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Activity Report 2013

Project-Team BANG

Nonlinear Analysis for Biology and Geophysical flows

IN COLLABORATION WITH: Laboratoire Jacques-Louis Lions

RESEARCH CENTER
Paris - Rocquencourt

THEME
Earth, Environmental and Energy Sciences

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Project-Team BANG

Keywords: Multiscale Analysis, Population Dynamics, Control Theory, Flow Modeling, Numerical Methods

Creation of the Project-Team: 2004 February 01, End of the Team: 2013 December 31.

1. Members

Research Scientists

Luís Lopes Neves de Almeida [CNRS, Senior Researcher, HdR]
Jean Clairambault [Inria, Senior Researcher, HdR]
Marie Doumic [Inria, Team leader, HdR]
Dirk Drasdo [Inria, Senior Researcher, HdR]
Jonathan Touboul [Inria, from Jul 2013 until Dec 2013]

Faculty Members

Alexander Lorz [Univ. Paris VI, Assistant Professor]
Benoît Perthame [Univ. Paris VI, Professor]
Nicolas Vauchelet [Univ. Paris VI, Assistant Professor]

Engineers

Tim Johann [Inria, granted by a BMBF contract]
Stéphanie Prigent [Inria, granted by FP7 MD-ERCSKIPPERAD project]

PhD Students

Aurora Armiento [Univ. Paris VII, granted by FP7 MD-ERCSKIPPERAD project, from Apr 2013]
François Bertaux [Ecole Polytechnique]
Noémie Boissier [Inria, granted by FP7 BANG– CP NOT0X project, from Nov 2013]
Thibault Bourgeron [Univ. Paris VI]
Géraldine Cellière [Univ. Paris VI]
Ján Eliaš [Univ. Paris VI]
Casimir Emako-Kazianou [Univ. Paris VI]
Sarah Eugène [Inria]
Hadjer Wafaâ Haffaf [Foreign government]
Nick Jagiella [Foreign government]
Johannes Neitsch [IZBI, Leipzig]
Adélaïde Olivier [ENSAE]
Cristóbal Quiñinao Montero [Foreign government, from Jan 2013]
Karina Vilches Ponce [CNRS, until Dec 2013]

Post-Doctoral Fellows

Annabelle Ballesta [Inria, until Jan 2013]
Ibrahim Cheddadi [Univ. Paris VI]
Rebecca Chisholm [Inria, from Dec 2013]
Stefan Hoehme [Research Associate, University of Leipzig]
Carola Kruse [Inria, granted by FP7 MD-ERCSKIPPERAD project, from Jul 2013]
Tommaso Lorenzi [Univ. Paris VI, on FSMP grant, from Nov 2013]
Paul Van Liedekerke [Inria, granted by FP7 - CP NOT0X project]
Yi Yin [Inria, granted by ANR SYNE2ARTI project]

Administrative Assistant

Nathalie Bonte [Inria]

2. Overall Objectives

2.1. Introduction

BANG (Biophysique, Analyse Numérique et Géophysique) is a continuation of the former project M3N. Historically, the BANG team has developed models, simulations and numerical algorithms for two kinds of problems involving dynamics or Partial Differential Equations (PDEs). Problems from life sciences (cell movement, early embryonic development, tissue growth and regeneration, cancer modelling, pharmacology,...) are considered.

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/). The remaining ("Biophysique") part of the BANG team (that itself has been arrested in December 2013) continues from 2014 on their research work in the new Inria team MAMBA ("Modelling and Analysis in Medical and Biological Applications"), created in January 2014 in continuity with BANG.

The common scientific features behind these biological and geophysical applications come from models involving coupled systems of PDEs (as Keller-Segel or Saint-Venant systems) that are solved (simulated) on computers involving new algorithms and from the methodology which aims at being close to experiments or real data. Within the applications to life sciences, data analysis, agent-based, ODE and PDE approaches are combined.

2.2. Highlights of the Year

Benoît Perthame was head of the team until January 2013 when he became head of the Laboratoire Jacques-Louis Lions of UPMC (Univ. Paris VI), a laboratory with around 200 members: University, CNRS or Inria permanent members, plus many non-permanents (PhD students, postdocs and engineers). Since then, Marie Doumic has been acting as the BANG team head and now heads the new team MAMBA.

3. Research Program

3.1. Introduction

The dynamics of complex physical or biophysical phenomena involving many particles, including biological cells - which can be seen as active particles -, can be represented efficiently either by explicitly considering the behaviour of each particle individually or by Partial Differential Equations which, under certain hypotheses, represent local averages over a sufficiently large number of particles.

Since the XIXth century this formalism has shown its efficiency and ability to explain both qualitative and quantitative behaviours. The knowledge that has been gathered on such physical models, on algorithms for solving them on computers, on industrial implementation, opens the hope for success when dealing with life sciences also. This is one of the main goals of BANG. At small spatial scales, or at spatial scales of individual matter components where heterogeneities in the medium occur, agent-based models are developed. They complement the partial differential equation models considered on scales at which averages over the individual components behave sufficiently smoothly.

3.2. Mathematical modelling

What are the relevant physical or biological variables, what are the possible dominant effects ruling their dynamics, how to analyse the information coming out from a mathematical model and interpret them in the real situations under consideration ? These are the questions leading to select a mathematical model, generally also to couple several of them in order to render all physical or biomedical features which are selected by specialist partners (engineers, physicists, physicians). These are usually based on the Navier-Stokes system for fluids (as in free surface fluid flows), on parabolic-hyperbolic equations (Saint-Venant system for shallow water, formerly studied flows of electrons/holes in semiconductors, Keller-Segel model of chemotaxis).

3.3. Multiscale analysis

The complete physical or biomedical description is usually complex and requires very small scales. Efficiency of computer resolution leads to simplifications using averages of quantities from one level to the upper next. Methods allowing to achieve that goal are numerous and mathematically deep. Some examples studied in BANG are

- Coupled multiscale modelling (description of tumours and tissues from the sub-cellular level to the organ scale).
- Description of cell motion from the individual to the collective scales.

