirk Drasdo, Géraldine Cellière, Adrian Friebel, Group Heinzle [Univ. Saarbruecken, Germany], Group Hengstler [IfADo, Germany], Stefan Hoehme, Tim Johann, Irène Reo [Vignon-Clementel], Paul Van Liedekerke, Eric Vibert [Hopital Paul Brousse], Group Zerial [Max-Planck Inst. for Molecular Genetics, Dresden, Germany], Groups Iflow, Notox, Vln.

7.4.1. Ammonia detoxification after drug-induced damage

Overdosing acetaminophen (APAP) is the main reason for acute liver failure in the US and UK. Overdose of APAP destroys the hepatocytes localised in the center of each liver lobule (pericentral damage), the repetitive functional and anatomical tissue units of liver. The Human has about 1 million of such lobules. As a consequence, the blood is not sufficiently detoxified from ammonia, which is toxic to the body and can lead to encephalopathy. In France about 1000 cases occur with ammonia toxicity each year. In recent papers we demonstrated by an integrated model that the widely accepted scheme of key reactions for ammonia detoxification is insufficient to explain ammonia detoxification after pericentral lobule damage and predicts a missing ammonia sink [71]. The integrated model couples ODEs representing the consensus reactions in the

spatial temporal liver lobule regeneration model. This finding has triggered new experiments leading to the identification of a widely ignored but fundamentally important ammonia sink mechanism. We could show by testing a number of different mechanisms within novel models that this sink mechanism was the only one able to explain the data [74] (and Geraldine Cellière's PhD thesis [3], 2016). The reaction turned out to have the potential to be used in therapeutics by injection of a molecular cocktail triggering it.
In a follow-up work, the ammonia detoxifying reactions have been integrated into each hepatocyte of the previously established tissue-level liver lobule model of regeneration. The final multi-level model simulates blood flow, transport of metabolites and detoxification of ammonia in every hepatocyte of a regenerating lobule. This multi-level model could validate the missing ammonia sink found in the integrated model in ref. [74] but yields differences to the integrated model if the ammonia sink mechanism is integrated. Still by reparameterisation, adding the ammonia sink mechanism, the model is able to explain the data but the results clearly show that spatio-temporal modelling can give results different from pure compartment modelling. In the case of quantitative modelling in pharmacology or toxicology this can be fundamental. We were able to analyse and generalise these findings.

7.4.2. Predicting in vivo drug toxicity from in vitro data

In vitro experiments on APAP (aka paracetamol, acetaminophen) have been used to calibrate a model of APAP drug toxicity using in vitro data, modifying this model to predict in vivo toxicity. This procedure is aimed at as a general pathway from cosmetic and pharmaceutical companies to eliminate or at least reduce animal experiments and, in perspective, permit a better prediction of drug toxicity in the Human. Three critical differences between in vitro and in vivo were stepwise integrated in the model calibrated with in vitro toxicity data to study their impact on in vivo toxicity predictions. (1) The temporal drug exposure profile, (2) the temporal concentration profile of a class of key enzymes, CYP enzymes. Only in hepatocytes in which CYP enzymes are present is APAP metabolised and can downstream cell death occur. (3) The liver architecture represents critical differences in the spatial distribution of the drug. The results are in preparation for publication (Géraldine Cellière's PhD thesis 2016, Cellière et. al., in preparation).

7.4.3. Liver cancer

The aggressiveness of a tumour may be reflected by its micro-architecture. To gain a deeper understanding of the mechanisms controlling the spatial organisation of tumors at early stages after tumour initiation, we used an agent-based spatio-temporal model previously established to simulate features of liver regeneration [76]. This model was further developed to simulate scenarios in early tumour development, when individual initiated hepatocytes gain increased proliferation capacity [37]. The model simulations were performed in realistic liver microarchitectures obtained from 3D reconstruction of confocal laser scanning micrographs. Interestingly, the here established model predicted that initially initiated hepatocytes arrange in elongated patterns. Only when the tumour progresses to cell numbers of approximately $4,000$ does it adopt spherical structures. This model prediction was validated by the analysis of initiated cells in a rat liver tumour initiation study using single doses of 250 mg/kg of the genotoxic carcinogen N-nitrosomorpholine (NNM). Indeed, small clusters of GST-P positive cells induced by NNM were elongated, almost columnar, while larger GDT-P positive foci of approximately the size of liver lobules, adopted spherical shapes. Simulation of numerous possible mechanisms demonstrated that only hepatocyte-sinusoidal-alignment (HSA), a previously discovered order mechanism involved in the coordination of liver tissue architecture, could explain the experimentally observed initial deviation from spherical shape. The present study demonstrates that the architecture of small hepatocellular tumour cell clusters early after initiation is still controlled by physiological control mechanisms. However, this coordinating influence is lost when the tumour grows to approximately $4,000$ cells, leading to further growth in spherical shape (Figure 4). Our findings stress the potential importance of organ micro-architecture in understanding tumour phenotypes.

