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**Université Pierre et Marie Curie
(Paris 6)**

Activity Report 2015

Project-Team MAMBA

Modelling and Analysis for Medical and
Biological Applications

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

RESEARCH CENTER
Paris - Rocquencourt

THEME
**Modeling and Control for Life Sci-
ences**

Table of contents

| | |
|---|-----------|
| 1. Members | 1 |
| 2. Overall Objectives | 3 |
| 2.1. Brief history of the project-team | 3 |
| 2.2. Present objectives | 3 |
| 3. Research Program | 3 |
| 3.1. Introduction | 3 |
| 3.2. PDE analysis and simulation | 4 |
| 3.3. Stochastic and agent-based models | 4 |
| 4. Application Domains | 5 |
| 4.1. Cancer modelling | 5 |
| 4.2. Cell motion | 6 |
| 4.3. Protein polymerisation | 6 |
| 4.4. Physics of tissue organisation | 7 |
| 4.5. Liver modelling | 7 |
| 5. Highlights of the Year | 8 |
| 6. New Software and Platforms | 8 |
| 6.1. TiQuant | 8 |
| 6.2. TiSim | 8 |
| 7. New Results | 9 |
| 7.1. Cancer | 9 |
| 7.1.1. Drug resistance | 9 |
| 7.1.2. Evolution and cancer, therapy optimisation | 9 |
| 7.1.3. Interactions between tumour cell populations and their cellular micro-environments | 10 |
| 7.1.4. Combining chemo- and immunotherapies | 10 |
| 7.1.5. Hele-Shaw model of tumour growth | 10 |
| 7.1.6. The p53 protein spatio-temporal dynamics | 10 |
| 7.1.7. Lung and breast cancer | 10 |
| 7.2. Aggregation Kinetics | 11 |
| 7.2.1. Heterogeneity as an intrinsic feature in biological dynamics | 11 |
| 7.2.2. Inverse Problems and Data Assimilation Applied to Protein Aggregation and other settings | 12 |
| 7.2.3. Time asymptotics for growth-fragmentation equations | 12 |
| 7.2.4. Cell aggregation by chemotaxis | 13 |
| 7.3. Liver modeling | 13 |
| 7.3.1. Ammonia detoxification after drug-induced damage | 13 |
| 7.3.2. Concepts of modeling of liver across all scales: multiscale liver modeling | 13 |
| 7.3.3. Predicting in vivo drug toxicity from in vitro data | 14 |
| 7.3.4. Miscellaneous | 14 |
| 7.4. Miscellaneous | 14 |
| 7.4.1. Network formation and neuroscience | 14 |
| 7.4.2. Microscopic approach of a time elapsed neural model | 14 |
| 7.4.3. Uncertainty propagation | 16 |
| 7.4.4. Simulation of tissue mechanics with agent-based models | 16 |
| 8. Partnerships and Cooperations | 16 |
| 8.1. National Initiatives | 16 |
| 8.1.1.1. ANR 2011-2014 Bimod | 16 |
| 8.1.1.2. ANR Blanc 2014-2018 “Kibord” | 16 |
| 8.1.1.3. ANR 2014-2017 IFLOW | 16 |
| 8.1.1.4. INSERM 2014 - 2016, INVADE. | 16 |

| | |
|--|-----------|
| 8.2. European Initiatives | 17 |
| 8.2.1. FP7 & H2020 Projects | 17 |
| 8.2.2. Collaborations in European Programs, except FP7 & H2020 | 17 |
| 8.2.3. Collaborations with Major European Organisations | 17 |
| 8.3. International Initiatives | 18 |
| 8.3.1. Inria International Partners | 18 |
| 8.3.2. Participation In other International Programs | 18 |
| 8.3.2.1. EuroMed3+3 programme | 18 |
| 8.3.2.2. CAPES-COFECUB project | 18 |
| 8.3.2.3. Convergence SU/FAPERJ programme | 18 |
| 8.4. International Research Visitors | 18 |
| 8.4.1. Visits of International Scientists | 18 |
| 8.4.2. Internships | 18 |
| 9. Dissemination | 19 |
| 9.1. Promoting Scientific Activities | 19 |
| 9.1.1. Scientific events organisation | 19 |
| 9.1.2. Scientific events selection | 19 |
| 9.1.2.1. Member of the conference program committees | 19 |
| 9.1.2.2. Reviewer | 19 |
| 9.1.3. Journal | 19 |
| 9.1.4. Invited talks | 19 |
| 9.1.5. Scientific expertise | 20 |
| 9.1.6. Research administration | 20 |
| 9.2. Teaching - Supervision - Juries | 20 |
| 9.2.1. Teaching | 20 |
| 9.2.2. Supervision | 20 |
| 9.2.3. Juries | 21 |
| 9.3. Popularisation | 21 |
| 10. Bibliography | 22 |

Project-Team MAMBA

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

Keywords:

Computer Science and Digital Science:

- 6. - Modeling, simulation and control
 - 6.1. - Mathematical Modeling
 - 6.1.1. - Continuous Modeling (PDE, ODE)
 - 6.1.2. - Stochastic Modeling (SPDE, SDE)
 - 6.1.3. - Discrete Modeling (multi-agent, people centered)
 - 6.1.4. - Multiscale modeling
 - 6.1.5. - Multiphysics modeling
 - 6.2.1. - Numerical analysis of PDE and ODE
 - 6.2.4. - Statistical methods
- 6.3. - Computation-data interaction
 - 6.3.1. - Inverse problems
 - 6.3.2. - Data assimilation

Other Research Topics and Application Domains:

- 1. - Life sciences
 - 1.1. - Biology
 - 1.1.10. - Mathematical biology
 - 1.1.2. - Molecular biology
 - 1.1.9. - Bioinformatics
 - 1.2. - Ecology
 - 1.3. - Neuroscience and cognitive science
 - 1.4. - Pathologies
- 2. - Health
 - 2.2. - Physiology and diseases
 - 2.2.3. - Cancer
 - 2.2.4. - Infectious diseases
 - 2.3. - Epidemiology
 - 2.4. - Therapies
 - 2.4.1. - Pharmacokinetics and dynamics
 - 2.4.2. - Drug resistance

The MAMBA team is located in two places in Paris: the Inria Paris research centre (2, rue Simone Iff from January 2016; formerly, until December 2015 in Rocquencourt) and the Jacques-Louis Lions Laboratory (LJLL) at Université Pierre et Marie Curie (UPMC), 4, place Jussieu.

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2. Overall Objectives

2.1. Brief history of the project-team

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

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.

2.2. Present objectives

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, [75], 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 or 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.

¹Drasdo, Hoehme, Block, *J. Stat. Phys.*, 2007

²as 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

³as in A. Friedman et al, Asymptotic limit in a cell differentiation model with consideration of transcription, *J. Diff. Eq.*, 2012

⁴as in R. Yvinec et al., Adiabatic reduction of stochastic gene expression with jump Markov processes, *J. Math. Biol.*, 2013.

⁵H. 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 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 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 ⁶ [67] [65]. 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 [82], [83], [81] [23]. Through multiscale analysis, they can be related to stochastic and free boundary models used in cancer modelling.

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 [63] or size/age tracking [89]) 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 [70], [71], some combining statistical and deterministic approaches [69] with application to raw experimental data [13], we plan to develop our methods to new structured-population models (or stochastic fragmentation processes as in [68]), useful for other types of data or populations (e.g. size/age tracking, polymer length distribution, fluorescence in single cells).

3.3. Stochastic and agent-based models

The link between stochastic processes and kinetic equations is a domain already present in our research ⁷ [69] 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 [68], 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 ⁸. 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 [72], [29]. This approach has advantages if the population of cells reveals inhomogeneities on small spatial scales as it occurs if organ architecture is represented [75], 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. [88]) and in lattice-free (or off-lattice) models, in which the position [72], [74] or even the shape (e.g. [29]) of the cell can change gradually. 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 ([29], [73]).

⁶B. Perthame, *Transport equations in biology*, Springer, 2007

⁷H. Byrne and D. Drasdo, Individual-based and continuum models of growing cell populations: a comparison, *J. Math. Biol.* 2009

⁸Cáceres, Carrillo, Perthame *J. Math. Neurosci.* 2011; Pakdaman, Perthame, Salort *Nonlinearity* 2010

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 [93].

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 relevant phenotypes – 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 [82], [81], [23], [41] are close to models used in ecology for adaptive dynamics.

Multi-scale modelling of EMT. The major step from a benign tumour that can be eradicated by surgery and an invasive cancer is the development step at which cells detach from the tumour mass and invade individually the surrounding tissue⁹. The invasion is preceded by a transition (called EMT - epithelial mesenchymal transition) of the cancer phenotype from an epithelial type to a mesenchymal type cell. We have so far worked on multi-scale modelling of EMT¹⁰, and the step by which invading cancer cells enter blood vessels, called intravasation¹¹. We currently perform *in vitro* simulations of cancer cell invasion for non-small cell lung cancer (NSCLC) cells having a 5-year survival fraction of about 20%, and for breast cancer. Under development (in collaboration with our biologist partners within the IUC for the experimental part) is also a phenotype-structured PDE model of the interactions between colonies of MCF7 breast cancer and adipocyte stromal support populations (see below, in “New results”, Lung and breast cancer).

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 [62], [81], [63], [80]. Prior to using optimisation methods, we design models of the targeted cell populations (healthy and tumour, including molecular or functional drug targets [61]) by PDEs or agent-based models [59], 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.

⁹Weinberg, The biology of cancer, Garland, 2007

¹⁰Ramis-Conde, Drasdo, Anderson, Chaplain, Biophys. J., 2008

¹¹Ramis-Conde, Chaplain, Anderson, Drasdo, Phys. Biol. 2009

4.2. 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 collaboration with biophysicists at Institut Curie in Paris, we develop and study ¹² mathematical models based on kinetic equations for bacterial travelling waves in a microchannel. These models have shown a remarkable quantitative agreement with experimental observations.

Cell motion arises also in the growth of solid tumours, which can be described through cell population models or multiphase flows ¹³. 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 ¹⁴, 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 ¹⁵. Asymptotic analysis makes a link between these different mechanistic models [91].

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 (including some involving members of this project like [57]). Several theoretical models have also been proposed recently for the advancement of tissue covering unoccupied areas (see, for instance, [58]). It is particularly interesting to study epithelial gap closure *in vivo*. However, the complexity of the process and the difficulty to measure relevant quantities directly and to control the parameters *in vivo*, lead biologists to seek alternative systems where epithelial gap closure can be studied under better-defined and better-controlled conditions. We extended our work from *in vivo* studies to *in vitro* situations taking advantage of a collaboration with the group of Benoît Ladoux who performed experiments on cell monolayers of human keratinocytes and of MDCK cells. We could single out some similar 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 our model we consider viscous behaviour in the tissue and some simple friction with the substrate, plus boundary terms associated to cable and lamellipodial forces. The numerical simulations obtained using this model are in good agreement with the experimental results [30], [27].

