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Activity Report 2014

Team MAMBA

Modelling and Analysis for Medical and Biological Applications

IN COLLABORATION WITH: Laboratoire Jacques-Louis Lions

RESEARCH CENTER
Paris - Rocquencourt

THEME
Modeling and Control for Life Sciences

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Team MAMBA

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Creation of the Team: 2014 January 01.

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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 (Biophysique, Analyse Numérique et Géophysique) 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, that 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 - which can be 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 presently face the difficulty to make sense of the data newly available by means of recent signal acquisition methods. Modelling through agent-based or continuous models is a unique way to explain (model) the observations and then compute, control and predict. 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], [57], 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.

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

[2] as in M. Sturrock et al., Spatial stochastic modelling of the Hes1 gene regulatory network: intrinsic noise can explain heterogeneity in embryonic stem cell differentiation, *Journal of The Royal Society Interface*, 2013

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

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

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

3.2. PDE analysis and simulation

PDEs arise at several levels of our models. Parabolic equations 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] [51] [50]. 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 [59], [60], [58] [40]. Through multiscale analysis, they can be related to stochastic and free boundary models used in cancer modelling.

3.3. Inverse problems

When studying biological populations (usually cells or big molecules) using PDE models, identification of the functions and parameters that govern the dynamics of a model may be achieved to a certain extent by statistics performed on individuals to reconstruct the probability distribution of their relevant characteristics in the population they constitute, but quantitative observations at the individual level (e.g., fluorescence in single cells [4]) 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.

3.4. Stochastic models

The link between stochastic processes and kinetic equations is a domain already present in our research [7] [53] and that we aim at developing 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 [52], enriching each other. Neuroscience is a domain where this is particularly true because noise contributes significantly to the activity of neurons; this is particularly true for networks where mean field limits are derived from stochastic individual-based models and lead to fundamental questions on well-posedness and behaviours of the system [8]. One strength and originality of our project is our close connections and collaborations not only with probability theorists but also with statisticians.

3.5. Agent-based models

Agent-based systems consider each component individually. For example, in agent-based systems of multi-cellular systems the basic modeling unit is the cell, and each cell is considered [54]. This approach has advantages if the population of cells reveals inhomogeneities on small spatial scales as it occurs if organ architecture is represented [57], 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 distinguished by lattice models (e.g. [62]) and lattice-free (or off-lattice) models, in which the position of the cell can change gradually (e.g. [54], [56]). The dynamics of cells in lattice-based models is usually described by rules chosen to mimic the behavior of a cell including its physical behavior. The advantage of this approach is that it is simpler and simulation times for a given number of cells are shorter than in lattice-free models. In contrast, most lattice-free models attempt to parameterize cells by measurable values with a direct physical or biological meaning hence permitting identification of physiologically meaningful parameter ranges. This improves model simulation feasibility, since simulated parameter sensitivity analyses 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 organization processes ([7]). 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 where the interplay of components at many levels is more and more precisely studied [19].

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

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 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) evolution from pre-malignancy to malignancy in cell populations, and b) in established cancer cell populations, evolution towards (drug-induced) drug resistance. Environmental pressure guiding evolution is of various natures, 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 [59], [58] [40] are akin 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 tissue [9]. 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 so far worked on multi-scale modelling of EMT [10], and the step by which invading cancer cells enter blood vessels, called intravasation [11]. We now perform in-vitro simulations of cancer cell invasion for Non Small Cell Lung Cancer (NSCLC) 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.

4.2. Cancer therapies and their optimisation

Drugs. 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 (i.e., this is not L^2 nor L^1, but L^∞ optimisation) in healthy cell populations and avoiding the emergence of resistant cell clones in cancer cell populations [49], [58] [4], [40]. Prior to using optimisation methods, we design models of the targeted cell populations (healthy and tumour, including molecular or functional drug targets [48]) by PDEs or agent-based models [3], and molecular pharmacological (pharmacokinetic-pharmacodynamic, PK-PD) models of the fate and effects of the drugs used, usually by ODE models. A particular aspect of such modelling is the representation of multi-cellular spatio-temporal patterns emerging from therapies.
Radiotherapy. Radiation is still a major treatment in cancer. We have recently published new results on this topic, pleae refer to the *New Results* section.

4.3. 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.

[9] Weinberg, The biology of cancer, Garland, 2007
[10] Ramis-Conde, Drasdo, Anderson, Chaplain, Biophys. J., 2008
[11] Ramis-Conde, Chaplain, Anderson, Drasdo, Phys. Biol. 2009
[12] N. Bournaveas, V. Calvez, S. Gutiérrez and B. Perthame, Global existence for a kinetic model of chemotaxis via dispersion and Strichartz estimates, *Comm. PDE*, 2008

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 include 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 [63].