7.5. Miscellaneous

Participants: M. Soledad Aronna [FGV, RIo de Janeiro], Bettina d'Avila Barros [FGV, Rio de Janeiro], Pierre-Alexandre Bliman, Noémie Boissier, Géraldine Cellière, Flávio C. Coelho [FGV, Rio de Janeiro],

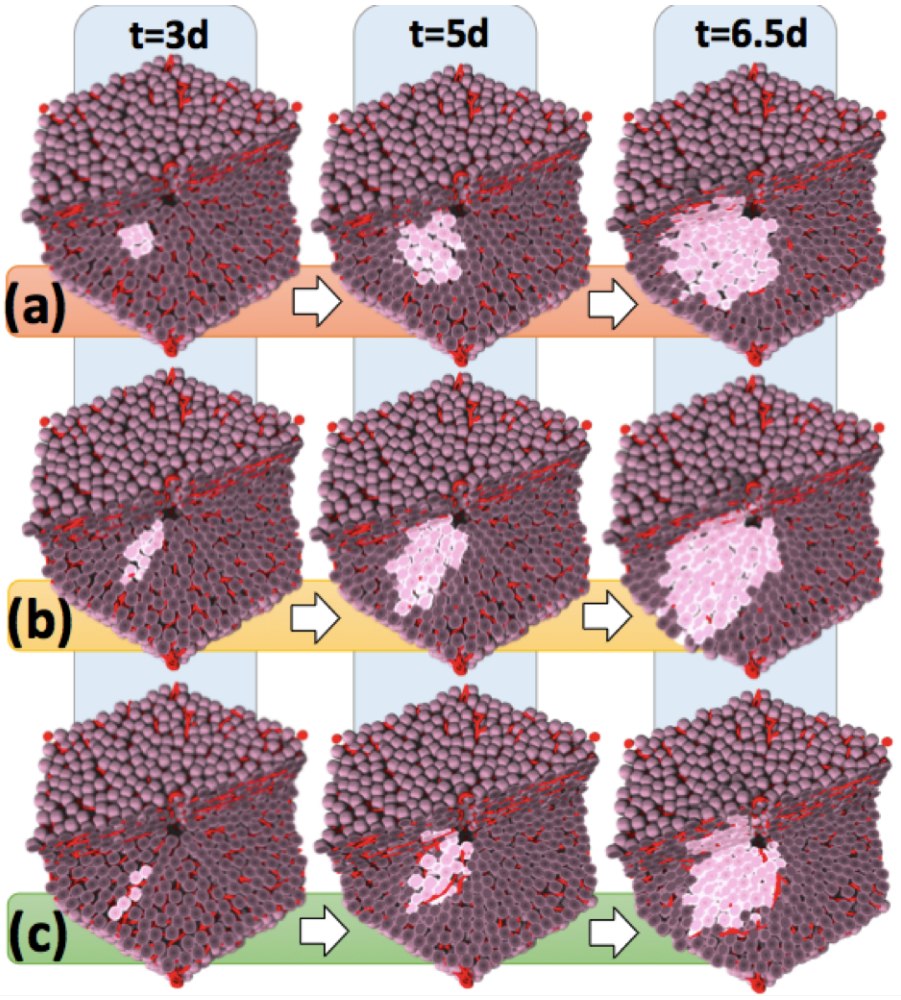

Figure 4. Scenarios of tumour growth in a single liver lobule in (a) absence of hepatocyte-sinusoidal-alignment (HSA), (b) presence of HSA, and (c) presence of HSA with elevated tangential friction impeding hepatocyte movement perpendicular to the columns formed along the sinusoids [35]. The images represent snapshots 3, 5 and 6.5 days after initiation, defined as the time point when a transformed hepatocyte adopts an increased proliferation rate. Notice that HSA (b, c) clearly causes early asymmetry of tumour cell assemblies (leftmost image column at 3 days) while with increasing tumour size this asymmetry is increasingly lost (right panel at 6.5 days). A one-cell thick column could be found if the movement perpendicular to the sinusoids was impeded by elevated shear forces, e.g., from tight junctions. This predicted evolutionary scenario reproduces the experimentally observed scenario.