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 [67], [65], or with stochastic models. One difficulty of this application is that the reactions imply both very small and very large scales for the sizes of polymers, experimental data giving only access to the time evolution of

¹²N. Bournaveas, V. Calvez, S. Gutiérrez and B. Perthame, Global existence for a kinetic model of chemotaxis via dispersion and Strichartz estimates, *Comm. PDE*, 2008

¹³J. Ranft et al, Fluidization 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.

¹⁴I. Ramis-Conde et al., *J. Phys. Biol.*, 2009

¹⁵Works by O. Saut, T. Colin, A. Iollo, N. Ayache, J. Lowengrub

size-averaged quantities. Moreover, there exists an intrinsic variability among experiments, which has to be distinguished from a lack of reproducibility [44].

The European starting grant SKIPPER^{AD}, which follows the ANR project TOPPAZ, came up very naturally from a cooperation established with Human Rezaei, a biologist expert in amyloid diseases at INRA Jouy-en-Josas. It allowed us to further develop new collaborations, in particular with W.F. 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 methods, linked to the ones previously developed for bacteria [13].

Moreover, this field of applications to human neurodegenerative diseases brings us new questions, 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. 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 (¹⁶, ¹⁷, ¹⁸). Centre-based growth models already account for many of the observed phenomena (e.g. ¹⁹, ²⁰). They furthermore allow calculation of the stress tensor in the tissue. Agent-based models resolving cells at higher resolution²¹ 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. This allows to relate stress and strain in tissues and the deformation and stress a cell feels at subcellular scale. We extended a deformable cell model towards cell division, which enables us to calculate precise stress - strain relationships for cells, which later can be used to calibrate forces in center-based models. This is fundamental to understand the impact of mechanical stress on cell cycle progression or other cell decisions. Moreover, we established a model to explain the proliferation pattern of cells growing in closed capsules.

4.5. 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, 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. ²²); only recently are approaches addressing the tissue scale being developed ([75], ²³, ²⁴, ²⁵, ²⁶). We are developing 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

¹⁶Ingber, Proc. Natl. Acad. Sci (USA), 2005

¹⁷Trepat et. al., Nat. Phys. 2009

¹⁸Alessandri et. al., Proc. Natl. Acad. Sci. (USA) 2013

¹⁹Drasdo and Hoehme, Phys. Biol. 2005

²⁰Drasdo and Hoehme, New Journal of Physics 2012

²¹Odenthal, Smeets, van Liedekerke, et. al., PloS Comput Biol. 2013

²²Diaz-Ochoa et. al. Frontiers in Pharmacology, 2013

²³Ricken, Dahmen, Dirsch, Biomech. Model. Mechanobiol. 2010

²⁴Debbaut et. al., J. Biomech. Eng. 2014

²⁵Siggers, Leungchavphongse, Ho, Repetto, Biomech. Model. Mechanobiol. 2014

²⁶Schwen et. al., PLoS Comput. Biol. 2014

pharmacokinetics in liver and liver cancer, and model-based prediction of in-vivo drug toxicity from in-vitro measurements²⁷. The research work is performed within the EU project NOTOX, the BMBF project Virtual Liver Network and the ANR project IFLOW.

5. Highlights of the Year

5.1. Highlights of the Year

Awards

Benoît Perthame is the 2015 laureate of the Inria - French Académie des Sciences Grand Prize: <http://www.inria.fr/en/institute/inria-in-brief/inria-awards/2015-prize-winners/benoit-perthame-grand-prize>.

6. New Software and Platforms

6.1. TiQuant

Tissue Quantifier

KEYWORDS: Systems Biology - Bioinformatics - Biology - Physiology

FUNCTIONAL DESCRIPTION

Systems biology and medicine on histological scales require the 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 has been little recognised thus far. 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, allowing 3D reconstructions of liver lobules down to a resolution of less than a micrometer. The software has been made available to the public by publication in ref. [14], together with a new surface reconstruction algorithm based on the morphological Watershed algorithm. We validated that this algorithm allows reconstruction of cell shapes from nucleus and blood microvessel information, and demonstrated that it allows a reliable estimate of liver lobules, the smallest repetitive functional and micro-anatomical liver units, that besides in pig are not anatomically separated.

A separate 2D version of it (TI-Quant-BF-2D) has been used to analyse the invasion pattern of non-small cell lung cancer (NSCLC) cells *in vitro* [24] (see below).

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

6.2. TiSim

Tissue Simulator

KEYWORDS: Systems Biology - Bioinformatics - Biology - Physiology

FUNCTIONAL DESCRIPTION

We advanced the complementary software TiSim (Tissue Simulator) that will soon be provided. TiSim allows agent-based simulations of multicellular systems and can be directly used by processed image data provided by TiQuant.

²⁷Godoy et al., *Arch Toxicol.* 2013 Aug;87(8):1315-1530

The software has been tested over the whole year including almost all group members to prepare it for submission and will present a number of application example to introduce a potential user into the software. These will be monolayer and multicellular spheroid growth, a multiscale modeling example and liver regeneration.

- Contact: Dirk Drasdo

7. New Results

7.1. Cancer

Participants: Luís Lopes Neves de Almeida, Rebecca Chisholm, Jean Clairambault, François Delhommeau [Haematology department, St Antoine Hospital, Paris], Dirk Drasdo, Ján Eliaš, Alexandre Escargueil [Cancer biology and therapeutics lab, St Antoine Hospital, Paris], Ghassen Haddad [ENIT, Tunis], Shalla Hanson [Department of mathematics, Duke University, Durham, NC], Pierre Hirsch [Haematology department, St Antoine Hospital, Paris], Groups Invade, Lungsysii, 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, Alexander Lorz, Benoît Perthame, 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], Emmanuel Trélat [LJLL, UPMC], Paul Van Liedekerke, Nicolas Vauchelet, Irène Vignon-Clementel [REO], Yi Yin.

7.1.1. Drug resistance

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. In one of them [23], a 1D space variable has been added to the phenotypic structure variable to account for drug diffusion in tumour spheroids. In another one, focusing on both Darwinian selection and Lamarckian-like (non-genetic) instruction, published in *Cancer Research* [41], where deterministic and agent-based modelling are processed in parallel, we have added advection and diffusion terms to the initial integro-differential model and considered a physiologically based 2-dimensional phenotypic structure variable. This model, designed to take account of previously published biological observations on (reversible) drug tolerance persistence in a cultured population of non-small cell lung cancer (NSCLC) cells [90], reproduces the observations and we propose to assess the model by testing biologically based hypotheses. This work, also presented in various conferences ([34], [35], [31]) is conducted in close collaboration with the INSERM-UPMC team “Cancer biology and therapeutics” (A. Larsen, A. Escargueil, M. Sabbah) at St Antoine Hospital. It has also led our postdoctoral fellows Rebecca Chisholm and Tommaso Lorenzi to prolong their work on the *Cancer Research* paper by publishing two more articles [21], [48], one of which is a joint work with Alexander Lorz. This work is currently continued from the point of view of optimal control in Camille Pouchol’s PhD thesis.

7.1.2. Evolution and cancer, therapy optimisation

Guided by our goal to understand and overcome drug resistance in cancer cell populations[41], we are considering cancer as an evolutionary phenomenon at two time scales: a large time scale (billions of years) of evolution of the genomes, from unicellular organisms to organised multicellularity (viewing cancer as more an archeoplasm than a neoplasm, an evolution backwards, following Davies and Lineweaver, *Phys Biol* 2011, and others [78], [66], [92], [79]) with shortcomings due to malfunctions in the processes of control of cell differentiation, and a short time scale (duration of a human life) of evolution in the “epigenetic landscape” of a given genome (as advocated by Sui Huang and Angela Pisco, e.g. recently in *Nature*, *Br J Cancer* and elsewhere [76], [77], [85], [86], [94]). It leads us to propose theoretical frameworks for innovative cancer therapeutics from this evolutionary biology viewpoint, taking into account the major clinical issue of drug resistance in cancer cell populations, as presented in [31] and exposed to a medical audience at the symposium “Réseau Cancer des Points Cardinaux” (http://www.frog-oncogeriatric.com/fichiers/evnmt_41.pdf).

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

A phenotype-structured model of the interactions between a breast cancer cell population (MCF7 cultured cells, collaboration with M. Sabbah, St Antoine Hospital) and its adipocyte stroma support cell population has been developed (T. Lorenzi, C. Pouchol, J. Clairambault) in the framework of Camille Pouchol's Inria internship ([56]). It has led to hiring C. Pouchol as a PhD student at UPMC (on a university grant "Interfaces pour le Vivant") on the same subject with perspectives in optimal therapeutic control, under the supervision of J. Clairambault, M. Sabbah and E. Trélat, see below "Supervision".

7.1.4. *Combining chemo- and immunotherapies*

Both from the point of view of interactions with the tumour micro-environment and of innovative anticancer therapies, it is necessary to take into account the immune response in cancer. This recently developed activity, (illustrated by presentations in session 70 in ICNAAM 2016 [32]) has led to the involvement in 2015 of Shalla Hanson as a PhD student in co-tutela between Duke University, NC and UPMC, see below "Supervision".

7.1.5. *Hele-Shaw model of tumour growth*

The mathematical analysis of macroscopic models of tumor growth with one type of cancer cells has been continued. On the one hand, in [47], the concept of viscosity solutions has been implemented for the case with active motion. On the other hand, the regularity of the free boundary is proved in [51] using methods developed for the standard Hele-Shaw equation and a new formulation.

7.1.6. *The p53 protein spatio-temporal dynamics*

Our previously developed spatio-temporal models for an intracellular dynamical response of the p53 protein to DNA damage, have been exploited further, and several testable biological hypotheses have been proposed in [33]. Among them, we suggest ideas that link spatio-temporal location of the p53 protein with a specific cell fate of a single cell in [33], [2] and, based on our new oscillator relying on both positive and negative regulation of p53 by Mdm2 (in tight cooperation with MdmX), we provide molecular insights into an excitability of the p53 network, i.e., we propose a molecular explanation for a full pulsatile response of p53 independently of input (ATM) signalling, challenging thus different fates of ATM downstream targets in the regulation of p53 in response to different stimuli, such as γ - and UV-radiation.

Our mathematical models, all included in J. Eliaš's PhD thesis [2] (defended on the 1st September 2015), contribute to understanding the variability of p53 in response to single and double strand breaks and reveal some new aspects of the core p53-Mdm2 protein feedback.

7.1.7. *Lung and breast cancer*

We developed an image analysis software and designed image analysis pipelines which we used to quantify the invasion pattern of non-small cell lung cancer (NSCLC) cells in multicellular spheroid *in vitro* experiments [24]. Based on the analyses, we demonstrated that the concomitant over-expression of FIR (far upstream element binding protein interacting repressor) and its splice variants drives NSCLC migration and dissemination.