3.4. Numerical Algorithms

Various numerical methods are used in BANG. They are based on finite elements (FreeFEM++), on finite volume methods, or on stochastic methods for individual agents. Algorithmic improvements are needed in order to take into account the specificity of each model, of their couplings, or their 3D features. These involve in particular deterministic models for the representation of intracellular signalling pathways, and also deterministic and stochastic agent-based models for the simulation of multi-cellular systems.

4. Application Domains

4.1. Proliferation dynamics and its control

This domain of research has historically been - and is still - very active in the Bang team, which is reflected in particular in B. Perthame's book of 2007 "Transport equations in biology" [1]. It may presently be divided in:

- Cell division cycle in structured cell populations.
- Physiological and pharmacological control of cell proliferation.
- Optimisation of cancer chemotherapy and cancer chemotherapy.
- Protein polymerisation and application to amyloid diseases.
- Inverse problem for growth-fragmentation equations.

4.2. Tissue growth, regeneration and cell movements

This research activity aims at studying mathematical models related to tumour development and tissue organisation. Among the many biological aspects, examples are:

- Biomedical aspects of cell-cell interactions at the local and whole organ level.
- Migration of cells in tissues.
- Growth control of living tissues and organs.
- Regenerative medicine.
- Early embryology, and biomechanical aspects of cell interactions.
- Chemotaxis, self-organisation in cell populations.

4.3. Neurosciences

Cortical networks are constituted of a large number of statistically similar neurons in interaction. Each neuron has a nonlinear dynamics and is subject to noise. Moreover, neurological treatment involve several timescales. Multiscale analysis, both in spatial (number of cells) and temporal hence also constitute mathematical foundations of our approaches to neurosciences. In addition to the techniques described in section 3.1 - 3.4, our approach of the activity of large cortical areas involve:

- limit theorems of stochastic interacting particles systems, such as coupling methods or large deviations techniques, as used in mathematical approaches to the statistical physics of gases
- bifurcation analysis of deterministic and stochastic differential equations used to analyse the qualitative behaviour of networks
- singular perturbation theory, geometrical and topological approaches in dynamical systems used to uncover the dynamics in the presence of multiple timescales.

4.4. Geophysical flows and environment

The BANG team has split in December 2012, giving rise to another team, ANGE (https://team.inria.fr/ange/), specialised in complex geophysical flows in interaction with the environment. Free surface flows as tsunamis, flows in rivers and costal areas and their ecological consequences are typical examples of applications developed in this new Inria team, based on algorithms for the free-surface Navier-Stokes equations.

5. Software and Platforms

5.1. Software and Platforms

5.1.1. Continuation of M3N

A large part of the software currently in use in the project-team was initiated and developed within former projects (Menusin, M3N).

5.1.2. CellSys

Participants: Geraldine Cellière [PhD student], Dirk Drasdo [correspondent], Stefan Höhme, Adrian Friebel [PhD student, University of Leipzig], Tim Johann [Software Engineer, University of Leipzig], Johannes Neitsch [PhD student], Paul Van Liedekerke [Research Engineer].

Based on an earlier submitted software (Hoehme and Drasdo, Bioinformatics, 2010) a modular computer simulation software for image analysis of tissue samples at histological scales, as well as for individual cell (agent)-based modeling of tumour and tissue growth, and tissue regeneration has been developed. Cell movement is solved either by systems of coupled equations of motion for each individual cell or by Kinetic Monte Carlo methods. The software uses a git framework to facilitate coordinated contributions of multiple developers. The image analysis part allows analysis of structures down to sub-cellular scale such as liver micro-capillaries and bile cannaliculi structures. So far, blood flow as well as growth and regeneration processes, fluxes of chemicals by diffusion and flow etc can be modelled, finite element solvers, ITK and VTK have been integrated.
The software CellSys is calibrated to allow use by external and internal researchers. The idea is to perspectively go open-source and offer consultancy for potential users.
Moreover in 2013 the image processing and analysis chain was refined to capture high resolution laser scanning micrographs. The algorithms were integrated into CELLSYS (see: software) and our experimental partner labs within the projects VLN and NOTOX were provided with the software to allow image analysis directly in their lab and with their people. Along the same line an experimental partner lab at the German Cancer center was provide with a small image analysis tool permitting them to efficiently analyze their bright field images on growing and invasive cancer cell populations in vitro (LUNGSYS).

6. New Results

6.1. Proliferation dynamics and its control

6.1.1. Proliferation dynamics in cell populations

Participants: José Luis Avila Alonso [DISCO project-team, Inria Saclay IdF], Annabelle Ballesta, Gregory Batt [CONTRAINTES project-team], François Bertaux, Frédérique Billy, Frédéric Bonnans [Commands project-team, Inria Saclay IdF], Catherine Bonnet [DISCO project-team, Inria Saclay IdF], Jean Clairambault, Marie Doumic, Xavier Dupuis [Commands project-team], Ján Eliaš, Germain Gillet [IBCP, Université Cl. Bernard Lyon 1], Pierre Hirsch [INSERM Paris (Team18 of UMR 872) Cordeliers Research Centre and St. Antoine Hospital, Paris], Pierre Magal [University Bordeaux II], Anna Marciniak-Czochra [Institute of Applied Mathematics, Universität Heidelberg], Jean-Pierre Marie [INSERM Paris (Team18 of UMR

872) Cordeliers Research Centre and St. Antoine Hospital, Paris], Roberto Natalini [IAC-CNR, Università Sapienza, Rome], Silviu Niculescu [DISCO project-team, Inria Saclay IdF], Hitay Özbay [Bilkent University, Ankara, Turkey], Benoît Perthame, Szymon Stoma [CONTRAINTES project-team], Ruoping Tang [INSERM Paris (Team18 of UMR 872) Cordeliers Research Centre and St. Antoine Hospital, Paris], Vitaly Volpert [CNRS Lyon, UMR5208, Camille Jordan Institute, Lyon], Jorge Zubelli [IMPA, Rio de Janeiro].