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, wound healing in vivo and morphogenetic movements involving closure of holes in epithelia have been the object of many studies (including some involving members of this project like [47]). Several theoretical models have also been proposed recently for the advancement of tissue covering unoccupied areas (see, for instance, [46]). 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 people to seek alternative systems where epithelial gap closure can be studied under better-defined and better-controlled conditions.

4.4. Contraction of acto-myosin structures in morphogenesis and tissue repair

In 2014, L. Almeida, I. Cheddadi, C. Emako-Kazianou, P. Bagnerini [16], A. Jacinto [17], P. Patricio [18], B. Ladoux [19] and N. Gov [20] have continued to investigate the dependence of physical and biological mechanisms of actomyosin cable formation and wound closure depending on the geometry of the wound and adhesion to the substrate, with particular emphasis on the effect of the wound edge curvature. We extended our work from in vivo studies to in vitro situations taking advantage of a collaboration with the group of Benoît Ladoux who did 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 very general across living beings.

In our model under development, we consider viscous behaviour and friction in the tissue plus boundary terms associated to cable and lamellipodial forces. The numerical simulations obtained using this model are in good agreement with the experimental results. This work is attracting considerable attention from the community.

4.5. Protein polymerisation

Protein polymerisation is the key feature of amyloid diseases, among which we can quote Alzheimer's, Prion (in particular variant Creutzfeldt-Jakob disease, epidemically linked to bovine spongiform encephalopathy, or so-called "mad cow", disease), Parkinson's, Huntington's diseases. 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 [51], [50]. Hence the European starting grant SKIPPER^{AD}, which follows the ANR project TOPPAZ, came up very naturally from the encounter with Human Rezaei, a biologist expert in amyloid diseases at INRA Jouy-en-Josas. Moreover, this field of applications brings new questions to us, which is both a stimulation for our mathematical research and a very promising tool for the biologists.

[13] J. 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.
[14] I. Ramis-Conde et al., J. Phys. Biol., 2009
[15] Works by O. Saut, T. Colin, A. Iollo, N. Ayache, J. Lowengrub
[16] Univ. Genova
[17] CEDOC, Lisbon
[18] CEDOC, Lisbon
[19] Inst. J. Monod
[20] Weizmann Institute

4.6. 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 ([21], [22], [23]). Centre-based growth models already permit to account for many of the observed phenomena (e.g. [24], [25]). They furthermore permit calculation of the stress tensor in the tissue. ABMs resolving cells at higher resolution [26] permit to calculate cell deformation as a response 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 permits relating 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, that 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.

4.7. Liver modelling

Liver is the main detoxifying organ of the human body and can regenerate up to about 70% of its mass. It pursues its task due to a complex tissue architecture, with hepatocytes aligning along micro-capillaries and forming a dense network. Incidence rate of liver diseases are steadily increasing, liver cancer ranks 6th among all cancers. About one person in 12 suffer from viral hepatitis, which makes 500 million people worldwide. Hepatitis B and C as well as misuse of drugs or alcohol are major reasons to develop 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. [27]); only recently are being developed approaches addressing the tissue scale ([57], [28], [29], [30], [31]). 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 pharmacokinetics in liver and liver cancer, and model-based prediction of in-vivo drug toxicity from in-vitro measurements [32]. The research work is performed within the EU project NOTOX, the BMBF project VIRTUAL LIVER NETWORK and the ANR project IFLOW.

5. New Software and Platforms

5.1. Logiciels

5.1.1. TiQuant

Systems biology and medicine on histological scales require quantification of images from histological image modalities such as confocal laser scanning or bright field microscopy. The latter can be used to calibrate the initial state of a mathematical model, and to evaluate its explanatory value, which hitherto has been little

[21] Ingber, Proc. Natl. Acad. Sci (USA), 2005
[22] Trepat et. al., Nat. Phys. 2009
[23] Alessandri et. al., Proc. Natl. Acad. Sci. (USA) 2013
[24] Drasdo and Hoehme, Phys. Biol. 2005
[25] Drasdo and Hoehme, New Journal of Physics 2012
[26] Odenthal, Smeets, van Liedekerke, et. al., PloS Comput Biol. 2013
[27] Diaz-Ochoa et. al. Frontiers in Pharmacology, 2013
[28] Ricken, Dahmen, Dirsch, Biomech. Model. Mechanobiol. 2010
[29] Debbaut et. al., J. Biomech. Eng. 2014
[30] Siggers, Leungchavphongse, Ho, Repetto, Biomech. Model. Mechanobiol. 2014
[31] Schwen et. al., PloS Comput. Biol. 2014
[32] Godoy et al., *Arch Toxicol. 2013* Aug;87(8):1315-1530

recognized ([7]). We generated a software for image analysis of histological material and demonstrated its use in analysing liver confocal micrografts, called TiQuant (Tissue Quantifier) [10]. The software is part of an analysis chain detailing protocols of imaging, image processing and analysis in liver tissue, permitting 3D reconstructions of liver lobules down to a resolution of less than a micrometer. (This work is a collaboration with the group of JG Hengstler, IfADo, Germany)