We developed an agent-based, centre-based model of cell migration in cancer invasion based upon experimental observations of cell shape and cell behaviour in multicellular spheroid experiments of breast and lung cancer cells. In these experiments, cells deform from a sphere into an oblong shape upon migration, and adopt a spherical shape again whenever they turn back to such spheroids. This was implemented. Moreover, we developed a 3D model for the extracellular matrix (ECM) in which the matrix is modelled by an irregular network of springs with nodes represented as elastic objects. Migrating cells anchor in the network to move, leading to network deformation. We implemented a number of different biological mechanisms of cell migration and cell-ECM interaction. We find that a relatively simple model is sufficient to explain all phenomena of a single invading cell (Palm et. al., in preparation).

The combination of image analysis and of the abovementioned refined invasion model should allow a quantitative model of multicellular invasion following the same line of research as for SK-MES-1 cells, where we inferred a multicellular spheroid growth model from image data within a pipeline of experiment, imaging, image analysis and modelling [17]. In that paper, we used spatial-temporal image data of cell nucleus distribution, cell proliferation, death, and ECM distribution for two growth conditions (oxygen and glucose) to calibrate a model which was then able to quantitatively correctly predict the growth kinetics of the tumor spheroids for two other growth conditions, one strongly glucose limited, another strongly oxygen-limited.

Finally, we developed an image analysis pipeline to estimate the number of cancer cells in a patient with non-small cell lung cancer (NSCLC) from non-invasive image modalities. The estimate bases upon cell counts from histological serial sections of the tumor which have been related to the D-value inferred from Diffusion Weighted (DW) MRI (Yi et. al., paper in preparation).

7.2. Aggregation Kinetics

Participants: Aurora Armiento, Tom Banks [CRSC, NCSU, Raleigh, USA], Thibault Bourgeron, José Antonio Carrillo [Imperial College, London, United Kingdom], Marie Doumic, Miguel Escobedo [Universidad del País Vasco, Bilbao, Spain], Sarah Eugène, Marc Hoffmann [Ceremade, Université Paris-Dauphine], François James [MAPMO, Université d'Orléans], Nathalie Krell [Université de Rennes 1], Carola Kruse, 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], Nicolas Vauchelet, Min Tang [Jiaotong University, Shanghai], Zhou Xu [IBCP, Paris], Wei-Feng Xue [University of Kent, United Kingdom].

7.2.1. Heterogeneity as an intrinsic feature in biological dynamics

Combining deterministic and probabilistic approaches, we investigated in two different applications - namely senescence and protein aggregation - the impact of heterogeneity on dynamical features of the considered populations.

Yeast Senescence and Telomere replication In eukaryotes, the absence of telomerase results in telomere shortening, eventually leading to replicative senescence, an arrested state that prevents further cell divisions. While replicative senescence is mainly controlled by telomere length, the heterogeneity of its onset is not well understood. Insights on this key question may have consequences both for cancer and aging issues.

In collaboration with T. Teixeira and Z. Xue from IBCP, we proposed a mathematical model based on the molecular mechanisms of telomere replication and shortening to decipher the causes of this heterogeneity [7]. Using simulations fitted on experimental data obtained from individual lineages of senescent *Saccharomyces cerevisiae* cells, we decompose the sources of senescence heterogeneity into interclonal and intracolonial components, and show that the latter is based on the asymmetry of the telomere replication mechanism. We also evidence telomere rank-switching events with distinct frequencies in short-lived versus long-lived lineages, revealing that telomere shortening dynamics display important variations. Thus, the intrinsic heterogeneity of replicative senescence and its consequences find their roots in the asymmetric structure of telomeres.

These promising first results lead us to an ongoing collaboration, and hopefully will allow still more insight on complex mechanisms not yet modelled mathematically.

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. To investigate 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, we formulated a new stochastic minimal model that is capable of describing the characteristics of amyloid growth curves despite its simplicity [44]. We then solved the stochastic differential equations of our model and gave a 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 demonstrated the application of our results to inform experiments in a convenient and clear way. 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.

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

As mathematical models become more complex with multiple states and many parameters to be estimated using experimental data, there is a need for critical analysis in model validation related to the reliability of parameter estimates obtained in model fitting. This leads to a fundamental question: how much information with respect to model validation can be expected in a given data set or collection of data sets?

In the biological context of amyloid formation, the question is to quantify to which extent a given model may be appropriately fitted and selected for, given relatively sparse data. Estimating reaction rates and size distributions of protein polymers is an important step towards understanding the mechanisms of protein misfolding and aggregation, a key feature for amyloid diseases. Specifically, experimental measurements often 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).

In a first study [4], in collaboration with H.T. Banks and H. Rezaei, we illustrated the use of tools (asymptotic theories of standard error quantification using appropriate statistical models, bootstrapping, model comparison techniques) in addition to sensitivity that may be employed to determine the information content in data sets. We do this in the context of recent models [87] for nucleated polymerisation in proteins, about which very little is known regarding the underlying mechanisms; thus the methodology we developed may be of great help to experimentalists.

In another study [39], related to a different biological setting (the frog olfactory tract), we use a method based on the Mellin transform, as in [64], to solve a spectral inverse problem arising from the modeling of the transduction of an odor into an electrical signal. The problem is to find the spatial distribution of CNG ion channels along the cilium of a frog, which allow a depolarizing influx of sodium ions, which initiate the electrical signal. This problem comes down to solving a Fredholm integral equation. We prove observability and continuity inequalities by estimating the Mellin transform of the kernel of this integral equation. We perform numerical computations using experimental data.

To get more insight into the estimation of reaction rates and size distributions of protein polymers, we are now developing an approach based on a data assimilation strategy. In this purpose, A. Armiento's Ph.D is focused on setting this 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). In [37] we proposed a general methodology, and we solved the problem theoretically and numerically in the case of a depolymerising system. We then applied 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.

7.2.3. *Time asymptotics for growth-fragmentation equations*

The long-term dynamics of fragmentation and growth-fragmentation equations has been for long an important research field for BANG then MAMBA research team. 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 [84] 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 [43]. 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 [60]. These results exemplify the continuing need for further analysis of these interesting equations.

7.2.4. Cell aggregation by chemotaxis

We follow our investigation on the kinetic model describing the chemotactic motion of bacteria. When taxis dominates the unbiased movements, the kinetic system is approximated by the aggregation equation. The study of such equation is challenging since blow-up in finite-time of solutions occurs. We have defined the notion of measure-valued solution [8] and we have proposed and studied a numerical scheme to simulate these solutions[18].

In another approach, more accuracy can be obtained with the kinetic model by adding an internal variable describing the methylation level of the internal receptors of bacteria. In [55] we have investigated the link between these kinetic models with an internal variable and the one without internal variable.

7.3. Liver modeling

Participants: 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.

7.3.1. 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 located in the center of each liver lobule (pericentral damage), the repetitive functional and anatomical tissue units of liver. Human has about a 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 of ammonia intoxication each year. In recent papers we demonstrated by an integrated model that the widely accepted key reactions scheme of ammonia detoxification is insufficient to explain ammonia detoxification after pericentral lobule damage and predicted a missing ammonia sink [73]. This finding has triggered new experiments leading to the identification of a widely ignored but fundamentally important ammonia sink mechanism We could show by a testing a number of different mechanisms within novel models that this sink mechanism was the only one able to explain the data [15]. The reaction turned out to have the potential to be therapeutically used by injection of a molecular cocktail triggering it. In the animal model death could be prevented using this cocktail hence providing a possible therapy approach for patients suffering from hyperammonemia. [15]. In a follow-up work, further models have been studied and classified by statistical methods to quantify model selection (Cellière et al., in preparation).

7.3.2. Concepts of modeling of liver across all scales: multiscale liver modeling

Based upon developed multiscale concepts [12], we developed a multi-level spatial temporal multiscale models of APAP (paracetamol, acetaminophen) toxicity and ammonia metabolism. In one of these models we integrated molecular pathways of APAP drug toxicity (PD); in another one, we represented the ammonia detoxification pathway into each individual hepatocyte of an agent-based model that describes the precise liver lobule architecture (compare with [73]). This allows us to study the impact of space and architecture on the drug toxicity and drug detoxification. We find in certain cases important differences between models that do represent architecture and those that do not (Cellière et al., in preparation).

7.3.3. Predicting *in vivo* drug toxicity from *in vitro* data

APAP (paracetamol, acetaminophen) *in vitro* experiments have been used to calibrate a model of APAP drug toxicity with *in vitro* data, and modify this model to predict *in vivo* toxicity. This procedure is aimed at as a general pathway among cosmetic and pharmaceutical companies to eliminate or at least reduce animal experiments and it should allow a better prediction of drug toxicity in human. Three critical differences between *in vitro* and *in vivo* settings 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, APAP is metabolised and downstream apoptosis can occur. (3) The liver architecture, that is responsible for critical differences in the spatial distribution of the drug. The results are in preparation for publication (Cellière et. al., in preparation).

7.3.4. Miscellaneous

In addition, regenerating lobules after partial hepatectomy were analysed by image analysis, and first simulations of blood and bile flow and molecular transport in those lobules simulated.

7.4. Miscellaneous

Participants: Noémie Boissier, Maria José Cáceres [Universidad de Granada], Julien Chevallier [Université de Nice], Géraldine Cellière, Marie Doumic, Dirk Drasdo, Adrian Friebel, Group Heinzle [Univ. Saarbruecken, Germany], Group Hengstler [IfADo, Germany], Stefan Hoehme, Tim Johann, Group Klingmueller [German Cancer Center, Heidelberg], Johannes Neitsch, Benoît Perthame, Patricia Reynaud [Université de Nice], Group Reo [Inria Paris - Rocquencourt], Paul Van Liedekerke, Eric Vibert [Hopital Paul Brousse], Yi Yin, Group Zerial [Max-Planck Inst. for Molecular Genetics, Dresden, Germany], Groups Iflow, Notox, Vln.

7.4.1. Network formation and neuroscience

Motivated by neurodevelopment and differentiation in developing tissues, a new explanation for sharp boundary formation is analysed in [25]; interestingly, this phenomenon relies on a limited diffusion of homeoproteins (collaboration with the Mycenae team).

Models for neural networks have been proposed which describe the probability to find a neuron for which a time s has elapsed since the last discharge. These are written under the form of a nonlinear age-structured equation where the total network activity modulates the firing rate. An inhomogeneous network of networks with variability on the refractory period is studied in [19].

We have also continued the analysis and numerical simulation of models for natural transportation networks formation based on an elliptic-parabolic system of partial differential equations. The model describes the pressure field using a Darcy's type equation and the dynamics of the conductance network under pressure force effects. Randomness in the material structure is represented by a linear diffusion term and conductance relaxation by an algebraic decay term [16]. Figure 1 below gives a numerical simulation of a network formed by such a model.