1. **Transition kernels in a McKendrick model of the cell division cycle.** This theme, after a rich harvest of publications (most of them in 2013 and even 2014), is awaiting new developments, since of the main two young researchers on this theme, F. Billy has concluded her 2-year Inria postdoc at Bang, leaving for an industrial company in November 2012, while O. Fercoq (team MaxPlus, Saclay) has defended his PhD thesis at École Polytechnique in September 2012, only to leave for a postdoc position dedicated to optimisation theory in Edinburgh.
2. **Modelling haematopoiesis with applications to AML.** This theme has been active through a collaboration with Inria teams Commands (F. Bonnans, X. Dupuis) and Disco (J.L. Avila Alonso, C. Bonnet, Hitay Özbay, S. Niculescu), and J.-P. Marie's team at St Antoine Hospital leukaemic tumour bank, where A. Ballesta, Cancéropole IdF-Inria postdoc has been detached (ending in January 2013) to identify parameters of a model of acute myeloblastic leukaemia (AML) in patient fresh cell cultures with and without anticancer drugs. This work has led to several presentations, and publications are in preparation. In a book chapter summing up the PhD work of J.L. Avila Alonso [26], and in two submitted conference papers [28], [29], a new model of haematopoiesis for AML is presented, including phases of the cell division cycle and maturation stages, with targets for therapeutic control.
3. **Hybrid models.** Systems combining PDEs and discrete representations in hybrid models, with applications to cancer growth and therapy, in particular for AML, are the object of study of the ANR program *Bimod*, coordinated by V. Volpert (Lyon), associating CNRS (V. Volpert, Lyon), Bordeaux II University (P. Magal) and the Bang project-team.
4. **Molecular model of apoptosis.**

   With G. Gilllet (professor at IBCP/Lyon), A. Ballesta and M. Doumic have designed a mathematical ODE model for the mitochondrial pathway of apoptosis, focused on the early phase of apoptosis (before the cytochrome C release). This model has been validated by experimental data carried out in G. Gillet's lab and applied to propose new therapeutic strategies against cancer [6].
5. **Molecular model of the activity of the p53 protein.** This work, firstly the object of Luna Dimitrio's PhD thesis [37], who left in 2012 for the pharmaceutic industry (SANOFI), has been continued since a new PhD student, Ján Eliaš, has taken over this theme in September 2012 in a new PhD thesis at UPMC, under the supervision of J. Clairambault and B. Perthame. His work has given rise in 2013 to 2 publications [14], [32].
6. **TRAIL - induced apoptosis in HELA cells** Explaining cell-to-cell variability is a major step towards understanding how cancer cells escape action of chemotherapeutic drugs. We set up and studied an integrated model of stochastic gene expression, deterministic translation and protein degradation capable of explaining fractional killing and reversible resistance in Hela cells in response to treatment with TNF-Related Apoptosis Inducing Ligand, TRAIL (Bertaux, Stoma, Drasdo, and Batt, submitted). The results of the model suggests that stochastic fluctuations are a fundamental determinant in understanding cell-to-cell variability, and identified relations between the characteristic time scales of the processes at which stochasticity should play a particular important role.

6.1.2. Physiological and pharmacological control of cell proliferation

Participants: Annabelle Ballesta, Frédérique Billy, Jean Clairambault, Sandrine Dulong [INSERM Villejuif (U 776)], Olivier Fercoq [MaxPlus project-team], Stéphane Gaubert [MaxPlus project-team], Thomas Lepoutre [Dracula project-team], Francis Lévi [INSERM Villejuif (U 776)].

1. *Periodic (circadian) control of cell proliferation in a theoretical model of the McKendrick type.* This theme (cf. supra "transition kernels...") has been continued [9], [27], [7], [8], [31]. Whereas transition kernels between cell cycle phases without control have been experimentally identified in cell cultures by FUCCI imaging [9], their circadian control remains elusive and has been modelled on the basis of gating by plain cosines representing the influence exerted on these transition kernels by circadian clocks. To go further, it would be necessary to have access by cell imaging to the activity of the best physiological candidates to such gating, namely the cyclin-Cdk complexes, together with the activities of the clock-controlled proteins Wee1 and p21, which thus far have remained unavailable to us through biological experimentation with imaging. A 12-year collaboration work with Francis Lévi on (circadian) chronotherapeutic optimisation in cancer is reported in [30].
2. *Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs.* This theme has continued to be developed with new publications for the drugs irinotecan [5], 5-fluorouracil and oxaliplatin [31], and with a recent mini-review by A. Ballesta and J. Clairambault on mathematical models of treatment of metastatic colorectal cancer [4].

6.1.3. Optimisation of cancer chemotherapy and cancer radiotherapy

Participants: Juan Carlos Alfonso [University Complutense, Madrid, Spain], Annabelle Ballesta, Frédérique Billy, Frédéric Bonnans [Commands project-team], Rebecca Chisholm, Jean Clairambault, Sandrine Dulong [INSERM Villejuif (U 776)], Xavier Dupuis [Commands project-team], Alexandre Escargueil [INSERM and UPMC, St Antoine Hospital], Olivier Fercoq [MaxPlus project-team], Stéphane Gaubert [MaxPlus project-team], Miguel Angel Herrero [University Complutense, Madrid, Spain], Michael Hochberg [ISEM, CNRS, Montpellier], Dirk Drasdo, Nick Jagiella, Francis Lévi [INSERM U 776, Villejuif], Thomas Lepoutre [Dracula project-team], Tommaso Lorenzi, Alexander Lorz, Luis Núñez [University Complutense, Madrid, Spain], Benoît Perthame, Emmanuel Trélat [LJLL, UPMC].