5.1.2. TiSim

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

6. New Results

6.1. Highlights of the Year

Benoît Perthame was invited as plenary speaker for the International Congress of Mathematicians ICM 2014 (Seoul, http://www.icm2014.org), that attracted more than 5000 participants. This is the first time that a mathematician working in mathematics applied to biology was invited at ICM, which is the most prestigious conference for mathematicians of all fields. This represents a consecration both for Benoît Perthame's work and for the MAMBA team, and more generally for the whole domain of mathematics applied to biology.

Marie Doumic was a plenary speaker at the ECMTB 2014 (Göteborg, http://ecmtb2014.org/ 600 participants).

Dirk Drasdo was invited speaker at the Systems Biology of Human Diseases conference (Harvard University, http://www.csb2.org/events/sbhd-2014).

Five articles are noteworthy in terms of bibliometry:

• (*Impact factor 11.2*) F. SCHLIESS, S. HOEHME, S. HENKEL, A. GHALLAB, D. DRIESCH, J. BÖTTGER, R. GUTHKE, M. PFAFF, J. HENGSTLER, R. GEBHARDT, D. HÄUSSINGER, D. DRASDO, S. ZELLMER. Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration, *Hepatology*, Dec. 2014, vol. 60, no 6, pp. 2040-2051, https://hal.inria.fr/hal-01110646 [17]

• (*Impact factor 10.4*) D. DRASDO, S. HOEHME, J. G. HENGSTLER. How predictive quantitative modeling of tissue organization can inform liver disease pathogenesis, *Journal of Hepatology*, Oct. 2014, vol. 61, no 4, pp. 951-956 [DOI : 10.1016/J.JHEP.2014.06.013], https://hal.inria.fr/hal-01110644 [7]

• (*Impact factor 10.7*) S.R.K. VEDULA, G. PEYRET, I. CHEDDADI, T. CHEN, A. BRUGUÉS, H. HIRATA, H. LOPEZ-MENENDEZ, Y. TOYAMA, L. NEVES DE ALMEIDA, X. TREPAT, C.T. LIM, B. LADOUX. Mechanics of epithelial closure over non-adherent environments, *Nature Communications*, Jan. 2015, vol. 6, art. number 6111[DOI : 10.1038/ncomms7111], http://www.nature.com/ncomms/2015/150122/ncomms7111/abs/ncomms7111.html (open access)

• (*Impact factor 7.5*) 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, no 1, 17 p. [DOI : 10.1186/1741-7007-12-17], https://hal.inria.fr/hal-00981312 [16]

• (*Impact factor 9.3*) 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, nongenetic instability and stress-induced adaptation, *Cancer Research* (Mathematical oncology), 10p.+suppl. mat., in press, Jan. 2015, https://hal.archives-ouvertes.fr/hal-01111271 [33]

6.2. Cancer

Participants: Luís Lopes Neves de Almeida, José Luis Avila Alonso [DISCO Inria team], Catherine Bonnet [DISCO Inria team], Rebecca Chisholm, Jean Clairambault, François Delhommeau [Hæmatology department, St Antoine Hospital, Paris], Luna Dimitrio [former PhD student and Mamba member], Ján Eliaš, Alexandre Escargueil [Cancer biology and therapeutics lab, St Antoine Hospital, Paris], Pierre Hirsch [Hæmatology department, St Antoine Hospital, Paris], Michal Kowalczyk [Univ. Santiago de Chile], Annette Larsen [Cancer biology and therapeutics lab, St Antoine Hospital, Paris], Tommaso Lorenzi, Alexander Lorz, Anna Marciniak-Czochra [Univ. Heidelberg], Roberto Natalini [IAC-CNR, Univ. Tor Vergata, Rome], Silviu Iulan Niculescu [DISCO Inria team], Hitay Özbay [Bilkent Univ., Ankara], Benoît Perthame, Andrada Maran, Fernando Quirós [Univ. Autónoma de Madrid], Michèle Sabbah [Cancer biology and therapeutics lab, St Antoine Hospital, Paris], Thomas Stiehl [Univ. Heidelberg], Min Tang [Jiaotong University, Shanghai], Emmanuel Trélat [LJLL, UPMC], Nicolas Vauchelet, Romain Yvinec [INRA Tours].