Marie Doumic, Benoît Perthame, Tales Rands Amazonas [FGV, Rio de Janeiro], Group Reo [Inria Paris - Rocquencourt], Edouard Ribes [SANOFI], Martin Strugarek, Nathan Toubiana [École Polytechnique], Paul Van Liedekerke, Nicolas Vauchelet, Jorge Zubelli [IMPA, Rio de Janeiro].

7.5.1. Diffusive waves generated by a travelling wave

Observations in developmental biology show that calcic waves, generated after fertilisation within the egg cell endoplasmic reticulum, propagate within the egg cell. This motivates to explore in which circumstances a travelling wave solution of a reaction-diffusion equation can generate a travelling wave for the diffusion equation. For this purpose, we construct analytical solutions for a system composed of a reaction-diffusion equation coupled with a purely diffusive equation. We consider both the monostable (of the Fisher-KPP type) and bistable cases. We use a piecewise linear reaction term so as to build explicit solutions, which leads us to compute exponential tails, the exponents of which are roots of second, third or fourth-order polynomials. These rise conditions on the coefficients for existence of a travelling wave of the diffusion equation. The question of positivity and monotonicity is only partially answered. See [49].

7.5.2. Dealing with uncertainty in modelling

Interval observers for time-varying uncertain epidemiological models. SIR models constitute an elementary class of deterministic models of evolution of epidemics. We examine here the issue of state estimation for such models, subjected to seasonal variations and uncertainties in the transmission rates. Direct or indirect (through a vector) transmission is considered. In both cases, the measurement is assumed to consist of the number of new infectives per unit time, that is the information usually provided by the public health systems. We construct classes of interval observers with estimate-dependent gain, and provide corresponding asymptotic error bounds.

7.5.3. Modelling strategic workforce planning with structured population equations

We initiated a promising collaboration with the human resource department of Sanofi (E. Ribes), aiming at proposing a unified modelling of workforce planning based on structured population equations. Strategic Workforce Planning is a company process providing best in class, economically sound, workforce management policies and goals. Despite the abundance of literature on the subject, this is a notorious challenge in terms of implementation. Reasons span from the youth of the field itself to broader data integration concerns that arise from gathering information from financial, human resource and business excellence systems. In [43], we set the first stones to a simple yet robust quantitative framework for Strategic Workforce Planning exercises. Firstly, a method based on structured equations is detailed. It is then used to answer two main workforce-related questions: how to optimally hire to keep labour costs flat? How to build an experience-constrained workforce at a minimal cost? Further developments are in progress.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

8.1.1.1. ANR Blanc 2014-2018 “Kibord”

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

8.1.1.2. ANR 2014-2017 IFLOW

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

8.1.1.3. ANR iLITE 2016 - 2020

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

8.1.2. ITMO Cancer

8.1.2.1. ITMO Cancer 2014 - 2016, INVADE.

Emmanuel Barillot, Institut Curie (coordinator). Partners: Groups from Institut Curie, Dirk Drasdo. Objective is a model for a better understanding of breast cancer invasion.

8.1.2.2. ITMO Cancer 2016 THE call

See above “Highlights of the year"

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

8.2.1.1. ERC Starting Grant SKIPPER^{AD}, 2012-2017, Principal Investigator: Marie Doumic.

This grant allowed to fund Sarah Eugène’s and Mathieu Mézache’s Ph.Ds, as well as to develop new collaborations as with Wei-Feng Xue in Canterbury, Piotr Gwiazda in Poland, Teresa Teixeira and Zhou Xu in IBCP.

8.3. International Initiatives

8.3.1. Participation in Other International Programs

8.3.1.1. International Initiatives

CAPES-COFECUB Modelling innovative control methods for dengue fever

- Brazilian part headed by Claudio Struchiner
- French part headed by Benoît Perthame

MOSTICAW 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
- Duration: 2016 - 2017
- Start year: 2016
- The spread of certain strains of the intracellular parasitic bacterium Wolbachia in populations of mosquitoes Aedes aegypti drastically reduces their competence as vector of dengue and other severe mosquito-borne viral diseases known as arboviral infections. In absence of vaccine, or of preventive or curative treatment, the release of mosquitoes infected by the bacterium has been recently considered a promising tool to control these diseases, and experimental introductions in wild populations are currently under way in Brazil and Colombia. A key question about this method concerns the effective strategies of release of the infected mosquitoes in the field that can be applied with limited cost to reach the desired state of complete exclusion of Wolbachia-free mosquitoes. The mathematical study of central topics is the core of this project. The scientific questions to be addressed during this project are related to the study of the dynamic and control of the key invasion mechanism on finite-dimensional compartments.