7.4.2. Microscopic approach of a time elapsed neural model

The spike trains are the main components of the information processing in the brain. To model spike trains several point processes have been investigated in the literature. More macroscopic approaches have also been studied, using partial differential equation models. With J. Chevallier, M. Cáceres and P. Reynaud-Bouret, we wanted to build a bridge between several point processes models (Poisson, Wold, Hawkes) that have been proved to statistically fit real spike trains data and age-structured partial differential equations as introduced by Pakdaman, Perthame and Salort. To do so, we focused on a seemingly simple one-neuron model, for which we stated the - nonlinear and strongly coupled - PDE model satisfied in average by its point measure when the process model is a Poisson, a Wold or a Hawkes process [10].

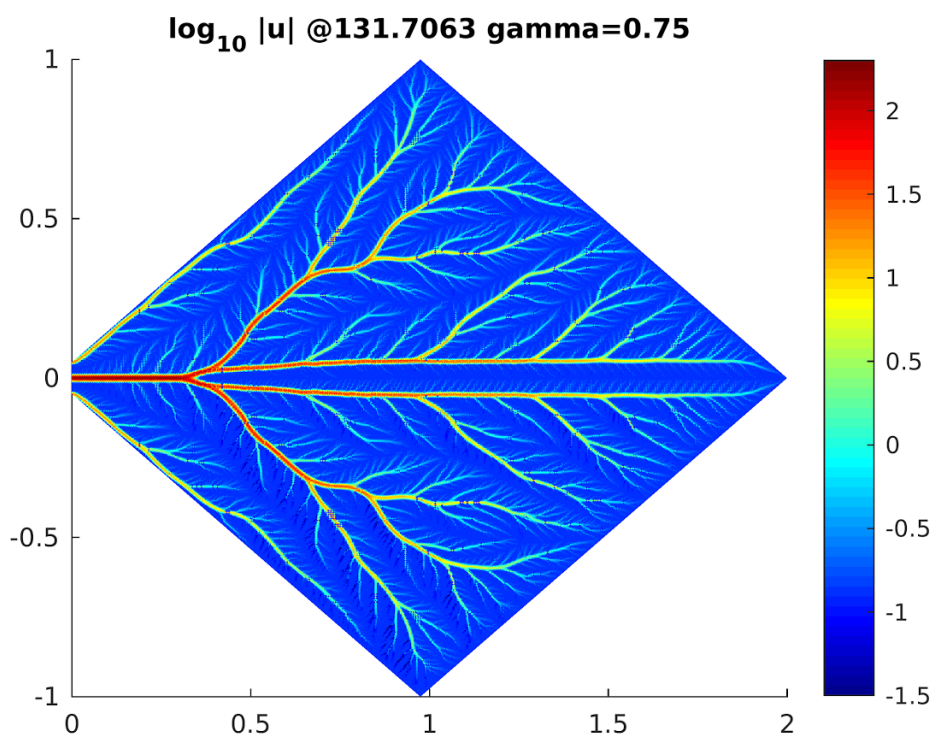


Figure 1. Network formation based on an elliptic-parabolic system of partial differential equations.

7.4.3. Uncertainty propagation

In [42], we study two intrusive methods for uncertainty propagation in scalar conservation laws based on their kinetic formulations. The first one is based on expansions on an orthogonal family of polynomials. The second method uses convolutions based on Jackson kernels. We prove that it satisfies BV bounds and converges to the entropy solution but with a spurious damping phenomenon. Therefore we introduce a second method, which is based on projection on layered Maxellians, and which arises as a minimisation of entropy. This new method satisfies the maximum principle by construction as well as partial entropy inequalities and thus provides an alternative to the standard method of moments which, in general, does not satisfy the maximum principle. Simple numerical simulations for the Burgers equation illustrate these theoretical results.

7.4.4. Simulation of tissue mechanics with agent-based models

In ref. [29] we study and discuss in how far mechanical effects of cells in tissue organisation and growth processes can be captured by agent-based models. We consider a wide range of agent-based models, i.e., lattice base models with one lattice site allowing for many cells or one cell at most, many lattice sites occupied by a single cells (so called Cellular Potts model, Lattice Gas Cellular Automaton approaches, center-based models and vertex models, in which the forces between cells are calculated as forces between the cell centers, as well as deformable cell models in which the cell surface is triangulated. We consider growth of monolayers and multicellular spheroids as reference problems. We also compare in this paper spatial resolution, the capability of the different approaches to represent the physics, cell shape, the computational efficiency and code access. In addition, models evaluating the mechanical effects of growing cell populations in elastic capsules were established and studied.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

8.1.1.1. ANR 2011-2014 Bimod

It has been prolonged until March 2015, time at which an international workshop on “Multi-scale and hybrid modelling in cell and cell population biology” has been held at UPMC, Paris (J. Clairambault and V. Volpert organisers), with 25-30 speakers on invitations. Its proceedings under the form of extended abstracts are available on a dedicated website: <http://www.itm-conferences.org/articles/itmconf/abs/2015/02/contents/contents.html>

8.1.1.2. ANR Blanc 2014-2018 “Kibord”

This recently accepted 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.

8.1.1.3. 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.

8.1.1.4. INSERM 2014 - 2016, INVADE.

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

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

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

This grant allowed to fund Sarah Eugène's Ph.D and M. Tournus's post-doc, as well as to develop the new collaborations with W-F. Xue in Canterbury and T. Teixeira in IBCP.

8.2.2. Collaborations in European Programs, except FP7 & H2020

8.2.2.1. *NOTOX*

Type: COOPERATION

Instrument: Integrated Project

Objectif: NC

Duration: January 2011 - December 2015

Inria contact: Dirk Drasdo

NOTOX developed and established a spectrum of systems biological tools including experimental and computational methods for (i) organotypic human cell cultures suitable for long term toxicity testing and (ii) the identification and analysis of pathways of toxicological relevance. NOTOX initially used available human HepaRG and primary liver cells as well as mouse small intestine cultures in 3D systems to generate own experimental data to develop and validate predictive mathematical and bioinformatic models characterizing long term toxicity responses. Cellular activities were monitored continuously by comprehensive analysis of released metabolites, peptides and proteins and by estimation of metabolic fluxes using ¹³C labelling techniques (fluxomics). At selected time points a part of the cells was removed for in-depth structural (3D-optical and electron microscopy tomography), transcriptomic, epigenomic, metabolomic, proteomic and fluxomic characterisations. Together with curated literature and genomic data the toxicological data was organised in a toxicological database (cooperation with DETECTIVE, COSMOS and TOXBANK). Physiological data including metabolism of test compounds have been incorporated into large-scale computer models that are based on material balancing and kinetics. Various “-omics” data and 3D structural information from organotypic cultures will be integrated using correlative bioinformatic tools. These data also served as a basis for large scale mathematical models. The overall objectives are to identify cellular and molecular signatures allowing prediction of long term toxicity, to design experimental systems for the identification of predictive endpoints and to integrate these into causal computer models.

Inria contributions were multilevel and multiscale models of drug toxicity and its consequences on ammonia detoxification and are detailed in the result section on liver modeling. Webpage: <http://notox-sb.eu/fp7-cosmetics-europe/>

8.2.3. Collaborations with Major European Organisations

U. Klingmüller: DKFZ (German Cancer Research Centre), Department for Systems Biology (Germany)

Role of HGF in liver regeneration. Lung cancer.

K. Breuhahn: University Hospital of Heidelberg, Pathology (Germany)

Lung cancer invasion. Role of HGF in liver regeneration.

JG Hengstler: Leibniz Center, IfADo (Germany)

Liver research, toxicology, regeneration.

University of Leipzig, Interdisciplinary center for bioinformatics (Germany)

Projects on tissue regeneration, software

8.3. International Initiatives

8.3.1. Inria International Partners

8.3.1.1. Declared Inria International Partners

1. German Research Ministry (BMBF) funded project on the systems biology of lung cancer. The major aim is to better understand the early metastasis formation and invasion of lung cancer, including therapeutical options. Data on all levels ranging from intracellular up to organ level will be used to establish successively an integrated multiscale model of cellular and migration decisions in lung cancer. A particular focus will be on dissecting how cellular organisation and communication in spheroid cultures and co-cultures of lung cancer cell lines with selected endothelial cells affects information processing and the proliferation and migration decisions downstream. To reveal the inhomogeneous spatio-temporal organisation in these tumour growth models, specific probes for medical imaging, quantify extracellular cytokine concentrations will be used, and the effects of pharmacological inhibitors be monitored. By data and model integration, parameters should be identified that critically determine early spread and facilitate to predict possibilities for improved therapeutic options. The project coordinator is Ursula Klingmueller, German Cancer Research Centre (DKFZ), Heidelberg (<http://www.lungsys.de/>)

2. German Research Ministry (BMBF) funded project on the systems biology of liver (Virtual Liver Network). The aim of the VLN project is to set up multiscale models of liver. The Virtual Liver will be a dynamic model that represents, rather than fully replicates, human liver physiology morphology and function, integrating quantitative data from all levels of organisation. Our part ranges from the intracellular up to the level of groups of liver lobules. A liver lobule is the basic repetitive functional unit of liver. Applications are explained in the text. The networks has 69 Principle Investigators organised in about 10 work packages, each of which have a number of sub-projects (<http://www.virtual-liver.de>).

8.3.2. Participation In other International Programs

8.3.2.1. EuroMed3+3 programme

The M3CD network (https://www.rocq.inria.fr/bang/M3CD_website/), coordinated by J. Clairambault, has led in 2015 as usual to bilateral visits (M. Adimy, J. Clairambault, to Marrakesh and to Tlemcen, T. Touaoula to Lyon, visits of students to Paris and Lyon). It has terminated its activities in 2015 by a meeting in September in Rabat (Morocco) together with other EuroMed3+3 networks. The future of EuroMed3+3 (<http://www.inria.fr/en/europe-international/international-relations/international-calls-for-projects/euromediterranean-3-3>) will be discussed in June 2016 in a meeting at the Sophia-Antipolis Inria research centre.

8.3.2.2. CAPES-COFECUB project

“Modeling innovative control methods for dengue fever”, in collaboration with Fondation Oswaldo Cruz (FioCruz), Rio de Janeiro, Brazil.

8.3.2.3. Convergence SU/FAPERJ programme

“Control and identification for mathematical models of dengue epidemics” in collaboration with IMPA, Rio de Janeiro, Brazil.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

Juan Calvo came for a one month visit in January and February, 2015, to work on a new model for long-term protein polymerisation (work in progress).

8.4.2. Internships

Andreas Buttenschön (Team of Thomas Hillen, University of Alberta, Canada) visits the team from December 2015 to May 2016 for be trained on agent-based modeling and the software tool TiSim.

Geert Peeters (Team Patrick Segers, University of Gent, Belgium) visited the German subgroup of the team in January 2015 for one week to be trained on the software tool TiQuant.