6.2.1. Drug resistance.

We have continued to develop our phenotypically based models of drug-induced drug resistance in cancer cell populations, representing their Darwinian evolution under drug pressure by integro-differential equations. In one of them [40], a 1D space variable has been added to the phenotypic structure variable to account for drug diffusion in tumour spheroids. In another one [33], where deterministic and agent-based modelling are processed in parallel, we have considered a physiologically based 2-dimensional phenotypic structure variable, in order to take account of previously published biological observations on (reversible) drug tolerance persistence in a population of non-small cell lung cancer (NSCLC) cells [33], reproducing the observations and assessing the model by testing biologically based hypotheses. Together with ongoing work with E. Trélat and A. Lorz on drug therapy optimisation, using such phenotype-based models to overcome drug resistance, this has represented a significant part of our work on the subject, which is conducted in close collaboration with the INSERM-UPMC team "Cancer biology and therapeutics" (A. Larsen, A. Escargueil, M. Sabbah) at St Antoine Hospital.

6.2.2. Reversible drug resistance and fractional killing in tumor cell population treatment.

We developed a model of drug resistance in TRAIL (TNF-Related Apoptosis Induced-Ligand) treatment in HeLa cell lines. The TRAIL signal transduction pathway is one of the best studied apoptosis pathways and hence permits detailed comparisons with data. Our model was able to explain experimental observations fractional killing and cell-to-cell variability, and predicted reversible resistance [3]. (Work in close collaboration with G. Batt and S. Stoma from the Inria team LIFEWARE.)

6.2.3. Radiotherapy.

Radiation is still a major treatment in cancer. We explored by extensive computer simulations using an agent-based model the consequences of spatially inhomogeneous irradiation. The model predicted that in the case of different competing sub-populations, namely cancer stem cells with unlimited division capacity, and cancer cells with limited division capacity, inhomogeneous radiation focusing higher doses at the tumour centre and lower doses at the tumour periphery should outperform homogeneous irradiation [12]. Cancer stem cells are believed to have a longer cell cycle duration than cancer cells, and are less radiosensitive than cancer cells, which is why they often survive radiation and lead to tumour relapse.

6.2.4. Intercellular interactions in epithelio-mesenchymal transition (EMT).

A PhD thesis on this subject, co-supervised by L. Almeida and M. Sabbah (INSERM team "Cancer biology and therapeutics", St Antoine) has begun at Fall. It is also based on phenotype-structured modelling of Darwinian evolution in cancer cell populations.

[33] Sharma *et al.*, Cell, April 2010

6.2.5. Interactions between tumour cell populations and their cellular micro-environment.

A phenotype-structured model of the interactions between a brest 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, J. Clairambault), which, beyond submitted proposals (ANR, Emergence Paris-Sorbonne Universités call), will be studied and experimentally identified in a forthcoming internship (January-June 2015) and PhD thesis in applied mathematics.

6.2.6. Hele-Shaw model of tumour growth.

In the growing field of mathematical analysis of mechanical domain of tumor growth, we focus on the rigorous link between cells models, relying on mechanical properties of cells, and free boundary problem, where the tumor is described by the dynamics of its boundary. The latter model is referred to Hele-Shaw model [44]. Benoît Perthame, Min Tang and Nicolas Vauchelet have proved the rigorous derivation of a geometric model of the Hele-Shaw type for a model with viscoelastic forces, constructing analytically traveling wave solutions of the Hele-Shaw model of tumor growth with nutrient that explain theoretically the numerical results observed. The limiting model exhibits travelling waves, which have been investigated in [43]. Another interesting feature for this model is the transversal instability occurring when the spatial dimension is greater than 1. Together with Fernando Quirós (Univ. Autónoma de Madrid), the aforementioned have also formulated a Hele-Shaw type free-boundary problem for a tumor growing under the combined effects of pressure forces, cell multiplication and active motion, the latter being the novelty of this study [61]. In order to understand the emergence of instabilities in the Hele-Shaw model with nutrients, Michal Kowalczyk (Univ. Chile, Santiago), Benoît Perthame and Nicolas Vauchelet have studied a related model of thermo-reactive diffusion where they can study the spectrum of the linearized system around a traveling wave and in which they can compute the transition to instability in terms of a parameter related to the ratio between heat conduction and molecular diffusion. However, the rigorous study of such instabilities for the whole system of equations is not reachable for the moment; only a study for a simplified model has been performed in [39].

6.2.7. Modelling and control of acute myeloblastic leukæmia (AML).

The collaboration with the Disco project-team has been continued, leading to one book chapter [25], four conference proceedings [21], [22], [23], [24] and JL Avila Alonso's PhD thesis defence.

In more detail:
Starting initially from a PDE model of hematopoiesis designed by Adimy *et al.* [34], we have derived several models of healthy or cancer cell dynamics in hematopoiesis and performed several stability analyses.

We have proposed in [25] a new mathematical model of the cell dynamics in acute myeloid leukæmia (AML) which takes into account the four different phases of the proliferating compartment as well the fast self-renewal phenomenon frequently observed in AML. As was the case in [25] this model is transformed into a distributed delay system and was analyzed here with input-output techniques. Local stability conditions for an equilibrium point of interest are derived in terms of a set of inequalities involving the parameters of the mathematical model.