- Pierre-Alexandre Bliman is International and Brazilian coordinator of the STIC Am-Sud project *MOdeling the Spread and (opTImal) Control of Arboviroses by Wolbachia* (MOSTICAW), 2016-2017. Partners: UBA (Argentina); FGV, Fiocruz, UFF (Brazil); UC, UTFSM (Chile), Universidad de Quindio, Universidad Autónoma de Occidente (Colombia), EPI MAMBA, INRA-Montpellier, CIRAD-Montpellier(France); UNA (Paraguay); Universidad Nacional Mayor de San Marcos (Peru).
- Pierre-Alexandre Bliman is also French coordinator of the ECOS-NORD project *New methods for the control of epidemics of dengue and arboviroses*, 2017-2019. Partner: Universidad del Valle, Cali, Colombia.

LiSym Liver Systems Medicine, BMBF funded project.

- Duration: 2016 - 2020
- Start year: 2016
- LiSym addresses liver diseases and regeneration, namely, steatosis, fibrosis and cirrhoses, and acutisation of chronic liver disease. It is composed of three subprojects and three junior research groups. Dirk Drasdo is co-coordinator of one of these three projects and participates in one of the others. He is also member of the leadership board.

8.4. International Research Visitors

8.4.1. Internships

- Andreas Buttenschoen (PhD student of Thomas Hillen, Univ. Edmonton, Alberta, Canada) has been welcomed in the MAMBA team, under Dirk Drasdo's supervision, for a 6-month internship within the framework of the Inria-MITACS programme. Program of the stay: Training on agent-based modeling of growth and cell migration; training on the software tool TiSim.
- Shalla Hanson (Duke University, Durham, NC) has been welcomed in the MAMBA team for a 6-month internship within the framework of the Chateaubriand programme. She is since October 2015 in a PhD thesis in co-tutela under the supervision of Michael Reed (Duke) and Jean Clairambault (MAMBA & UPMC).

8.4.2. Visits to International Teams

8.4.2.1. Sabbatical programme

BLIMAN Pierre-Alexandre

Date: Jun 2014 - Jul 2016

Escola de Matemática Aplicada

Institution: Fundação Getulio Vargas, Rio de Janeiro, Brazil

Chargé de mission at Direction des Partenariats Européens et Internationaux (DPEI), Inria

DOUMIC-JAUFFRET Marie

Date: Jun 2016 - Jul 2017

Institution: Wolfgang Pauli Institute, University of Vienna (Austria)

Sabbatical

8.4.2.2. Research Stays Abroad

STRUGAREK Martin

Date: Oct 2016

Institution: Fundação Oswaldo Cruz, Rio de Janeiro

Programme CAPES-COFECUB "Modelling innovative control methods for dengue fever"

VAUCHELET Nicolas

Date: Jan-Feb 2016

Institution: IMPA, Rio de Janeiro

Teaching collaboration between IMPA, Rio and UPMC, Paris

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. General Chair, Scientific Chair

Pierre-Alexandre Bliman: Chairman of the Conference on Mathematical Modeling and Control of Communicable Diseases, Fundação Getulio Vargas, Rio de Janeiro (RJ), Brazil, January 11-15, 2016
Marie Doumic: Chair at the Summer School PDE and Probability for Life Sciences, CIRM, Luminy, July 4-8, 2016.

9.1.1.2. Member of the Organising Committees

Luis Almeida, Benoît Perthame and Nicolas Vauchelet: Co-organisers of the "Second meeting on mathematical modeling and control in epidemic spread", Laboratoire Jacques-Louis Lions, UPMC, Paris, May 23, 2016
Jean Clairambault: co-organiser of the mini-symposium "Heterogeneity, evolution and drug resistance in cancer", ECMTB, Nottingham, England, July 12, 2016
Marie Doumic: co-organiser of the workshop on "Models in Cancer Therapy", WPI, Vienna, 1-2 july, 2016; mini-symposium organisation at the ECMTB, Nottingham, England, July 2016; mini-course and chair at CIMPA school in Moka, Mauritius, December 2016
Dirk Drasdo: co-coordinator of the modelling workpackage in ANR RHU project iLITE (coordinator: Jean-Charles Duclos-Vallée, Paul Brousse Hospital, Villejuif)
Dirk Drasdo: member of the scientific leadership team of the Liver Systems Medicine grant composed of three subprojects and three junior research groups, each subproject composed of about 10 PIs