8.4.2.1. *Research stays abroad*

Nicolas Vauchelet stayed two months at IMPA, Rio de Janeiro, Brazil, in the framework of a teaching agreement between UPMC and IMPA.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. *Scientific events organisation*

9.1.1.1. *General chair, scientific chair*

L. Almeida organiser: “Mathematical modeling and new methods for dengue control” meeting in Rio de Janeiro (Brazil), June 1 and 8, 2015

J. Clairambault and V. Volpert organisers: “Workshop on hybrid and multiscale models in cell and cell population biology”, UPMC, Paris, 16-18 mars 2015, <http://www.itm-conferences.org/articles/itmconf/abs/2015/02/contents/contents.html>

J. Clairambault organiser: Session #70 “Mathematical models and methods to investigate heterogeneity in cell and cell population biology”, 13th ICNAAM, Rhodes, Greece, Sep 23-29, 2015

M. Tournus organiser: mini-symposium at SMAI 2015 on ‘Coagulation/Fragmentation : stochastic and deterministic approaches”

9.1.2. *Scientific events selection*

9.1.2.1. *Member of the conference program committees*

J. Clairambault, member of the scientific committee of the conference “Present challenges of mathematics in oncology and biology of cancer”, CIRM, Luminy, Dec 7-11 2015

9.1.2.2. *Reviewer*

J. Clairambault for Indian Control Conference 2016

9.1.3. *Journal*

9.1.3.1. *Reviewer - Reviewing activities*

J. Clairambault in 2015 for Applicable Analysis, Bull Math Biol, BMC Biol, BMC Cancer, Cancer Research, J Theor Biol, Nonlinear Biomed Physics, Springer books, Stem Cells Intl

9.1.4. *Invited talks*

L. Almeida: Workshop on mathematical methods and modelling of biophysical phenomena, Cabo Frio, Brazil (March 2015); Workshop on Mathematical and Physical Methods for Biological Systems, Shanghai, China (June 2015); Workshop on biofilms modelling, Rouen (October 2015); Workshop en Biomathématiques, Rabat, Maroc (Novembre 2015)

J. Clairambault: 1) Conferences “Sciences et société”, Nancy and Epinal (France), October 2015; 2) Seminar, Dept. of Mathematics, Duke University, Durham (NC), October 2015; 3) Workshop on Models in cancer therapy, WPI, Vienna (Austria), July 2015; 4) {MB}2 conference, Métabief (France), July 2015; 5) Fifth International Conference on Multiscale Modelling and Methods: Upscaling in Engineering and Medicine, Moscow, Bauman University, June 2015; 6) 15e journée “Calcul scientifique et modélisation mathématique”, Amiens (France), June 2015; 7) Seminar and courses, Dept. of Mathematics, Tlemcen University (Algeria), April 2015; 8) INCA seminar “Ciência extramuros”, Rio de Janeiro, February 2015; 9) Workshop “Mathematical Methods and Modelling of Biophysical Phenomena”, Cabo Frio, Brazil, March 2015; 10) BIRS workshop “Partial differential equations and cancer”, Banff (Alberta) and Mathematical Biology Seminar, University of Alberta, Edmonton (Alberta), February 2015.

M. Doumic: plenary speaker to MPDE15, Universidade Federal Fluminense (UFF Niteroi), Brazil; invitation to minisymposia in SIAM PD15, Phoenix, December 2015, by Piotr Gwiązda; in ICIAM, Beijing, August 2015, by Agnieszka Świerczewska; in Applied Inverse Problems Conference 2015, Helsinki, by Jan-F. Pietschmann. Invitation of Magali Tournus to a minisymposium by David Bortz in SMB 2015, Atlanta, June 30-July 3, 2015.

D. Drasdo: D. Drasdo: EASL conference, 4/2015 (I) (European Association for Study in the Liver, several thousand attendees) (hepatology); Workshop Edmonton (Canada) 2/2015 (not able to come); Workshop Ohio MBI 4/2015 (cancer invasion); Bordeaux, 5/2015; Workshop at ICMS, Edinburgh, on cancer invasion (mathematical biology) 5/2015; Conference CYTO 2015 (cytology), Glasgow 6/2015 (plenary speaker); Hepatinov workshop, 12/2015 (hepatology)

N. Vauchelet: Second Mokalien Meeting, Univ Paris-Dauphine (Nov. 2015); ICIAM 2015, Beijing, China (Aug. 2015); Workshop on Mathematical and Physical Methods for Biological Systems, Shanghai, China (June 2015); Workshop on mathematical methods and modelling of biophysical phenomena, Cabo Frio, Brazil (March 2015); Working group in biomathematics, Universidade Federal Fluminense (Niteroi), Brazil (Feb. 2015).

9.1.5. Scientific expertise

J. Clairambault in 2015 for Belgian FNRS, Swiss NSF

9.1.6. Research administration

L. Almeida: member CID 51 of Comité National de la Recherche Scientifique

L. Almeida and J. Clairambault: members of the bureau of the “Interfaces pour le Vivant” doctoral programme of UPMC

D. Drasdo member of scientific leadership team of virtual liver network

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence: J. Clairambault, “Modélisation de la croissance cellulaire et tissulaire”, course 2 hours, L2 Parcours Médecine-Sciences UPMC, France, January 2015

Licence: N. Vauchelet, in charge of the double major academic course in mathematics and informatics: student followup, implementation of the Summer programme

Master: L. Almeida and T. Lorenzi, International course at the University of Verona (Italy): “Phenotype-structured equations” (24h).

Master: M. Doumic, course on inverse problems and applications in population dynamics (24 hours)

Master: D. Drasdo, Mathematical Biology, UPMC: “Agent-based models of tissue organisation” (24 hours)

Master: N. Vauchelet, “Introduction to mathematical modelling of biophysical phenomena” (24 hours) at UPMC and IMPA

Doctorat: J. Clairambault, course UFF Niteroi (Rio de Janeiro), “Continuous models of cell population growth dynamics to optimise anticancer treatments”, 3 hours, February 2015

Doctorat: J. Clairambault, course Tlemcen University, “Continuous models of cell population growth dynamics to optimise anticancer treatments”, 3 hours, April 2015 Clem

9.2.2. Supervision

PhD defence: Thibault Bourgeron, “Linear and nonlinear structured population models”, UPMC, June 29, 2015, supervision by M. Doumic and B. Perthame

PhD defence: Ján Eliaš, “p53 intracellular spatio-temporal dynamics”, UPMC, September 1, 2015, [2], supervision by J. Clairambault and B. Perthame

PhD defence: Adélaïde Olivier, “Analyse statistique des modèles de croissance-fragmentation”, Paris IX-Dauphine, November 27, 2015, [3], supervision by M. Doumic and M. Hoffmann (Prof. Univ. Paris-Dauphine)

PhD defence: Cristobal Quiñinao, “Mathematical modelling in Neuroscience: collective behaviour of neuronal networks and the role of local homeoproteins diffusion in morphogenesis”, UPMC, June 2, 2015, supervision by S. Mischler, B. Perthame and J. Touboul

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: François Bertaux (since September 2011, manuscript submitted October 2015), supervision by Dirk Drasdo and Gregory Batt

PhD in progress: Noémie Boissier (since November 2013), supervision by Dirk Drasdo and Irène Vignon-Clementel

PhD in progress: Géraldine Cellière (since October 2012), supervision by Dirk Drasdo, Andrei Zinovyev and Emmanuel Barillot (Institut Curie)

PhD in progress: Sarah Eugène, “Stochasticity in nucleation dynamics”, UPMC, begun September 2013, M. Doumic and Ph. Robert (Inria Paris-Rocquencourt, RAP project-team)

PhD in progress: Casimir Emako-Kazianou, UPMC, L. Almeida and N. Vauchelet

PhD in progress: Adrian Friebel (since June 2011), supervision by Dirk Drasdo and Stefan Hoehme

PhD in progress: Ghassen Haddad, “Optimisation of cancer treatments: application to bladder cancer”, UPMC in co-tutela with ENIT Tunis, begun October 2015, 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, J. Clairambault and M. Reed (Duke)

PhD in progress: Johannes Neitsch, Univ. Leipzig (since June 2011), supervision by Dirk Drasdo and Paul Van Liedekerke

PhD in progress: Camille Pouchol, “Modelling interactions between tumour cells and adipocytes in breast cancer”, UPMC, begun September 2015, J. Clairambault, M. Sabbah, and E. Trélat

PhD in progress: Antonin Prunet, UPMC, begun October 2014, L. Almeida and M. Sabbah

PhD in progress: Andrada Quillas Maran, “Modelling early leukaemogenesis”, UPMC, begun March 2014, J. Clairambault and B. Perthame

PhD in progress: Martin Strugarek, “Structured population dynamics for transmissible diseases”, UPMC, begun October 2015, N. Vauchelet and B. Perthame

PhD in progress: Cécile Taing, UPMC, begun October 2014, A. Lorz and B. Perthame

9.2.3. Juries

- J. Clairambault: Arnaud Poret, PhD defence, Jul 1, 2015, Lyon I (Computational biology) *member of the jury*
- J. Clairambault: Ján Eliaš, PhD defence, Sep 1, 2015, UPMC (Applied mathematics) *supervisor*
- M. Doumic: M. Doumic: Ján Eliaš, PhD defence, Sep 1, 2015, UPMC (Applied mathematics) *member of the jury*,
- M. Doumic: Adélaïde Olivier, PhD defence, Nov 27, 2015, Paris IX-Dauphine (Applied mathematics) *supervisor*,
- M. Doumic: Thibault Bourgeron, PhD defence, Jun 29, 2015, UPMC (Applied mathematics) *supervisor*

9.3. Popularisation

- Article J. Clairambault, “My personal journey in mathematical biology and medicine”. Society for Mathematical Biology Newsletter 28(1):11-12, January 2015 [36], <http://www.smb.org/publications/newsletter/vol28no1.pdf>
- Conferences “Sciences et société”, J. Clairambault, “Comment décrire et optimiser l’action des médicaments contre le cancer”, <https://numerique.univ-lorraine.fr/node/513>. IUT Nancy, October 8 and IUT Epinal, October 9, 2015.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

- [1] T. BOURGERON. *Problèmes directs et inverses pour quelques équations intégro-différentielles de la biologie*, Université Pierre et Marie Curie - Paris VI, June 2015, <https://tel.archives-ouvertes.fr/tel-01257203>
- [2] J. ELIAŠ. *Mathematical model of the role and temporal dynamics of protein p53 after drug-induced DNA damage*, Université Pierre et Marie Curie - Paris VI, September 2015, <https://hal.archives-ouvertes.fr/tel-01252038>
- [3] A. OLIVIER. *Statistical analysis of growth-fragmentation models*, Université Paris-Dauphine, November 2015, <https://hal.archives-ouvertes.fr/tel-01235239>