We have also studied a coupled delay model for healthy and cancer cell dynamics in AML consisting of two stages of maturation for cancer cells and three stages of maturation for healthy cells. For a particular healthy equilibrium point, locally stability conditions involving the parameters of the mathematical model have been obtained [22], [23].

We have performed in [21] a stability analysis of both the PDE model of healthy hæmatopoiesis and a coupled PDE model of healthy and cancer cell dynamics. The stability conditions obtained here in the time domain strengthen the idea that fast self-renewal plays an important role in AML.

A time-domain stability analysis by means of Lyapunov-Krasovskii functionals has been performed on the delay system modeling healthy hematopoiesis for a strictly positive equilibrium point of interest.

[34] Adimy, M., Crauste, F., El Abllaoui, A. Discrete maturity-structured model of cell differentiation with applications to acute myelogenous leukemia, *J. Biol. Sys.*, 16(3):395-424, 2008

Furthermore, a working collaboration on AML modelling with Anna Marciniak-Czochra (Univ. Heidelberg) was also initiated by the end of 2014 by a visit of three of us (C. Bonnet, J. Clairambault, T. Lorenzi) to Heidelberg and a visit of T. Stiehl, A. Marciniak-Czochra PhD student, to Paris. The topics we plan to investigate are, beyond the role of fast self renewal in AML cell populations, the part played by clonal heterogeneity in leukæmic cell populations and the issues it raises in therapeutics, a well known clinical problem in clinical hæmatology.

Let us also mention that on the subject of early leukæmogenesis, Andrada Qillas Maran has undertaken a PhD thesis under the supervision of J. Clairambault and B. Perthame. Models relying on piecewise deterministic Markov processes (PDMPs), designed and studied by R. Yvinec (INRA Tours) for the single-cell part of the model under construction, will be used in collaboration with him. Our clinical referents in hæmatology for this PhD work are F. Delhommeau and P. Hirsch (St Antoine Hospital).

6.2.8. *The p53 protein spatio-temporal dynamics.*

The development of our molecular-based model of the spatio-temporal intracellular dynamics of the p53 protein (the so-called “guardian of the genome") has been continued [55], [9], leading us also, more generally, to propose a modelling frame dedicated to the dynamics of intracellular proteins and their gene regulatory networks [8].

6.2.9. *Others.*

In a collaboration with ANGE, B. Perthame has studied a data assimilation algorithm for multidimensional hyperbolic conservation laws using kinetic schemes and kinetic formulations.

6.3. Aggregation kinetics

Participants: Tom Banks, Thibault Bourgeron, Marc Hoffmann, Marie Doumic-Jauffret, Nathalie Krell, Benoît Perthame, Stéphanie Prigent, Human Rezaei, Nathalie Robert, Léon Matar Tine [Univ. Lyon and Dracula Inria team], Jorge Zubelli [IMPA, Rio de Janeiro].

6.3.1. *Time Asymptotics for Fragmentation Equations*

Fragmentation and growth-fragmentation equations is a family of problems with varied and wide applications. This paper is devoted to description of the long time time asymptotics of two critical cases of these equations, when the division rate is constant and the growth rate is linear or zero. The study of these cases may be reduced to the study of the following fragmentation equation:

$$\frac{\partial}{\partial t}u(t,x) + u(t,x) = \int_x^\infty k_0(xy)u(t,y)dy.$$

Using the Mellin transform of the equation, we determine the long time behavior of the solutions. Our results show in particular the strong dependence of this asymptotic behavior with respect to the initial data.

6.3.2. *Estimating the division rate in a size-structured population.*

The problem which was considered in [5] consists in estimating the division rate from the stable size distribution of the population, which is easily measured, but non-smooth. We propose a method based on the Mellin transform for growth-fragmentation equations with self-similar kernels. We build a sequence of functions which converges to the density of the population in division, simultaneously in several weighted L^2 spaces, as the measurement error goes to 0. This improves previous results for self-similar kernels [35] and allows us to understand the partial results for general fragmentation kernels [36]. Numerical simulations confirm the theoretical results. Moreover, our numerical method is tested on real biological data, arising from a bacteria growth and fission experiment.

[35] Perthame and Zubelli, *Inv. Prob.*, 2007
[36] Doumic and Tine, *J. Math. Biol.*, 2012

6.3.3. What governs bacterial growth? The "sizer" vs the "timer" model

We applied the previously seen inverse problem methodology [5] to a fundamental biological problem: what governs the bacterial growth?