9.1.2. Scientific Events Selection

9.1.2.1. Chair of Conference Program Committees

Pierre-Alexandre Bliman: Program chairman of the 1st meeting of the STIC AmSud project MOSTICAW, Asunción, Paraguay, October 5–9 2016

9.1.2.2. Member of the Conference Program Committees

Pierre-Alexandre Bliman: Member of the Conference Editorial Board of European Control Association (EUCA), actuating for 15th European Control Conference, Aalborg, Denmark, June-July 2016

9.1.2.3. Reviewer

Pierre-Alexandre Bliman: Reviewer for the 55th IEEE Conference on Decision and Control, Las Vegas, USA, December 2016.
Dirk Drasdo: member of the reviewing committee for foundation of "Einstein Center for Regeneration in Compromised Patients Medicine", Berlin, April 2016

9.1.3. Journal

9.1.3.1. Member of the Editorial Boards

Dirk Drasdo is member of the boards of *TheScientificWorldJOURNAL* and *Royal Society open science* (UK) and was guest editor for *PloS Comput. Biol.* (2016)
Benoît Perthame is member of the boards of *Communications in PDEs, M3AS, NoDEA, Mathematical Medicine and Biology*

9.1.3.2. Reviewer - Reviewing Activities

Pierre-Alexandre Bliman: Reviewer for the journals *Automatica, IET Control Theory & Applications, Memórias do Instituto Oswaldo Cruz*
Jean Clairambault: Reviewer for the journals *Evolutionary Applications, Bulletin of Mathematical Biology, Mathematical Modelling of Natural Phenomena, Journal of Inorganic and Organometallic Polymers and Materials, Journal of Theoretical Biology, British Journal of Cancer, PLoS Computational Biology, BMC Cancer*
Marie Doumic: Reviewer for the journals *Inverse Problems, Analytical Biochemistry, European Journal of Applied Mathematics, Bull. of Math. Biology, Comm. in Math. Sciences*
Dirk Drasdo: Reviewer for *Nature, Scientific Reports* and other journals
Nicolas Vauchelet: Reviewer for Transaction AMS, SIAM J. Numer. Anal., M3AS, J. Optim. Theory Appl., Math. Reviews

9.1.4. Invited Talks and Courses

Luis Almeida: EMS (European Mathematical Society) Diderot Mathematical Forum, Paris, March 15, 2016
Luis Almeida: IWorkshop "Models in cancer therapy", WPI, Vienna, Austria, July 1-2, 2016
Luis Almeida: Master course on Reaction-Diffusion Equations Arising in the Mathematical Modelling of Population Dynamics, Univ. Verona, October 2016
Pierre-Alexandre Bliman: Keynote speaker at the International conference on Digital Sciences and Technologies for Health, Paris, France, June 10, 2016
Pierre-Alexandre Bliman: Seminars at UMR ESPACE-DEV, Université de Guyane, Cayenne, France, December 2016
Pierre-Alexandre Bliman: Seminars at Laboratoire de Mathématiques et Dynamique de Populations, Université Cadi Ayyad, Marrakesh, Morocco, December 2016
Jean Clairambault: 2h course at the Winter School and Workshop "Nonlocal aspects in mathematical biology", Bedlewo, Poland, January 27, 2016
Jean Clairambault: French-Serbian Novi Sad Oncology Congress, Novi Sad, Serbia, March 18-19, 2016
Jean Clairambault: Journées du département ONCO, Nantes, May 3-4, 2016
Jean Clairambault: Workshop "Le cancer en équations", Rabat, Morocco, May 5-6, 2016
Jean Clairambault: First Waterloo University - Sorbonne Universités Seminar, Waterloo, Ontario, Canada, May 9-11, 2016
Jean Clairambault: 3h course at the BIOMAT Summer school "Cell dynamics and polymerization", Granada, Spain, June 1-3, 2016
Jean Clairambault: 4.5h course at the CIMPA Summer school "Mathematical modeling in Biology and Medicine", Santiago de Cuba, June 14-15-16, 2016
Jean Clairambault: Workshop "Models in cancer therapy", WPI, Vienna, Austria, July 1-2, 2016
Jean Clairambault: International conference "Mathematical models in biology and medicine", Moscow, October 31-November 3, 2016
Jean Clairambault: 4h course at the Winter school "Mathematical Models of Tumour and Disease", Jiaotong University, Shanghai, December 5-6-7-8, 2016
Jean Clairambault: Workshop on mathematical biology, Jiaotong University, Shanghai, December 10, 2016
Jean Clairambault: Workshop on Mathematical Modelling and Computation in Medicine/Biology, Tsinghua International Mathematics Forum (TSIMF), Sanya, Hainan, China, December 12-16, 2016
Marie Doumic: Plenary Speaker at the Diderot Mathematical Forum, March 15; seminar at the Polish Academy of Sciences (Warsaw), March 2016
Marie Doumic: 3h course at the BioMat2016 Conference in Granada, Spain, 1-3 June 2016; seminar in Orsay, June 16, 2016
Marie Doumic: Workshop on fragmentation processes, November 17, Villetaneuse; workshop on "Recent contributions of women in PDEs", Vienna, November 28-30, 2016
Marie Doumic: 4.5h course at the CIMPA Winter school, Moka, Mauritius, December 4-16, 2016
Dirk Drasdo: Workshop OPENTOX Basel, March 2016