Articles in International Peer-Reviewed Journals

- [4] H. T. BANKS, M. DOUMIC, C. KRUSE, S. PRIGENT, H. REZAEI. *Information Content in Data Sets for a Nucleated-Polymerization Model*, in "Journal of Biological Dynamics", June 2015, vol. 9, n^o 1, 26 p. [DOI : 10.1080/17513758.2015.1050465], <https://hal.inria.fr/hal-01123847>
- [5] L. BOUDIN, C. GRANDMONT, A. LORZ, A. MOUSSA. *Modelling and numerics for respiratory aerosols*, in "Communications in Computational Physics", September 2015, vol. 18, n^o 3, pp. 723-756 [DOI : 10.4208/CICP.180714.200415A], <https://hal.archives-ouvertes.fr/hal-01044590>
- [6] A.-C. BOULANGER, P. MOIREAU, B. PERTHAME, J. SAINTE-MARIE. *Data Assimilation for hyperbolic conservation laws. A Luenberger observer approach based on a kinetic description*, in "Communications in Mathematical Sciences", March 2015, vol. 13, n^o 3, pp. 587 – 622 [DOI : 10.4310/CMS.2015.v13.N3.A1], <https://hal.archives-ouvertes.fr/hal-00924559>
- [7] T. BOURGERON, Z. XU, M. DOUMIC, M. T. TEIXEIRA. *The asymmetry of telomere replication contributes to replicative senescence heterogeneity*, in "Scientific Reports", October 2015, vol. 5, n^o 15326, pp. 1-11 [DOI : 10.1038/SREP15326], <https://hal.archives-ouvertes.fr/hal-01225251>
- [8] J. A. CARRILLO, F. JAMES, F. LAGOUTIÈRE, N. VAUCHELET. *The Filippov characteristic flow for the aggregation equation with mildly singular potentials*, in "Journal of Differential Equations", 2016, vol. 260, n^o 1, pp. 304-338, 33 pages, <https://hal.archives-ouvertes.fr/hal-01061991>
- [9] J. CARRILLO, B. PERTHAME, D. SALORT, D. SMETS. *Qualitative Properties of Solutions for the Noisy Integrate & Fire model in Computational Neuroscience*, in "Nonlinearity", August 2015, vol. 28, n^o 9 [DOI : 10.1088/0951-7715/28/9/3365], <https://hal.archives-ouvertes.fr/hal-01079381>

- [10] J. CHEVALLIER, M. J. CACERES, M. DOUMIC, P. REYNAUD-BOURET. *Microscopic approach of a time elapsed neural model*, in "Mathematical Models and Methods in Applied Sciences", December 2015 [DOI : 10.1142/S021820251550058X], <http://hal.upmc.fr/hal-01159215>
- [11] R. H. CHISHOLM, T. LORENZI, A. LORZ, A. K. LARSEN, L. N. DE ALMEIDA, A. ESCARGUEIL, J. CLAIRAMBAULT. *Emergence of Drug Tolerance in Cancer Cell Populations: An Evolutionary Outcome of Selection, Nongenetic Instability, and Stress-Induced Adaptation*, in "Cancer Research", March 2015, vol. 75, n^o 6, pp. 930-939 [DOI : 10.1158/0008-5472.CAN-14-2103], <https://hal.inria.fr/hal-01237893>
- [12] L. A. D'ALESSANDRO, S. HOEHME, A. HENNEY, D. DRASDO, U. KLINGMÜLLER. *Unraveling liver complexity from molecular to organ level: Challenges and perspectives*, in "Progress in Biophysics and Molecular Biology", January 2015 [DOI : 10.1016/J.PBIOMOLBIO.2014.11.005], <https://hal.inria.fr/hal-01257160>
- [13] M. DOUMIC, M. HOFFMANN, N. KRELL, L. ROBERT. *Statistical estimation of a growth-fragmentation model observed on a genealogical tree*, in "Bernoulli", 2015, vol. 21, n^o 3, pp. 1760-1799, 46 pages, 4 figures, <https://hal.archives-ouvertes.fr/hal-01102799>
- [14] A. FRIEBEL, J. NEITSCH, T. JOHANN, S. HAMMAD, D. DRASDO, S. HOEHME. *TiQuant: software for tissue analysis, quantification and surface reconstruction*, in "Bioinformatics", June 2015 [DOI : 10.1093/BIOINFORMATICS/BTV346], <https://hal.inria.fr/hal-01257137>
- [15] A. GHALLAB, G. CELLIERE, S. HENKEL, D. DRIESCH, S. HOEHME, U. HOFMANN, S. ZELLMER, P. GODOY, A. SACHINIDIS, M. BLASZKEWICZ, R. REIF, R. MARCHAN, L. KUEPFER, D. HÄUSSINGER, D. DRASDO, G. GEBHARDT, J. G. HENGSTLER. *Model-guided identification of a therapeutic strategy to reduce hyperammonemia in liver diseases*, in "Journal of Hepatology", November 2015 [DOI : 10.1016/J.JHEP.2015.11.018], <https://hal.archives-ouvertes.fr/hal-01257127>
- [16] J. HASKOVEC, P. MARKOWICH, B. PERTHAME. *Mathematical Analysis of a System for Biological Network Formation*, in "Communications in Partial Differential Equations", May 2015, vol. 40, n^o 5, pp. 918-956 [DOI : 10.1080/03605302.2014.968792], <http://hal.upmc.fr/hal-00998344>
- [17] N. JAGIELLA, B. MÜLLER, M. MÜLLER, I. VIGNON-CLEMENTEL, D. DRASDO. *Inferring growth control mechanisms in growing multi-cellular spheroids of NSCLC cells from spatial-temporal image data*, in "PLoS Computational Biology", 2016, <https://hal.inria.fr/hal-01244593>
- [18] F. JAMES, N. VAUCHELET. *Numerical methods for one-dimensional aggregation equations*, in "SIAM Journal on Numerical Analysis", 2015, vol. 53, n^o 2, pp. 895-916 [DOI : 10.1137/140959997], <https://hal.archives-ouvertes.fr/hal-00955971>
- [19] M.-J. KANG, B. PERTHAME, D. SALORT. *Dynamics of time elapsed inhomogeneous neuron network model*, in "Comptes Rendus Mathématique", September 2015, n^o 353, pp. 1111-1115 [DOI : 10.1016/J.CRMA.2015.09.029], <http://hal.upmc.fr/hal-01241300>
- [20] M. KOLWALCZYK, B. PERTHAME, N. VAUCHELET. *Transversal instability for the thermodynamical reaction-diffusion system*, in "Chinese Annals of Mathematics - Series B", 2015, vol. 36, n^o 5, pp. 871-882, 13 pages, <https://hal.archives-ouvertes.fr/hal-00939013>

- [21] T. LORENZI, R. H. CHISHOLM, L. DESVILLETES, B. D. HUGHES. *Dissecting the dynamics of epigenetic changes in phenotype-structured populations exposed to fluctuating environments*, in "Journal of Theoretical Biology", September 2015, vol. 386, pp. 166-176 [DOI : 10.1016/J.JTBI.2015.08.031], <https://hal.inria.fr/hal-01237890>
- [22] T. LORENZI, R. H. CHISHOLM, M. MELENSI, A. LORZ, M. DELITALA. *Mathematical model reveals how regulating the three phases of T-cell response could counteract immune evasion*, in "Immunology", December 2015, vol. 146, n^o 2, pp. 271-280 [DOI : 10.1111/IMM.12500], <https://hal.inria.fr/hal-01237852>
- [23] A. LORZ, T. LORENZI, J. CLAIRAMBAULT, A. ESCARGUEIL, B. PERTHAME. *Modeling the effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors*, in "Bulletin of Mathematical Biology", January 2015, vol. 77, n^o 1, pp. 1-22 [DOI : 10.1007/s11538-014-0046-4], <http://hal.upmc.fr/hal-00921266>
- [24] B. MÜLLER, M. BOVET, Y. YIN, D. STICHE, M. MALZ, M. GONZÁLEZ-VALLINAS, A. MIDDLETON, V. EHEMANN, J. SCHMITT, T. MULEY, M. MEISTER, E. HERPEL, S. SINGER, A. WARTH, P. SCHIRMACHER, D. DRASDO, F. MATTHÄUS, K. BREUHAHN. *Concomitant expression of far upstream element (FUSE) binding protein (FBP) interacting repressor (FIR) and its splice variants induce migration and invasion of non-small cell lung cancer (NSCLC) cells*, in "Journal of Pathology", September 2015 [DOI : 10.1002/PATH.4588], <https://hal.inria.fr/hal-01256752>
- [25] B. PERTHAME, C. QUIÑINAO, J. TOUBOUL. *Competition and boundary formation in heterogeneous media: Application to neuronal differentiation*, in "Mathematical Models and Methods in Applied Sciences (M3AS)", 2015, vol. 25, n^o 13, pp. 2477-2502 [DOI : 10.1142/S0218202515400151], <https://hal.archives-ouvertes.fr/hal-01054813>
- [26] B. PERTHAME, N. VAUCHELET. *Incompressible limit of mechanical model of tumor growth with viscosity*, in "Philosophical transactions of the Royal Society of London. Series A: Mathematical and physical sciences", 2015, vol. 373, 20140283 p. , 16 pages, <https://hal.archives-ouvertes.fr/hal-01066494>
- [27] A. RAVASIO, I. CHEDDADI, T. CHEN, T. PEREIRA, H. T. ONG, C. BERTOCCHI, A. BRUGUES, A. JACINTO, A. J. KABLA, Y. TOYAMA, X. TREPAT, N. GOV, L. NEVES DE ALMEIDA, B. LADOUX. *Gap geometry dictates epithelial closure efficiency*, in "Nature Communications", July 2015, vol. 6 [DOI : 10.1038/NCOMMS8683], <https://hal.archives-ouvertes.fr/hal-01245750>
- [28] C. J. TORNEY, T. LORENZI, I. D. COUZIN, S. A. LEVIN. *Social information use and the evolution of unresponsiveness in collective systems*, in "Journal of the Royal Society Interface", February 2015 [DOI : 10.1098/RSIF.2014.0893], <https://hal.inria.fr/hal-01237894>
- [29] P. VAN LIEDEKERKE, M. PALM, N. JAGIELLA, D. DRASDO. *Simulating tissue mechanics with Agent Based Models: concepts and perspectives*, in "Computational Particle Mechanics", November 2015, vol. 2, n^o 4, <https://hal.inria.fr/hal-01220539>
- [30] S. R. K. VEDULA, G. PEYRET, I. CHEDDADI, T. CHEN, A. BRUGUÉS, H. HIRATA, H. LOPEZ-MENENDEZ, Y. TOYAMA, L. N. DE ALMEIDA, X. TREPAT, C. T. LIM, B. LADOUX. *Mechanics of epithelial closure over non-adherent environments*, in "Nature Communications", January 2015, vol. 6, Article number: 6111 [DOI : 10.1038/NCOMMS7111], <https://hal.archives-ouvertes.fr/hal-01218402>