Many organisms coordinate cell growth and division through size control mechanisms: cells must reach a critical size to trigger a cell cycle event. Bacterial division is often assumed to be controlled in this way, but experimental evidence to support this assumption is still lacking. Theoretical arguments show that size control is required to maintain size homeostasis in the case of exponential growth of individual cells. Nevertheless, if the growth law deviates slightly from exponential for very small cells, homeostasis can be maintained with a simple 'timer' triggering division. Therefore, deciding whether division control in bacteria relies on a 'timer' or 'sizer' mechanism requires quantitative comparisons between models and data.

The timer and sizer hypotheses find a natural expression in models based on partial differential equations. Here we test these models with recent data on single-cell growth of Escherichia coli. We demonstrate that a size-independent timer mechanism for division control, though theoretically possible, is quantitatively incompatible with the data and extremely sensitive to slight variations in the growth law. In contrast, a sizer model is robust and fits the data well. In addition, we tested the effect of variability in individual growth rates and noise in septum positioning and found that size control is robust to this phenotypic noise.

Confrontations between cell cycle models and data usually suffer from a lack of high-quality data and suitable statistical estimation techniques. In the study [16] we had overcome these limitations by using high precision measurements of tens of thousands of single bacterial cells combined with recent statistical inference methods to estimate the division rate within the models. We therefore provided the first precise quantitative assessment of different cell cycle models.

6.3.4. Size distribution of amyloid fibrils. Mathematical models and experimental data.

More than twenty types of proteins can adopt misfolded conformations, which can co-aggregate into amyloid fibrils, and are related to pathologies such as Alzheimer's disease. In [15], we surveyed mathematical models for aggregation chain reactions, and discussed the ability to use them to understand amyloid distributions. Numerous reactions have been proposed to play a role in their aggregation kinetics, though the relative importance of each reaction in vivo is unclear: these include activation steps, with nucleation compared to initiation, disaggregation steps, with depolymerization compared to fragmentation, and additional processes such as filament coalescence or secondary nucleation. We have statistically analysed the shape of the size distribution of prion fibrils, with the specific example of truncated data due to the experimental technique (electron microscopy). A model of polymerization and depolymerization succeeds in explaining this distribution. It is a very plausible scheme though, as evidenced in the review of other mathematical models, other types of reactions could also give rise to the same type of distributions.

To clarify how these fibrils are able to incorporate additional units, prion fibril aggregation and disaggregation kinetics were experimentally studied using Static Light Scattering (SLS) [45]. Values that are functions of $\sum i^2 c_i$ (for $i > 0$) with c_i being the concentration of fibrils of size i, were then measured as a function of time. An initial model, adapted from the Becker-Döring system that considers all fibrils to react similarly is not able to reproduce the observed in vitro behaviour. Our second model involves an additional compartment of fibrils unable to incorporate more prion units. This model leads to kinetic coefficients which are biologically plausible and correctly simulates the first experimental steps for prion aggregation.

In the formation of large clusters out of small particles, the initializing step is called the nucleation, and consists in the spontaneous reaction of agents which aggregate into small and stable polymers called nucleus. After this early step, the polymers are involved into a bunch of reactions such as polymerization, fragmentation and coalescence. Since there may be several orders of magnitude between the size of a particle and the size of an aggregate, building efficient numerical schemes to capture accurately the kinetics of the reaction is a delicate step of key importance. In [29], we propose a conservative scheme, based on finite volume methods on an adaptive grid, which is able to render out the early steps of the reaction as well as the later chain reactions.

6.4. Liver organ modelling

Participants: Noémie Boissier, Dirk Drasdo, Géraldine Cellière, Adrian Friebel, Group Heinzle [Univ. Saarbruecken, Germany], Group Hengstler [IfADo, Germany], Stefan Hoehme, Tim Johann, Group Klingmueller [German Cancer Center, Heidelberg], Johannes Neitsch, 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.

6.4.1. Ammonia detoxification after drug-induced damage.

The model for ammonia detoxification after drug-induced damage (see above) identified a systematic deviation between data and results that would be expected from the current standard model for ammonia detoxification in healthy liver [37] ([17], [6]) (see also comments/editorials in [38]). The findings triggered a series of new experiments identifying reversibility of the glutamate-dehydrogenase reaction in hepatocytes, and in blood (Ghallab et. al., subm.). It could be shown in an animal model that the newly recognized reactions can be therapeutically used to significantly reduce the concentration of toxic ammonia after drug-induced damage. (Work in close collaboration with partners of the project VLN (BMBF, Germany) and EU-NOTOX.

6.4.2. Systematic analysis strategies permitting quantitative conclusions in systems medicine and biology.

Based on the examples from liver regeneration after drug-induced damage [57] [17]) systematic iterative strategies can be inferred to enable identification of mechanisms underlying complex processes in spatial temporal tissue organisation and organ functioning. These use an iterative application of a pipeline of imaging, image analysis and modeling, quantitative models by parameterization of model components by measurable parameters for which the physiological ranges are known, and systematic simulated parameter sensitivity analyses [7].