Dirk Drasdo: Workshop Biomath/Bioinfo/BioStat of Cancer, Lyon, June 2016
Dirk Drasdo: CMBBE (14th international Symposium on Computational Methods in Biomechanics and Biomedical Engineering), Tel Aviv, September 2016
Benoît Perthame: Seminar, University of Chicago, January 2016
Benoît Perthame: Distinguished lecture, Hong Kong Polytechnic University, February 2016
Benoît Perthame: Seminar, Basel, Switzerland, March 2016
Benoît Perthame: Seminar, Padova, April 2016
Benoît Perthame: Course in mathematical biology, Edmonton, Alberta, Canada, May 2016
Benoît Perthame: Course on "Kinetic equations for cell motility", Porto Ercole, Italy, June 2016
Benoît Perthame: Conference in honour of Peter Markowich's 60th birthday, Beijing, July 2016
Benoît Perthame: Conference on "Kinetics and quantum dynamics", Shanghai, July 2016
Benoît Perthame: Course on "Adaptive evolution", Valparaiso, September 27-30, 2016
Benoît Perthame: Conference on "SCL with rough fluxes", Mittag-Leffler Institute, Stockholm, September 12-15, 2016
Benoît Perthame: Seminar, ETH Zürich, October 18-19, 2016
Benoît Perthame: Conference in honour of Peter Markowich's 60th birthday, KAUST, Saudi Arabia, October 31-November 3, 2016
Benoît Perthame: Conference on "Networks and collective behaviours", Seoul, November 7-10, 2016
Benoît Perthame: Courses, Analysis school, Cotonou, Benin, December 5-9, 2016
Camille Pouchol: Winter School and Workshop "Nonlocal aspects in mathematical biology", Bedlewo, Poland, January 27, 2016
Camille Pouchol: International conference "Mathematical models in biology and medicine", Moscow, October 31-November 3, 2016
Nicolas Vauchelet: 4h course at Imperial College, London, October 2016, UK
Nicolas Vauchelet: 3h course at the CIMPA Summer school "Mathematical modeling in Biology and Medicine", Santiago de Cuba, June 2016, Cuba
Nicolas Vauchelet: INdAM Workshop "Interactions between Analysis and Innovative Algorithmics", Rome, May 2016, Italy

9.1.5. Scientific Expertise

Pierre-Alexandre Bliman: Member of the Scientific committee of the ANR program "Environnement, pathogènes et maladies émergentes ou ré-émergentes - One health"
Pierre-Alexandre Bliman: Expert for the Belgium agency FNRS, for the Dutch agency NWO
Pierre-Alexandre Bliman: Reviewer for the European PhD Award on Control for Complex and Heterogeneous Systems
Pierre-Alexandre Bliman: Member of the National network of specialists of Zika and related diseases (Rede Nacional de Especialistas em Zika e doenças correlatas, RENEZIKA), Health Ministry of Brazil
Pierre-Alexandre Bliman: Member of the Brazilian National Institute for Science and Technology (INCT)
Jean Clairambault: Expert for Belgian FNRS, for the Moffitt Center (Tampa, FL), for the University of Yaoundé (Cameroon), for the BBSRC (UK), for the ERC (Consolidator Grant 2016), for the Royal Society of Edinburgh
Dirk Drasdo: Member of the program committee for SBMC 2016 (Conference on Systems Biology of Mammalian Cells) in Munich

9.1.6. Research Administration

Luis Almeida: Member of the bureau of CID 51 of the Comité National de la Recherche Scientifique
Luis Ameida: in charge of the Major MathBio of the speciality "Mathematics of modelling", M2 level, UPMC
Jean Clairambault: member of the bureau of the IPV (Interfaces pour le Vivant) doctoral funding programme of UPMC, representative of ED 386 (since 2014)
Jean Clairambault: member of the expert group of ITMO Cancer, representative of Inria (since 2008)
Marie Doumic: member of the selection committee for an assistant professor position in Grenoble