International Conferences with Proceedings

- [31] L. ALMEIDA, R. CHISHOLM, J. CLAIRAMBAULT, A. ESCARGUEIL, T. LORENZI, A. LORZ, E. TRÉLAT. *Phenotype heterogeneity in cancer cell populations*, in "ICNAAM 2015 Session 70: "Mathematical models and methods to investigate heterogeneity in cell and cell population biology"", Rhodes, Greece, Jean Clairambault, September 2015, <https://hal.inria.fr/hal-01249242>
- [32] L. BARBARROUX, J. CLAIRAMBAULT, N. COGAN, J. ELIAŠ, S. HANSON, M. KIMMEL, T. LORENZI. *Preface to Session 70 " Mathematical models and methods to investigate heterogeneity in cell and cell population biology "*, in "ICNAAM 2015 Session 70: "Mathematical models and methods to investigate heterogeneity in cell and cell population biology"", Rhodes, Greece, Organiser Session 70: Jean Clairambault , September 2015, <https://hal.inria.fr/hal-01249244>
- [33] J. CLAIRAMBAULT, J. ELIAŠ. *Diverse spatio-temporal dynamical patterns of p53 and cell fate decisions*, in "ICNAAM 2015 Session 70: "Mathematical models and methods to investigate heterogeneity in cell and cell population biology"", Rhodes, Greece, Jean Clairambault, September 2015, 4 p. , <https://hal.archives-ouvertes.fr/hal-01246826>
- [34] T. LORENZI, R. H. CHISHOLM, A. LORZ, A. K. LARSEN, L. NEVES DE ALMEIDA, A. ESCARGUEIL, J. CLAIRAMBAULT. *Emergence of cytotoxic resistance in cancer cell populations*, in "Workshop on Multiscale and Hybrid Modelling in Cell and Cell Population Biology", Paris, France, V. Volpert and J. Clairambault, March 2015 [DOI : 10.1051/ITMCONF/20150500009], <https://hal.inria.fr/hal-01249235>
- [35] T. LORENZI, R. H. CHISHOLM, A. LORZ, A. K. LARSEN, L. NEVES DE ALMEIDA, A. ESCARGUEIL, J. CLAIRAMBAULT. *Emergence of cytotoxic resistance in cancer cell populations: single-cell mechanisms and population-level consequences*, in "ICNAAM 2015 Session 70: "Mathematical models and methods to investigate heterogeneity in cell and cell population biology"", Rhodes, Greece, Jean Clairambault, September 2015, <https://hal.inria.fr/hal-01249239>

Scientific Popularization

- [36] J. CLAIRAMBAULT. *My Personal Journey In Mathematical Biology & Medicine*, in "Society of Mathematical Biology Newsletter", January 2015, vol. 28, n^o 1, 2 p. , <https://hal.inria.fr/hal-01109000>

Other Publications

- [37] A. ARMIENTO, M. DOUMIC, P. MOIREAU, H. REZAEI. *Estimation from Moments Measurements for Amyloid Degradation*, December 2015, working paper or preprint, <https://hal.archives-ouvertes.fr/hal-01248255>
- [38] S. V. BITSEKI PENDA, A. OLIVIER. *Autoregressive Functions Estimation in Nonlinear Bifurcating Autoregressive Models*, June 2015, working paper or preprint, <https://hal.archives-ouvertes.fr/hal-01159255>
- [39] T. BOURGERON, C. CONCA, R. LECAROS. *Determining the distribution of calcium channels in the olfactory system*, March 2015, working paper or preprint, <https://hal.inria.fr/hal-01132095>
- [40] M. BURGER, A. LORZ, M.-T. WOLFRAM. *On a Boltzmann mean field model for knowledge growth*, June 2015, working paper or preprint, <https://hal.archives-ouvertes.fr/hal-01163491>
- [41] R. H. CHISHOLM, T. LORENZI, A. LORZ, A. K. LARSEN, L. ALMEIDA, A. ESCARGUEIL, J. CLAIRAMBAULT. *Emergence of drug tolerance in cancer cell populations: an evolutionary outcome of selection, non-genetic instability and stress-induced adaptation*, January 2015, First submitted version, <https://hal.archives-ouvertes.fr/hal-01111271>

- [42] B. DESPRÉS, B. PERTHAME. *Uncertainty propagation; intrusive kinetic formulations of scalar conservation laws*, 2015, working paper or preprint, <http://hal.upmc.fr/hal-01146188>
- [43] M. DOUMIC, M. ESCOBEDO. *Time Asymptotics for a Critical Case in Fragmentation and Growth-Fragmentation Equations*, January 2015, working paper or preprint, <https://hal.inria.fr/hal-01080361>
- [44] S. EUGENE, W.-F. XUE, P. ROBERT, M. DOUMIC. *Insights into the variability of nucleated amyloid polymerization by a minimalistic model of stochastic protein assembly*, September 2015, working paper or preprint, <https://hal.inria.fr/hal-01205549>
- [45] J. HASKOVEC, P. MARKOWICH, B. PERTHAME, M. SCHLOTTBOM. *Notes on a PDE System for Biological Network Formation*, October 2015, working paper or preprint, <https://hal.archives-ouvertes.fr/hal-01232080>
- [46] M. HOFFMANN, A. OLIVIER. *Nonparametric estimation of the division rate of an age dependent branching process*, January 2016, working paper or preprint [DOI : 10.1016/J.SPA.2015.11.009], <https://hal.archives-ouvertes.fr/hal-01254203>
- [47] I. C. KIM, B. PERTHAME, P. E. SOUGANIDIS. *Free boundary problems for tumor growth: a viscosity solutions approach*, May 2015, working paper or preprint, <http://hal.upmc.fr/hal-01155696>
- [48] T. LORENZI, R. H. CHISHOLM, A. LORZ. *Effects of an advection term in nonlocal Lotka-Volterra equations*, December 2015, <https://hal.archives-ouvertes.fr/hal-01237529>
- [49] T. LORENZI, A. LORZ, B. PERTHAME. *On interfaces between two cell populations with different mobilities and proliferation rates*, January 2016, working paper or preprint, <https://hal.inria.fr/hal-01257180>
- [50] A. LORZ, B. PERTHAME, C. TAING. *Dirac concentrations in a chemostat model of adaptive evolution*, October 2015, working paper or preprint, <http://hal.upmc.fr/hal-01255449>
- [51] A. MELLETT, B. PERTHAME, F. QUIROS. *A Hele-Shaw Problem for Tumor Growth*, December 2015, working paper or preprint, <http://hal.upmc.fr/hal-01241309>
- [52] S. K. PALANIAPPAN, F. BERTAUX, M. PICHENE, E. FABRE, G. BATT, B. GENEST. *Approximating the dynamics of the Hybrid Stochastic-Deterministic Apoptosis pathway*, CMSB 2015, 2015, CMSB 2015, Poster, <https://hal.archives-ouvertes.fr/hal-01245034>
- [53] B. PENDA, M. HOFFMANN, A. OLIVIER. *Adaptive Estimation for Bifurcating Markov Chains*, January 2016, working paper or preprint, <https://hal.archives-ouvertes.fr/hal-01254200>
- [54] B. PERTHAME, P. E. SOUGANIDIS. *Rare mutations limit of a steady state dispersion trait model*, August 2015, working paper or preprint, <http://hal.upmc.fr/hal-01149029>
- [55] B. PERTHAME, M. TANG, N. VAUCHELET. *Derivation of the bacterial run-and-tumble kinetic equation from a model with biochemical pathway*, March 2015, working paper or preprint, <http://hal.upmc.fr/hal-01131101>
- [56] C. POUCHOL. *Modelling interactions between tumour cells and supporting adipocytes in breast cancer*, UPMC, September 2015, <https://hal.inria.fr/hal-01252122>

References in notes

- [57] L. ALMEIDA, P. BAGNERINI, A. HABBAL. *Modeling actin cable contraction*, in "Computer and mathematics with applications", 2012, vol. 64, n^o 3, pp. 310-321, <https://hal.inria.fr/hal-00648724>
- [58] L. ALMEIDA, P. BAGNERINI, A. HABBAL, S. NOSELLI, F. SERMAN. *A Mathematical Model for Dorsal Closure*, in "Journal of Theoretical Biology", January 2011, vol. 268, n^o 1, pp. 105-119 [DOI : 10.1016/J.JTBI.2010.09.029], <https://hal.inria.fr/inria-00544350>
- [59] F. BERTAUX, S. STOMA, D. DRASDO, G. BATT. *Modeling Dynamics of Cell-to-Cell Variability in TRAIL-Induced Apoptosis Explains Fractional Killing and Predicts Reversible Resistance*, in "PLoS Computational Biology", 2014, vol. 10, n^o 10, 14 p. [DOI : 10.1371/JOURNAL.PCBI.1003893.s016], <https://hal.inria.fr/hal-00942885>
- [60] J. BERTOIN, A. R. WATSON. *Probabilistic aspects of critical growth-fragmentation equations*, in "ArXiv e-prints", June 2015
- [61] F. BILLY, J. CLAIRAMBAULT. *Designing proliferating cell population models with functional targets for control by anti-cancer drugs*, in "Discrete and Continuous Dynamical Systems - Series B", 2013, vol. 18, n^o 4, pp. 865 - 889, 24 pages [DOI : 10.3934/DCDSB.2013.18.865], <https://hal.archives-ouvertes.fr/hal-00726195>
- [62] F. BILLY, J. CLAIRAMBAULT, O. FERCOQ. *Optimisation of cancer drug treatments using cell population dynamics*, in "Mathematical Methods and Models in Biomedicine", U. LEDZEWICZ, H. SCHÄTTLER, A. FRIEDMAN, E. KASHDAN (editors), Lecture Notes on Mathematical Modelling in the Life Sciences, Springer New York, January 2013, 265 p. [DOI : 10.1007/978-1-4614-4178-6_10], <https://hal.archives-ouvertes.fr/hal-00770366>
- [63] F. BILLY, J. CLAIRAMBAULT, O. FERCOQ, S. GAUBERT, T. LÉPOUTRE, T. OUILLOIN, S. SAITO. *Synchronisation and control of proliferation in cycling cell population models with age structure*, in "Mathematics and Computers in Simulation", February 2014, vol. 96, pp. 66-94 [DOI : 10.1016/J.MATCOM.2012.03.005], <https://hal.archives-ouvertes.fr/hal-00662885>
- [64] T. BOURGERON, M. DOUMIC, M. ESCOBEDO. *Estimating the division rate of the growth-fragmentation equation with a self-similar kernel*, in "Inverse Problems", Jan 2014, vol. 30, n^o 2, 025007 p. , <http://dx.doi.org/10.1088/0266-5611/30/2/025007>
- [65] V. CALVEZ, M. DOUMIC, P. GABRIEL. *Self-similarity in a General Aggregation-Fragmentation Problem ; Application to Fitness Analysis*, in "J. Maths Pures Appl.", November 2010, vol. 98, pp. 1-27, <https://hal.archives-ouvertes.fr/hal-00539279>
- [66] P. C. W. DAVIES, C. H. LINEWEAVER. *Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors*, in "Phys Biol", Feb 2011, vol. 8, n^o 1, 015001 p. , <http://dx.doi.org/10.1088/1478-3975/8/1/015001>
- [67] M. DOUMIC, P. GABRIEL. *Eigenelements of a General Aggregation-Fragmentation Model*, in "Mathematical Models and Methods in Applied Sciences", May 2010, vol. 20, pp. 757-783, <https://hal.archives-ouvertes.fr/hal-00408088>