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

Collaboration with Merrimack Pharmaceuticals on spatial-temporal modeling of drug action.

8. Partnerships and Cooperations

8.1. Regional Initiatives

DIGITEO Project (DIM LSC) ALMA

Project title: Mathematical Analysis of Acute Myeloid Leukemia (AML) and its treatments

September 2014 - August 2017

Coordinator: Catherine Bonnet, Disco team, Saclay-IdF

Other partners: Inria Paris-Rocquencourt (Mamba team), France, L2S, France, UPMC (LJLL), St Antoine Hospital, Paris

Abstract: this project follows the regional projects ALMA (2010-2014) and ALMA2 (2011-2013). Starting from the work of J. L. Avila Alonso's PhD thesis in ALMA the aim of this project is to provide a refined coupled model of healthy and cancer cell dynamics in AML whose (stability) analysis will enable evaluation of polychemiotherapies delivered in the case of AML which have a high level of Flt-3 duplication (Flt-3-ITD).

[37] Haeussinger D., Eur. J. Biochem, 1983; Gebhardt R and Mecke, D. EMBO J 1983
[38] Wierling, C. Hepatology, 60(6) 2014; and: Widera, A., EXCLI Journal, 13, 2014

8.2. National Initiatives

8.2.1. ANR

8.2.1.1. ANR 2011-2014 Bimod.

It has been prolonged until 2015, time at which an international workshop in Paris on "Multi-scale and hybrid modelling in cell and cell population biology" is organised, with 25-30 speakers on invitations.

8.2.1.2. Submitted ANR 2015 call "Défi de tous les savoirs".

"Mathematical modelling of dynamics in interacting cell populations" (MMDICP) project submitted for 2015.

8.2.1.3. ANR Blanc 2014-2018 "Kibord".

This recently accepted project gather 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.

8.2.1.4. 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.

8.2.1.5. 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.

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

8.3.1.1. NOTOX

Type: COOPERATION

Instrument: Integrated Project

Duration: January 2011 - December 2015

Inria contact: Dirk Drasdo

NOTOX will develop and establish 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 will initially use 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 will be 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 will be removed for in-depth structural (3D-optical and electron microscopy tomography), transcriptomic, epigenomic, metabolomic, proteomic and fluxomic characterisations ("-omics data"). When applicable, cells derived from human stem cells (hESC or iPS) and available human organ simulating systems or even a multi-organ platform developed in SCREENTOX and HEMIBIO will be investigated using developed methods. Together with curated literature and genomic data these toxicological data will be organised in a toxicological database (cooperation with DETECTIVE, COSMOS and TOXBANK). Physiological data including metabolism of test compounds will be 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 serve 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.

Webpage: http://notox-sb.eu/fp7-cosmetics-europe/

8.3.2. Collaborations with Major European Organizations

U. Klingmüller: DKFZ (German Cancer Center), Department for Systemsbiology (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

Nick Jagiella, Helmholz Center, Institute of Computational Biology

Image guided model parameterisation

8.4. International Initiatives

8.4.1. German Bundesministerium für Bildung und Forschung (BMBF) initiatives

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 quantitive 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 available on the web site. 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/).

8.4.2. Participation In other International Programs

Participation in the EuroMed3+3 governed by Inria. The M3CD network (https://www.rocq.inria.fr/bang/M3CD_website/), coordinated by J. Clairambault, has continued and extended its activities, giving rise to new participations: Politecnico di Torino (M. Delitala), Universidad de Valladolid (Ó. Angulo), to stays of students (Y. Bourfia) and researchers (M. Adimy) and to the organisation of a new workshop in Marrakesh in January 2014. The mid-term report is available on the website. The University of Tlemcen (T. Touaoula) has joined in from January 2015.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

Invitation of Min Tang (Shanghai Jao Tong University, China) during one month at UPMC.

8.5.1.1. Internships

Eugenio Lella, Mathematics: Towards a spatio-temporal hybrid mathematical model to simulate drug toxicity in vitro. (2014, master thesis)

8.5.1.2. 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. Journal

9.1.1.1. member of the editorial board

- Scientific World Journal (Dirk Drasdo)

9.1.1.2. reviewer

- J. Clairambault in 2014 for PLoS Comp Biol, Seminars Canc Biol, Cancer Research, MMNP, Canc Cell Intnl, J Theor Biol, Bull Math Biol, J Math Biol, Future Medicine, Math BioSci, Math BioSci Eng, Non Linear Biomed Physics, Theor Biol Med Modelling
- M. Doumic in 2014 for Ann. IHP Non-Lin., Journal of Mathematical Biology, Proc. London Math. Society, habilitation of M. Ribot.
- D. Drasdo in 2014 for e.g. Nature, Bioinformatics, PLoS Comput Biol, habilitation of A. Zinovyev (Inst. Curie, habil. at ENS Rue d'Ulm), CaSyM Roadmap (Coordinating Action Systems Medicine: Implementation of Systems Medicine across Europe)