1. **Limiting unwanted toxic side effects: age-structured models of the cell cycle.** Optimising cancer chemotherapy, in particular chronotherapy, is the final aim of these activities. A classical numerical method of optimization under the constraint of limiting toxicity to healthy tissues has been applied to the McKendrick model of the cell cycle divided in phases, endowed with physiologically based targets for both internal (circadian) and external (pharmacological) control. This model has been partly biologically identified on continuous FUCCI recordings of proliferating NIH3T3 cells in culture media; these data were made available to us within the C5Sys consortium, an ERASYSBIO+ European project. Then additional theoretical characteristics establishing hypothetical differences between healthy and cancer cell populations, relying on different responses to physiological circadian clock influences on gating by Cyclin-Cdk complexes between cell cycle phases, have been used to solve the optimization problem, proposing an optimal drug infusion regimen [7], [8], [27], [9]. Using an even more complex McKendrick-like model of the cell cycle, a connection with previously established PK-PD ODE models of the anticancer drugs 5-Fluorouracil and Oxaliplatin has been established, proposing optimized combined drug delivery flows to solve the same optimization problem [31].
2. **Limiting drug resistance in cancer cell populations: cell Darwinism.** This theoretical activity has been continued also in more general settings taking into account another major issue of anticancer treatment, namely resistance to drugs in cancer cells. To this latter aim, we have developed another type of models based on integro-differential equations, which are inspired from those used in ecology for Darwinian evolution [22]. These are aimed at studying another major issue in cancer therapy: appearance of resistances to treatment in tumour cell populations. Indeed, these cell populations, because of their heterogeneity and genomic instability, present an ability to adapt and evolve (in the Darwinian sense) that is much higher than in healthy cell populations [7], [18], [35]. The time scales under investigation, much shorter than in ecology, are however much longer than in microbiology, and are those of clinical treatments. Theoretical optimization of external controls representing combined cytotoxic and cytostatic treatments on these models with the aim to limit the emergence of drug resistance are presently under assessment, in collaboration with Emmanuel Trélat (LJLL, UPMC), paper in preparation.

3. **Molecular aspects: ABC transporters.** From a molecular point of view, studying drug resistance leads to the study of ABC transporters, which is one of the tracks followed by A. Ballesta, following her PhD thesis, in collaboration with F. Lévi's INSERM team in Villejuif [4], [5].
4. **Optimisation of cell kill in AML.** Underway is also the use of methods of optimal control methods developed by the Commands project-team (Frédéric Bonnans, Xavier Dupuis) to optimise therapies in the treatment of Acute Myeloblastic Leukaemia (AML). X. Dupuis has lately produced a paper [40], accepted for publication in Math. Mod. Phys. Phenom, on optimisation of a combined treatment using a cytotoxic drug (representing Aracytin) and a cytostatic drug (representing AC220, an antagonist of Flt-3 receptors). This work is led in conjunction with the DISCO team, cf. supra "Modelling haematopoiesis with applications to AML").
5. **Estimating dose painting effects in radiotherapy: a mathematical model.** Tumor heterogeneity is widely considered to be a determinant factor in tumor progression and in particular in its recurrence after therapy. Unfortunately, current medical techniques are unable to deduce clinically relevant information about tumor heterogeneity by means of non-invasive methods. As a consequence, when radiotherapy is used as a treatment of choice, radiation dosimetries are prescribed under the assumption that the malignancy targeted is of a homogeneous nature. In this work we discuss the possible effects of different radiation dose distributions on heterogeneous tumors by means of an individual cell-based model. To that end, a case is considered where two tumor cell phenotypes are present, which strongly differ in their respective cell cycle duration and radiosensitivity properties. We show herein that, as a consequence of such differences, the spatial distribution of such phenotypes, as the resulting tumor heterogeneity, can be predicted as growth proceeds. As a consequence, heterogeneous dosimetries can be selected to enhance tumor control by boosting radiation in the region occupied by the more radioresistant tumor cell phenotype. It is also shown that, when compared with homogeneous dose distributions as those being currently delivered in clinical practice, such heterogeneous radiation dosimetries fare always better than their homogeneous counterparts (Alfonso et. al., PLoS One accepted [3]).

6.1.4. Protein polymerisation and application to amyloid diseases

Participants: Annabelle Ballesta, Vincent Calvez [ENS Lyon], Marie Doumic, Pierre Gabriel, Hadjer Wafaâ Haffaf, Benoît Perthame, Stéphanie Prigent [BPCP, INRA Jouy-en-Josas], Human Rezaei [BPCP, INRA Jouy-en-Josas], Léon Matar Tine [SIMPAF project-team, Inria Lille Nord-Europe].

Published in PLoS One in collaboration with the team of biologists led by H. Rezaei [44], a new and very complete PDE model for protein polymerisation has been designed. Following F. Charles's work, A. Ballesta has applied this model to Huntington's disease (PolyQ expansion) and compared it with its ODE counterpart, leading to a better understanding of the leading mechanisms responsible for PolyQ fibrillisation. New applications of this framework model are in progress with H.W. Haffaf and S. Prigent.

The eigenvalue problem playing a major role in the representation of Prion proliferation dynamics and, in a more general way, of many fragmentation-coalescence phenomena, the article [36] investigated the dependency of the principal eigenvector and eigenvalue upon its parameters. We exhibited possible nonmonotonic dependency on the parameters, opposite to what would have been conjectured on the basis of some simple cases.

6.1.5. Inverse problem in growth-fragmentation equations

Participants: Marie Doumic, Marc Hoffmann [ENSAE], Nathalie Krell [Univ. Rennes I], Patricia Reynaud [CNRS, Nice Univ.], Lydia Robert [UPMC], Vincent Rivoirard [Paris IX Univ.], Léon Matar Tine [SIMPAF project-team, Inria Lille Nord-Europe].