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Pierre-Alexandre Bliman: *Análise*, Escola de Matemática Aplicada, Fundação Getulio Vargas, Rio de Janeiro, Brazil (60 h)
Pierre-Alexandre Bliman: *Introdução à Teoria do controle*, Escola de Matemática Aplicada, Fundação Getulio Vargas, Rio de Janeiro, Brazil (60 h)
Marie Doumic: Master course on inverse problems and applications in population dynamics (24 h)
Dirk Drasdo: Master M2, Mathematical biology, on "Agent-based models of tissue organization", from January 2016 to April 2016 at Paris VI (Mathematics department, in 10 units per semester, total 24h)

9.2.2. Supervision

9.2.2.1. PhD defences in 2016

- PhD defence: François Bertaux, " Cell-based multi-scale modeling for systems and synthetic biology: from stochastic gene expression in single cells to spatially organized cell populations" [1], UPMC, June 2016, supervision by G. Batt (Lifeware, Inria Saclay) and D. Drasdo
- PhD defence: Youssef Bourfia, "Modélisation et Analyse de Modèles en Dynamique Cellulaire avec Applications à des Problèmes Liés aux Cancers" [2], Cadi Ayyad University, Marrakesh, December 28, 2016, supervision by M. Adimy (Lyon), J. Clairambault and H. Hbid (Marrakesh)
- PhD defence: Géraldine Cellière: "Multi-scale modeling of drug and detox-metabolism in liver" [3], Ecole du Vivant, Univ. Paris-Diderot, July 2016, supervision by D. Drasdo
- PhD defence: Casimir Emako, "Study of two-species chemotaxis model" [4], March 17, 2016, supervision by L. Almeida and N. Vauchelet
- PhD defence: Sarah Eugène, "Stochastic modelling in molecular biology: a probabilistic analysis of protein polymerisation and telomere shortening" [5], September 30, 2016, supervision by M. Doumic and Ph. Robert (Inria Paris, RAP team)

9.2.2.2. Ongoing PhD theses

- PhD in progress: Aurora Armiento, "Inverse problems for aggregation kinetics", UPMC, begun September 2013, supervision by M. Doumic and Ph. Moireau (Inria Saclay, M3DISIM team)
- PhD in progress: Noémie Boissier (since November 2013), supervision by D. Drasdo and I. Vignon-Clementel
- PhD in progress: Walid Djema, "Analysis of an AML model enabling evaluation of polychemotherapies delivered in the case of AML which have a high level of Flt-3 duplication (Flt-3-ITD)", supervision by C. Bonnet (DISCO, Saclay), J. Clairambault, and F. Mazenc (DISCO, Saclay)
- PhD in progress: Adrian Friebel, "Software of image processing and analysis of liver tissue at histological scales.", supervision by D. Drasdo and S. Hoehme
- PhD in progress: Ghassen Haddad, "Optimisation of cancer treatments: application to bladder cancer", UPMC in co-tutela with ENIT Tunis, begun October 2015, supervision by J. Clairambault and S. Ben Miled (Tunis)
- PhD in progress: Shalla Hanson, "Modelling evolution of interactions between cancer and immune cells in solid tumours", UPMC in co-tutela with Duke University, begun October 2015, supervision by J. Clairambault and M. Reed (Duke)
- PhD in progress: Hugo Martin, "New structured population models for bacterial growth", begun October 2016, supervision by M. Doumic in co-tutela with Pierre Gabriel (Versailles)
- PhD in progress: Mathieu Mézache, begun October 2016, , "Oscillatory dynamics in protein aggregation", supervision by M. Doumic in co-tutela with Human Rezaei (INRA)
- PhD in progress: Johannes Neitsch, "Growth and regeneration modeling based on an agent-based model with deformable cells", (since June 2011) supervision by D. Drasdo and P. Van Liedekerke

- PhD in progress: Pastor Pérez-Estigarribia, Universidad Nacional de Asunción, Paraguay, supervision by C. Schaerer and P.-A. Bliman
- PhD in progress: Camille Pouchol, "Modelling interactions between tumour cells and adipocytes in breast cancer", UPMC, begun September 2015, supervision by J. Clairambault, M. Sabbah, and E. Trélat
- PhD in progress: Antonin Prunet, UPMC, begun October 2014, supervision by L. Almeida and M. Sabbah
- PhD in progress: Andrada Quillas Maran, "Modelling early leukaemogenesis", UPMC, begun March 2014, supervision by J. Clairambault, F. Delhommeau and B. Perthame
- PhD in progress: Martin Strugarek, "Structured population dynamics for transmissible diseases", UPMC, begun October 2015, supervision by N. Vauchelet and B. Perthame
- PhD in progress: Cécile Taing, UPMC, begun October 2014, supervision by A. Lorz and B. Perthame