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence: J. Clairambault, Modélisation de la croissance cellulaire et tissulaire, 2 h de cours magistral, L2 Parcours Médecine-Sciences UPMC, France

Master: J. Clairambault, Mathematical biology, M2 Mathématiques appliquées, 6 h de cours magistral (in English), UPMC, France

Master: J. Clairambault, Modélisation de l'optimisation thérapeutique en cancérologie, 4 h de cours magistral, M2 Pharmacologie, Rennes, france

Doctorat: J. Clairambault, Modélisation de la croissance cellulaire et tissulaire, 2 h de cours magistral, DESC Oncologie, UPMC, France

Summer/Winter schools: J. Clairambault, Winter school BIOMAT La Falda (Córdoba, Argentina), August 2014, 3 h of conference classes (en castellano)

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" (24h)

9.2.2. Supervision

HdR: Nicolas Vauchelet, "Contributions mathématiques à l'étude de modèles décrivant le mouvement de particules confinées et de micro-organismes", UPMC, 08/12/2014

PhD: Hadjer Wafaâ Haffaf, "Analyse de l'agrégation des protéines dans les maladies neurodégénératives amyloïdes - Application aux maladies à prion", UPMC, defended 14/10/17, Marie Doumic

PhD in progress: Aurora Armiento, “Inverse problems for aggregation kinetics”, begun September 2013, M. Doumic and P. Moireau (Inria Saclay, M3DISIM team)

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

PhD in progress: Adélaïde Olivier, “Nonparametric estimation of the division rate in branching process”, begun September 2012, M. Doumic and M. Hoffmann (Prof. Univ. Paris-Dauphine)

PhD in progress: Thibault Bourgeron, “Linear and nonlinear structured population models”, begun September 2012, M. Doumic and B. Perthame

PhD in progress: Ján Eliaš, “p53 intracellular spatio-temporal dynamics”, begun October 2012, J. Clairambault and B. Perthame

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

PhD in progress: Antonin Prunet, begun October 2014, L. Almeida and A. Escargueil

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

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

PhD in progress: François Bertaux (since September 2011), supervision by Dirk Drasdo and Gregory Batt

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

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

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

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

9.2.3. Juries

- J. Clairambault: José Luis Avila, PhD defence, 02/07/2014, Paris XI (Applied mathematics)
- J. Clairambault (Reviewer) : Hossein Ayoub, PhD defence, 04/07/2014, Bordeaux (Applied mathematics)
- J. Clairambault: Nathalie Eymard, PhD defence, 04/12/2014, Lyon (Applied mathematics)
- J. Clairambault: Niklas Hartung, PhD defence, 15/12/2014, Marseille (Applied mathematics)
- M. Doumic: H.W. Haffaf, PhD defence, 17/10/2014, UPMC (Applied mathematics)
- M. Doumic: N. Vauchelet, habilitation thesis, 8/12/2014, UPMC (Applied mathematics)
- M. Doumic: M. Ribot, habilitation thesis, 12/12/2014, UPMC (Applied mathematics)
- D. Drasdo: A. Zinovyev, habilitation thesis, 04/04/2014, ENS (Computational Biology)

9.3. Popularization in international bulletins

- Article Clairambault, J. “My personal journey in mathematical biology and medicine”. Society for Mathematical Biology Newsletter 28(1):11-12, January 2015 [27], http://www.smb.org/publications/newsletter/vol28no1.pdf
- Article Clairambault, J. “Perspectives on new and less new opportunities for mathematical biology as applied to biological and clinical medicine”. Society for Mathematical Biology Newsletter 27(2):14-15, May 2014 [26], http://www.smb.org/publications/newsletter/vol27no2.pdf

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

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[2] N. VAUCHELET. *Contributions mathématiques à l'étude de modèles décrivant le mouvement de particules confinées et de micro-organismes*, Université Pierre et Marie Curie, December 2014, Habilitation à diriger des recherches, https://hal.archives-ouvertes.fr/tel-01111810

Articles in International Peer-Reviewed Journals

[3] 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

[4] F. BILLY, J. CLAIRAMBAULT, O. FERCOQ, S. GAUBERT, T. LEPOUTRE, T. OUILLON, 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

[5] T. BOURGERON, M. DOUMIC-JAUFFRET, M. ESCOBEDO. *Estimating the Division Rate of the Self-Similar Growth-Fragmentation Equation*, in "Inverse Problem", January 2014, vol. 30, n^{o} 2, 025007, 28 p. , https://hal.inria.fr/hal-00858488

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