In collaboration with statisticians (M. Hoffman, Professor at Université de Marne-la-Vallée, V. Rivoirard, MC at Université d'Orsay, and P. Reynaud, CR CNRS at Université de Nice), in the article [38] published in SIAM Num. Anal., we explored a statistical viewpoint on the cell division problem. In contrast to a deterministic inverse problem approach, we take the perspective of statistical inference. By estimating statistically each

term of the eigenvalue problem and by suitably inverting a certain linear operator, we are able to construct an estimator of the division rate that achieves the same optimal error bound as in related deterministic inverse problems. Our procedure relies on kernel methods with automatic bandwidth selection. It is inspired by model selection and recent results of Goldenschluger and Lepski.

An extension of this work, which consists of the statistical estimation of a branching process modelling the same growth and fragmentation dynamics, has been submitted in [12], in collaboration with N. Krell, M. Hoffmann and L. Robert. Such methods are indeed successfully applied to investigate bacterial growth, in collaboration with L. Robert (INRA and UPMC), see Figure 1.

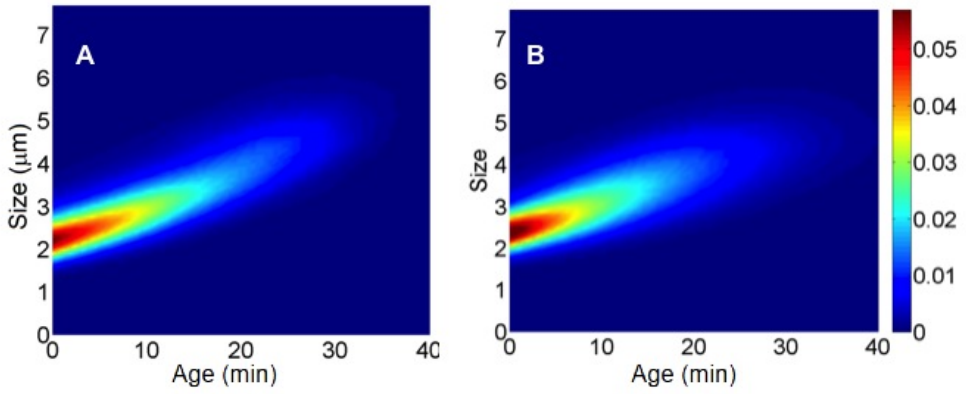

Figure 1. Age and Size Distribution of a bacterial culture (E. coli): comparison between the experimental distribution (A) and the best-fit simulation (B). The methods developed in [38] and [12] allowed us to discriminate between a size-dependent and an age-dependent division rate.

In [13], we generalised the inverse techniques proposed previously in [39], [43], in order to adapt them to general fragmentation kernels and growth speeds. The potential applications of this problem are numerous, ranging from polymerisation processes to the cell division cycle. An extension of this work, using refined estimates the Mellin transform of the equation, has just been accepted for publication in *Inverse Problems* [10].

6.2. Tissue growth, regeneration and cell movements

6.2.1. Chemotaxis, self-organisation of cell communities (KPP-Fisher and Keller-Segel)

Participants: Luís Lopes Neves de Almeida, Nikolaos Bournaveas [Univ. Edinburgh], Axel Buguin [UPMC, Institut Curie], Vincent Calvez [ENS Lyon], Casimir Emako-Kazianou, François James [univ. Orléans], Alexander Lorz, Grégoire Nadin [UPMC], Benoît Perthame, Jonathan Saragosti [Institut Curie], Pascal Silberzan [Institut Curie], Min Tang [Shanghai Jiaotong University], Nicolas Vauchelet.

Chemotaxis denotes the ability of some cells to undergo a directed movement in response to an extracellular chemical substance. A mathematical description of chemotaxis is a major issue in order to understand collective movements of bacterial colonies. Numerous mathematical models, at various scales, have been proposed, allowing for a good description of cell aggregation under chemotaxis at the macroscopic level, the first of all being that of Keller-Segel (1971), that is now at the centre of an abundant international scientific literature.

At the cell scale, one uses kinetic equations for which numerical simulations have been performed. Behaviour of solutions can be understood by performing a hydrodynamical limit of the kinetic equation. It leads to aggregation type equations for which finite time blow up is observed [42]. Then measure solutions for this system should be considered. A theoretical framework for the existence of weak solutions has then been developed [17], [34] where duality solutions for such system has been investigated which are equivalent to gradient flow solutions [33].

Our understanding of traveling waves has progressed considerably in three directions: fitting continuous models and IBMs [21], fitting precisely models with experiments based on known biological values of parameters, and opening new paradigms: traveling waves can connect a dynamically unstable state to a Turing unstable state, certainly the stable wave connects the unstable state to a pulsating state.

6.2.2. Single-cell-based and continuum models of avascular tumours

Participants: Ibrahim Cheddadi, Dirk Drasdo, Benoît Perthame, Min Tang [Shanghai Jiaotong University], Nicolas Vauchelet, Irène Vignon-Clémentel [REO project-team].

The recent biomechanical theory of cancer growth considers solid tumours as liquid-like materials comprising elastic components. In this fluid mechanical view, the expansion ability of a solid tumour into a host tissue is mainly driven by either diffusion of cells (emerging on the mesoscopic scale by coarse graining from the cell micro-motility) or by cell division depending either on the local cell density (contact inhibition), on mechanical stress in the tumour, or both. For the two by two degenerate parabolic/elliptic reaction-diffusion system that results from this modelling, we prove there are always travelling waves above a minimal speed and we analyse their shapes. They appear to be complex with composite shapes and discontinuities. Several small parameters allow for analytical solutions; in particular the incompressible cells limit is very singular and related to the Hele-Shaw equation. These singular travelling waves are recovered numerically. See [21]. Besides this work, a direct comparison with agent-based and continuum models has been performed, showing very good agreement over a large parameter range.