9.2.2.3. Graduate thesis defences in 2016

- Graduate thesis defence: Bettina D'Avila Barros, Escola de Matemática Aplicada, Fundação Getulio Vargas, Brazil, advisor P.-A. Bliman
- Graduate thesis (ENSAE 2nd year internship) defence: Hicham Janati [46], Malakoff, France, December 2016, supervision by J. Clairambault and M. Doumic
- Graduate thesis defence: Tales Amazonas Rands, Escola de Matemática Aplicada, Fundação Getulio Vargas, Brazil, advisor P.-A. Bliman

9.2.3. Juries

- Luis Almeida: Casimir Emako, UPMC 17/03/2016
- Luis Almeida (reviewer): Perrine Berment, Univ. Bordeaux 06/07/2016
- Luis Almeida: Thibault Liard, UPMC 04/11/2016
- Pierre-Alexandre Bliman: Hafiz Ahmed, Université de Lille, 22/09/2016
- Pierre-Alexandre Bliman: Youssef Bourfia, Université Cadi Ayyad, Maroc & UPMC, 28/12/2016
- Jean Clairambault (reviewer): Douglas Friesen, University of Edmonton, remote defence committee member, 23/02/2016
- Jean Clairambault: Tiphaine Obara, Nancy, 07/10/2016
- Jean Clairambault: Youssef Bourfia, Université Cadi Ayyad, Maroc & UPMC, 28/12/2016
- Marie Doumic (reviewer): Etienne Baratchart, Université de Bordeaux, 2016
- Marie Doumic: Casimir Emako, UPMC, 2016
- Marie Doumic: Sarah Eugène, UPMC, 2016
- Dirk Drasdo: François Bertaux, UPMC, 2016
- Dirk Drasdo: Geraldine Cellière, Ecole du Vivant, Univ. Paris-Diderot, 2016
- Benoît Perthame (reviewer): Thierry Pichard, Université de Bordeaux
- Benoît Perthame: Vincent Renault, UPMC
- Benoît Perthame: Julien Chevalier, Université de Nice-Sophia Antipolis
- Benoît Perthame: Thibault Balois, LPS-ENS
- Nicolas Vauchelet: Casimir Emako, UPMC, March 2016
- Nicolas Vauchelet: Pierre-Louis Colin, Université Lille 1, June 2016

9.3. Popularisation

Marie Doumic: Invited talk in the "Science et société" dissemination conference (http://www.iecl.univ-lorraine.fr/Cycle-Conferences-Sciences-et-Societe/lanceur.php?action=accueil) in Nancy, May 26, 2016

Nicolas Vauchelet : talks for Animath (http://www.animath.fr/) in two high schools : Lycée Racine and Lycée Notre-Dame de Bourg-la-Reine, March 2016

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Publications of the year

Doctoral Dissertations and Habilitation Theses

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[2] Y. BOURFIA. *Mathematical Modeling in Cellular Dynamics: Applications to Cancer Research*, Université Paris 6 - Pierre et Marie Curie ; Université Cadi Ayyad, December 2016, https://hal.archives-ouvertes.fr/tel-01426296

[3] G. CELLIERE. *Multi-scale modeling of hepatic drug toxicity and its consequences on ammonia detoxification*, MAMBA - Modelling and Analysis for Medical and Biological Applications, LJLL - Laboratoire Jacques-Louis Lions, Inria Paris-Rocquencourt, Universite Paris 7 Diderot, 2016, 221 p.

[4] C. EMAKO KAZIANOU. *Study of two-species chemotaxis models*, Université Pierre et Marie Curie - Paris VI, March 2016, https://tel.archives-ouvertes.fr/tel-01365414

[5] S. EUGENE. *Stochastic modelling in molecular biology: a probabilistic analysis of protein polymerisation and telomere shortening*, UPMC LJLL, September 2016, https://hal.inria.fr/tel-01377561

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[6] A. ARMIENTO, M. DOUMIC, P. MOIREAU, H. REZAEI. *Estimation from Moments Measurements for Amyloid Depolymerisation*, in "Journal of Theoretical Biology", March 2016 [*DOI :* 10.1016/J.JTBI.2016.02.037], https://hal.archives-ouvertes.fr/hal-01248255

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