- [68] M. DOUMIC, M. HOFFMANN, N. KRELL, L. ROBERT. *Statistical estimation of a growth-fragmentation model observed on a genealogical tree*, October 2012, 46 pages, 4 figures, <https://hal.archives-ouvertes.fr/hal-00763601>
- [69] M. DOUMIC, M. HOFFMANN, P. REYNAUD-BOURET, V. RIVOIRARD. *Nonparametric estimation of the division rate of a size-structured population*, in "SIAM Journal on Numerical Analysis", April 2012, vol. 50, n^o 2, pp. 925–950 [DOI : 10.1137/110828344], <https://hal.archives-ouvertes.fr/hal-00578694>
- [70] M. DOUMIC, P. MAIA, J. ZUBELLI. *On the Calibration of a Size-Structured Population Model from Experimental Data*, in "Acta Biotheoretica", 2010, vol. 58, n^o 4, pp. 405–413, <http://dx.doi.org/10.1007/s10441-010-9114-9>
- [71] M. DOUMIC, L. TINE. *Estimating the Division Rate for the Growth-Fragmentation Equation*, in "Journal of Mathematical Biology", 2013, vol. 67, n^o 1, pp. 69–103, <http://dx.doi.org/10.1007/s00285-012-0553-6>
- [72] D. DRASDO, S. HOEHME, M. BLOCK. *On the Role of Physics in the Growth and Pattern Formation of Multi-Cellular Systems: What can we Learn from Individual-Cell Based Models?*, in "Journal of Statistical Physics", 2007, vol. 128, n^o 1-2, pp. 287–345, <http://dx.doi.org/10.1007/s10955-007-9289-x>
- [73] D. DRASDO, S. HOEHME, J. G. HENGSTLER. *How predictive quantitative modeling of tissue organization can inform liver disease pathogenesis*, in "Journal of Hepatology", October 2014, vol. 61, n^o 4, pp. 951–956 [DOI : 10.1016/J.JHEP.2014.06.013], <https://hal.inria.fr/hal-01110644>
- [74] J. GALLE, G. AUST, G. SCHALLER, T. BEYER, D. DRASDO. *Individual cell-based models of the spatial-temporal organization of multicellular systems—achievements and limitations*, in "Cytometry. Part A : the journal of the International Society for Analytical Cytology", July 2006, vol. 69, n^o 7, pp. 704–10 [DOI : 10.1002/CYTO.A.20287], <http://www.ncbi.nlm.nih.gov/pubmed/16807896>
- [75] S. HOEHME, M. BRULPORT, A. BAUER, E. BEDAWY, W. SCHORMANN, M. HERMES, V. PUPPE, R. GEBHARDT, S. ZELLMER, M. SCHWARZ, E. BOCKAMP, T. TIMMEL, J. G. HENGSTLER, D. DRASDO. *Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration*, in "Proceedings of the National Academy of Sciences", 2010, vol. 107, n^o 23, pp. 10371–10376
- [76] S. HUANG. *The molecular and mathematical basis of Waddington's epigenetic landscape: a framework for post-Darwinian biology?*, in "Bioessays", Feb 2012, vol. 34, n^o 2, pp. 149–157, <http://dx.doi.org/10.1002/bies.201100031>
- [77] S. HUANG. *Genetic and non-genetic instability in tumor progression: link between the fitness landscape and the epigenetic landscape of cancer cells*, in "Cancer Metastasis Rev", Dec 2013, vol. 32, n^o 3-4, pp. 423–448, <http://dx.doi.org/10.1007/s10555-013-9435-7>
- [78] L. ISRAEL. *Tumour progression: random mutations or an integrated survival response to cellular stress conserved from unicellular organisms?*, in "J Theor Biol", Feb 1996, vol. 178, n^o 4, pp. 375–380, <http://dx.doi.org/10.1006/jtbi.1996.0033>
- [79] C. H. LINEWEAVER, P. C. W. DAVIES, M. D. VINCENT. *Targeting cancer's weaknesses (not its strengths): Therapeutic strategies suggested by the atavistic model*, in "Bioessays", Sep 2014, vol. 36, n^o 9, pp. 827–835, <http://dx.doi.org/10.1002/bies.201400070>

- [80] A. LORZ, T. LORENZI, J. CLAIRAMBAULT, A. ESCARGUEIL, B. PERTHAME. *Modeling the effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors*, in "Bulletin of Mathematical Biology", January 2015, vol. 77, n^o 1, pp. 1-22 [DOI : 10.1007/s11538-014-0046-4], <http://hal.upmc.fr/hal-00921266>
- [81] A. LORZ, T. LORENZI, M. E. HOCHBERG, J. CLAIRAMBAULT, B. PERTHAME. *Populational adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies*, in "ESAIM: Mathematical Modelling and Numerical Analysis", March 2013, 23 p. [DOI : 10.1051/M2AN/2012031], <https://hal.archives-ouvertes.fr/hal-00714274>
- [82] A. LORZ, S. MIRRAHIMI, B. PERTHAME. *Dirac mass dynamics in a multidimensional nonlocal parabolic equation*, in "Communications in Partial Differential Equations", 2011, vol. 36, pp. 1071-1098 [DOI : 10.1080/03605302.2010.538784], <https://hal.archives-ouvertes.fr/hal-00533693>
- [83] S. MIRRAHIMI, B. PERTHAME, J. Y. WAKANO. *Evolution of species trait through resource competition*, in "Journal of Mathematical Biology", June 2012, vol. 64, n^o 7, pp. 1189-1223, 28 pages [DOI : 10.1007/s00285-011-0447-z], <https://hal.archives-ouvertes.fr/hal-00566888>
- [84] S. MISCHLER, J. SCHER. *Spectral analysis of semigroups and growth-fragmentation equations*, October 2013, working paper or preprint, <https://hal.archives-ouvertes.fr/hal-00877870>
- [85] A. O. PISCO, A. BROCK, J. ZHOU, A. MOOR, M. MOJTAHEDI, D. JACKSON, S. HUANG. *Non-Darwinian dynamics in therapy-induced cancer drug resistance*, in "Nat Commun", 2013, vol. 4, 2467 p. , <http://dx.doi.org/10.1038/ncomms3467>
- [86] A. O. PISCO, S. HUANG. *Non-genetic cancer cell plasticity and therapy-induced stemness in tumour relapse: 'What does not kill me strengthens me'*, in "Br J Cancer", May 2015, vol. 112, n^o 11, pp. 1725–1732, <http://dx.doi.org/10.1038/bjc.2015.146>
- [87] S. PRIGENT, A. BALLESTA, F. CHARLES, N. LENUZZA, P. GABRIEL, L. M. TINE, H. REZAEI, M. DOUMIC. *An efficient kinetic model for assemblies of amyloid fibrils and its application to polyglutamine aggregation*, in "PLoS ONE", 2012, vol. 7, n^o 11, e43273 p. [DOI : 10.1371/JOURNAL.PONE.0043273], <https://hal.archives-ouvertes.fr/hal-00778052>
- [88] M. RADSZUWEIT, M. BLOCK, J. G. HENGSTLER, E. SCHÖLL, D. DRASDO. *Comparing the growth kinetics of cell populations in two and three dimensions*, in "Phys. Rev. E", May 2009, vol. 79, 051907, <http://link.aps.org/doi/10.1103/PhysRevE.79.051907>
- [89] L. ROBERT, M. HOFFMANN, N. KRELL, S. AYMERICH, J. ROBERT, M. DOUMIC. *Division in Escherichia coli is triggered by a size-sensing rather than a timing mechanism*, in "BMC Biology", 2014, vol. 12, n^o 1, 17 p. [DOI : 10.1186/1741-7007-12-17], <https://hal.inria.fr/hal-00981312>
- [90] S. V. SHARMA, D. Y. LEE, B. LI, M. P. QUINLAN, F. TAKAHASHI, S. MAHESWARAN, U. MCDERMOTT, N. AZIZIAN, L. ZOU, M. A. FISCHBACH, K.-K. WONG, K. BRANDSTETTER, B. WITTNER, S. RAMASWAMY, M. CLASSON, J. SETTLEMAN. *A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations*, in "Cell", Apr 2010, vol. 141, n^o 1, pp. 69–80, <http://dx.doi.org/10.1016/j.cell.2010.02.027>

- [91] M. TANG, N. VAUCHELET, I. CHEDDADI, I. VIGNON-CLEMENTEL, D. DRASDO, B. PERTHAME. *Composite waves for a cell population system modelling tumor growth and invasion*, in "Chinese Annals of Mathematics - Series B", 2013, vol. 34B, n^o 2, pp. 295-318 [DOI : 10.1007/s11401-007-0001-x], <https://hal.archives-ouvertes.fr/hal-00685063>
- [92] M. VINCENT. *Cancer: a de-repression of a default survival program common to all cells?: a life-history perspective on the nature of cancer*, in "Bioessays", Jan 2012, vol. 34, n^o 1, pp. 72–82, <http://dx.doi.org/10.1002/bies.201100049>
- [93] O. WOLKENHAUER, C. AUFRAY, O. BRASS, J. CLAIRAMBAULT, A. DEUTSCH, D. DRASDO, F. GERVA-SIO, L. PREZIOSI, P. MAINI, A. MARCINIAK-CZOCHRA, C. KOSSOW, L. KUEPFER, K. RATEITSCHAK, I. RAMIS-CONDE, B. RIBBA, A. SCHUPPERT, R. SMALLWOOD, G. STAMATAKOS, F. WINTER, H. BYRNE. *Enabling multiscale modeling in systems medicine: From reactions in cells to organ physiology*, in "Genome Medicine", May 2014, vol. 6, n^o 21, 3 p. , <https://hal.inria.fr/hal-01109002>
- [94] J. X. ZHOU, M. D. S. ALIYU, E. AURELL, S. HUANG. *Quasi-potential landscape in complex multi-stable systems*, in "Journal of The Royal Society Interface", Aug 2012, vol. 9, n^o 77, pp. 3539–3553, <http://dx.doi.org/10.1098/rsif.2012.0434>