6.2.3. Single cell-based models of tumour growth, tissue regeneration

Participants: Gregory Batt [CONTRAINTES project-team], François Bertaux, Noémie Boissier, Kai Breuhahn [German Cancer Centre, Heidelberg], Petru Bucur [Hopital Paul Brousse, Paris], Géraldine Cellière, Chadha Chettaoui, Ibrahim Cheddadi, Dirk Drasdo, Adrian Friebel, Rolf Gebhardt [Univ. of Leipzig, Germany], Adriano Henney [Director Virtual Liver Network and VLN consortium], Jan G. Hengstler [Leibniz Research Centre, Dortmund, Germany and CANCERSYS consortium], Stefan Höhme [Research Associate, University of Leipzig], Elmar Heinzle [University of Saarbrücken and NOTOX consortium], Nick Jagiella, Ursula Klingmüller [German Cancer Centre, Heidelberg and LungSys Consortium], Pierre Nassoy [Institut Curie, Paris and Univ. of Bordeaux], Johannes Neitsch, Benoît Perthame, Jens Timmer [University of Leipzig, Germany], Irène Vignon-Clémentel [REO project-team], Paul Van Liedekerke, Eric Vibert [Hôpital Paul Brousse, Villejuif], Ron Weiss [MIT, USA].

1. **Ammonia metabolism in healthy and damaged liver** The model on ammonia detoxification in liver, integrating a compartment model for the glutamine synthetase-active peri-central and the glutamine-inactive peri-portal liver lobule compartment (see Bang report 2012) with the spatial -

temporal model of liver regeneration after drug-induced peri-central damage [41] has been extended to include the mass balance of other body compartments. The analysis shows that some body compartments that in the healthy liver produce ammonia, in the damaged liver detoxify blood from ammonia. The detoxification model of liver in combination with the body ammonia balance can be found in ref. (Schliess et. al., Hepatology, accepted [20]).

2. **Drug metabolism in hepatocytes** Since the begining of 2013 animal experiments for testing of cosmetics are forbidden within the EU. This has triggered initiatives towards how modeling may help to investigate drug toxicity, circumventing animal testing. The basic conceptual idea is to test drugs (cosmetics, perspectively also other drugs) in in-vitro systems such as monolayers, sandwich cultures, or multi-cellular spheroids, and use the emerging data to infer the expected toxicity in-vivo using novel experimental and computational approaches [16]. We have integrated an intracellular mathematical model of paracetamol drug metabolism in a mathematical agent-based cell model for monolayer and multi-cellular spheroids and compared simulation results with experimental findings in the same systems. We find that cell-to-cell variabilty can largely explain the experimentally observed cell population survival fractions. The mathematical model is now refined based on measurements of intermediate drug metabolites.
3. **Cell mechanics and its impact on cell proliferation** A novel numerical methodology has been developed to simulate the mechanics of cells and tissues using a continuum approach. Analogously to the Center Based Models, particles are used to represent (parts of) the cells but rather than discrete interactions they represent a continuum. This approach can be used for tissue mechanics simulations in where the individual cell-cell interactions are discarded but instead a constitutive law is proffered [23].
   Moreover, a new model in where cell adhesion dynamics is addressed. The cell model is constructed by a triangulated surface and a coarse-grained internal scaffolding structure. A model cell can adapt to realistic cell shapes, and is able to interact with a substrate or other cells. The parameters in this model can be determined by canonical experiments performed on cells informing about cell deformation, compression and cell-cell adhesion [19].
   A computational model for the confined growth of cells in a capsule has been developed. This model represents a realistic simulation tool for a novel experimental system (Institut Curie, Prof P. Nassoy) in where cells are grown in an elastic environment to mimic the effects of mechanical stress on cells and while monitoring their fate. Model parameter calibration is now ongoing to reproduce the correct quantitative behavior of the cells in order to unravel the relationship between cell mechanical stress and cell behavior.
4. **Playing the game of life with yeast cells** Within a collaboration with a synthetic biology lab at MIT, multicellular modelling of engineered yeast cell populations is performed. Those cells secrete a messenger molecule (IP) which diffuse in the medium, bind to other cells, and trigger a signalling cascade, which finally induces expression of lethal genes. A model has been established based on our single-cell-based model framework associated with PDE simulations, and it is currently used to explain and guide experiments conducted at the MIT. In 2013, the project has achieved significant progress on several aspects. First, we were able to quantitatively reproduce newly produced, rich data on the signaling cascade behavior with a kinetic model describing signaling reactions. Second, comparison between simulations and data allowed to identify key characteristics of the death module, which is positioned downstream of the signaling cascade: there is a rapid and stochastic commitment to death, followed by a deterministic and long delay (2-4 cell generations) needed before cells actually die. Finally, data production and analysis iterations with our collaborators alloweded to optimize the procedures for experimental measurements and the quantitative analysis of data in a synergistic manner.
5. **Other projects in short** Further progress have been achieved on the reconstruction of lung cancer micro-architecture from bright field micrographs. In partial hepatectomy (PHx), pig data on the changes of microarchitecture during regeneration after PHx have been generated and stained now being processed. The image processing chain for liver architecture reconstruction has been refined

and extensive analysis has been performed on the architecture of the bile canaliculi network in healthy liver and in disease states of liver. Moreover, non-small-cell lung cancer cell invasion pattern have been analyzed leading to interesting observations now being studied by modelling.
For multi-scale modeling of liver regeneration after drug-induced pericentral damage, integration of a molecular model of hepatocyte growth factor signalling with an agent-based model of liver regeneration has been extended to include blood flow in the lobule, as well as the contributions of the body compartment to the degradation and production of hepatocyte growth factor (HGF).

6.2.4. Modelling flows in tissues

Participants: Noémie Boissier, Lutz Brusch [TU Dresden], Dirk Drasdo, Adrian Friebel [IZBI, University of Leipzig], Stefan Hoehme [IZBI, University of Leipzig], Nick Jagiella [Inria and IZBI, University of Leipzig], Hans-Ulrich Kauczor [University of Heidelberg, Germany], Fabian Kiessling [University Clinics, Technical University of Aachen, Germany], Ursula Klingmueller [German Cancer Research Centre (DKFZ), Heidelberg, Germany], Hendrik Laue [Fraunhofer Mevis, Bremen, Germany], Ivo Sbazarini [MPI for Molecular Cell Biology and Genetics, Dresden, Germany], Irène Vignon-Clémentel [REO project-team], Marino Zerial [MPI for Molecular Cell Biology and Genetics, Dresden, Germany].

1. **Flow and perfusion scenarios in cancer.** We started reconstruction of the blood vessel system of lung cancers removed by surgery. For this purpose, patients underwent DCE-MRI prior to surgery. Part of the tumors after surgery was sliced and stained for nuclei, proliferation and endothelial cells. The slice data were recorded (Mevis, Luebeck) to allow identification of the position of the indiviudal structures in 3D space. The structures were then segmented. The work turned out to be particularly challenging because of staining artifacts for which image algorithms had to correct for. Nevertheless, last results look promising so that at least the network formed by larger vessels can be segmented and reconstructed in 3D. The so emerging data will be used for modeling of blood flow using the models developed in 2012.
2. **Flow in liver lobules.** We integrated blood flow in the new software CellSys (see above under software) and refined the algorithms. Moreover, we increased the resolution of the capillaries by triangulating them from high resolution confocal scanning micrographs.

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

Participants: Luís Lopes Neves de Almeida, P. Bagnerini [Univ. Genova], A. Habbal [Univ. Nice], A. Jacinto [CEDOC, Lisbon], M. Novaga [Univ. Padova], A. Chambolle [École Polytechnique].

In 2013 we continued to investigate the dependence of physical and biological mechanisms of actomyosin cable formation and wound closure depending on the geometry of the wound, with particular emphasis on the effect of the wound edge curvature.

When the actomyosin cable starts to contract and the wound starts to close we have noticed that the behavior of the cable is related with the local curvature of the wound edge. This led us to study the curves evolving by positive part of their curvature in a Euclidean framework. A model where we consider viscous behavior and friction in the tissue plus boundary terms associated to cable and lamellipodial forces is under development. The numerical simulations obtained using this model are in good agreement with the previous experimental results and we are pursuing the model development by challenging it with new experiments.

6.3. Neurosciences

Participants: Jonathan Touboul, Gilles Wainrib, Tanguy Cabana, Mathieu Galtier, Luis Garcia Del Molino, Khashayar Pakdaman.

We pursued our studies of disordered networks of the brain and collective phenomena in neuroscience. We have been more interested this year in the role of disorder in the spontaneous emergence of synchronized activity. In order to study these phenomena, we have been establishing limit equations for randomly coupled networks [11], and the analysis of this equation reveal a number of transitions due to the level of disorder in the connectivity. A universal transition observed in such randomly coupled networks is a transition to chaotic activity for large levels of noise. These transitions were investigated [24] and were shown to be related to an explosion of complexity at the edge of chaos, i.e. the number of equilibria is exponentially large with the network size at the phase transition, and the exponential factor was related to the Lyapunov exponent. These large-scale limits give rise to nonlinear reduced equations that we have been introducing in [15]. Eventually, when considering that the network is structured into different populations and that the connectivity weights satisfy a balance condition, which is postulated as a natural scaling of the synaptic input, we have shown that the network shows random transitions to periodic activity depending on the spectrum of the random connectivity matrix [25], yielding up and down states or synchronized oscillations depending on the eigenvalue of larger real part of the connectivity matrix.

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. CIRB-Collège de France

Jonathan Touboul is leading the team "Mathematical Neuroscience Laboratory" in the Centre for Interdisciplinary Research in Biology of the Collège de France. Several collaborations have been initiated, two postdocs have been recruited (Jérôme Ribot and Alberto Romagnoni), student scholarships have been provided and 3 PhD students have started their research in the laboratory (C. Quiñinao and L. C. García del Molino in 2012, Tanguy Cabana in 2013).

7.1.2. DIGITEO and Cancéropôle IdF

The DIGITEO IdF LSC *ALMA* and *ALMA2* programs, coordinated by C. Bonnet (DISCO team, Inria Saclay IdF) studies a model of leukaemia based on previous works by M. Adimy and F. Crauste (Lyon), with theoretical model design adjustments and analysis in J. L. Avila Alonso's Ph D thesis (supervised by C. Bonnet, S. Niculescu and J. Clairambault) and experimental parameter identification initiated by F. Merhi, Bang postdoc (Dec. 2010-Nov. 2011), then continued by A. Ballesta (Sep. 2011-Feb. 2013), Bang postdoc detached at INSERM, working at St. Antoine Hospital (Paris), under the supervision of J. Clairambault and C. Bonnet to link experimental and theoretical aspects and of J.-P. Marie and R.P. Tang (INSERM-UPMC) to supervise biological experiments on leukaemic cells. ALMA has been granted for 3 years, beginning in December 2010.

A. Ballesta's postdoc at St. Antoine Hospital, granted by Cancéropôle IdF *ALMA2* has led to increased collaboration of the same with the Commands Inria team (F. Bonnans, X. Dupuis, Saclay) with the aim to design optimisation procedures for anti-leukaemic therapies by cytosine arabinoside and by an anti-Flt3 targeted agent (see above "Optimisation of cancer chemotherapy").

7.2. National Initiatives

7.2.1. ANR and other national projects

7.2.1.1. ANR program Bimod

This ANR program, coordinated by V. Volpert (Lyon), involves 3 partners: CNRS (Institut Camille Jordan) in Lyon (V. Volpert), University Bordeaux II (P. Magal) and Inria (Bang project-team and DISCO team, Saclay IdF). It associates PDE models, both spatial and physiologically structured, with individual-based models in *hybrid models* to represent cancer growth (leukaemia and colorectal cancer) and therapy. It has been granted for 4 years, beginning in December 2010.

7.2.1.2. ANR Sine2Arti

Participation in the ANR project Sine2Arti. The project considers tissue homeostasis and cell reprogramming. The project is coordinated by Gregory Batt (coordinator, Contraintes research team, Inria), PIs are Oded Maler (Univ. of Grenoble) and Dirk Drasdo, an external collaborator is Ron Weiss (MIT)

7.2.1.3. GDR DarEvCan

The GDR DarEvCan, for Darwinian Evolution and Cancer, is a interdisciplinary consortium which associates 10 teams in France around the theme of evolution and cancer, in particular evolution of cancer cell populations towards drug resistance [18]. It has held its first national meeting in December 2011 in Paris, another one in April 2012 in Montpellier, and has organised an international conference in Roscoff in November 2013 http://www.cnrs.fr/insb/cjm/archives/2013/Hochberg_e.html, to which J. Clairambault presented an invited talk on behalf of the Bang team. The Bang team takes an active part in its development, which relies mainly on applying methods from evolutionary theory to cancer biology [22] (http:///www.darevcan.univ-montp2.fr/).

7.2.1.4. PEPS PTI 'Ondes de concentration en bactéries'

People of the BANG team are involved in this project funded by the CNRS. This is a collaboration with biophysicists of the Institut Curie dedicated to the description of the collective motion of bacteria by chemotaxis.

7.2.1.5. PEPS PTI 'Neuro-Info' (Jonathan Touboul)

Jonathan Touboul obtained a support of the CNRS for a collaboration with Princeton University on the information in biological systems, including neuronal networks and quorum sensing.

7.2.1.6. PEPS PTI 'NeuroGauge' (Jonathan Touboul and Alberto Romagnoni)

Alberto Romagnoni (Postdoc in the Mathematical Neuroscience Team) and Jonathan Touboul obtained a support from the CNRS program PEPS PTI in order to use tools from the non-abelian gauge theory for the modeling of the visual cortex. This is a collaboration with theoretical physicists from U. Autonoma of Madrid (Carlos Pena).

7.2.1.7. ITMO-Cancer grant PhysCancer

Participation in the ITMO-Cancer (Aviesan) project Physics of Cancer. The project studies the impact of a constraining extracellular material on the growth and division of cells and cellular aggregates. The project is coordinated by Pierre Nassoy (Institut Curie), collaborators are Dirk Drasdo and Christophe Lamaze (INSERM).

7.2.1.8. INVADE

Participation in the project INVADE (INSERM). The project studies invasion patterns of breast cancer cells. The project is coordinated by Emmanuel Barillot (Inst. Curie), collaborators include Dirk Drasdo and other groups from Institut Curie.

7.3. European Initiatives

7.3.1. FP7 Projects

7.3.1.1. ERASysbio+ C5Sys European network.

This European program (http://www.erasysbio.net/index.php?index=272) has begun in April 2010 to end up in June 2013, with the title "Circadian and cell cycle clock systems in cancer". Coordinated by F. Lévi (Villejuif) and D. Rand (Warwick), it studied both from a theoretical and from an experimental viewpoint the relationships between molecular circadian clocks and the cell division cycle, in cancer and in healthy tissues. A postdoctoral fellow (F. Billy) has been hired at Inria-Bang until November 2012 on this funding, giving rise to various publications in 2013 [7], [8], [9], [27].

7.3.1.2. NOTOX

Type: COOPERATION

Instrument: Integrated Project

Objective: NC

Duration: January 2011 - December 2015

Coordinator: Elmar Heinzle, Universität des Saarlandes, Saarbrücken

Partner: Centre National de la Recherche Scientifique, Strasbourg

Partner: Stichting Het Nederlands Kanker Instituut - Antoni Van Leeuwenhoek Ziekenhuis, Amsterdam

Partner: Karolinska Institutet, Stockholm

Partner: Insilico Biotechnology AG, Stuttgart

Partner: Institut National de Recherche en Informatique et en Automatique, Rocquencourt

Partner: Deutsches Forschungszentrum für Künstliche Intelligenz GmbH, Saarbrücken

Partner: Forschungsgesellschaft für Arbeitsphysiologie und Arbeitsschutz e.V, Dortmund

Partner: Biopredic International, F35760 St. Grégoire

Partner: Weizmann Institute of Science, Rehovot, Israel

Partner: Cambridge Cell Networks Ltd, Cambridge, UK

Partner: European Research and Project Office GmbH, Saarbrücken

Inria contact: Dirk Drasdo

Abstract: 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. 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/

7.3.1.3. ERC Starting Grant SKIPPER^{AD}

Type: IDEAS

Instrument: ERC Starting Grant

Duration: December 2012 - November 2017

Coordinator: Marie Doumic

Partner: INRA Jouy-en-Josas, France

Inria contact: Marie Doumic

Abstract: Amyloid diseases are of increasing concern in our aging society. These diseases all involve the aggregation of misfolded proteins, called amyloid, which are specific for each disease (PrP for Prion, Abeta for Alzheimer's). When misfolded these proteins propagate the abnormal configuration and aggregate to others, forming very long polymers also called fibrils. Elucidating the intrinsic mechanisms of these chain reactions is a major challenge of molecular biology: do polymers break or coalesce? Do specific sizes polymerize faster? What is the size of the so-called nucleus, i.e., the minimum stable size for polymers? On which part of the reactions should a treatment focus to arrest the disease ? Up to now, only very partial and partially justified answers have been provided. This is mainly due to the extremely high complexity of the considered processes, which may possibly involve an infinite number of species and reactions (and thus, an infinite system of equations).

The great challenge of this project is to design new mathematical methods in order to model fibril reactions, analyse experimental data, help the biologists to discover the key mechanisms of polymerization in these diseases, predict the effects of new therapies. Our approach is based on a new mathematical model which consists in the nonlinear coupling of a size-structured Partial Differential Equation (PDE) of fragmentation-coalescence type, with a small number of Ordinary Differential Equations. On the one hand, we shall solve new and broad mathematical issues, in the fields of PDE analysis, numerical analysis and statistics. These problems are mathematically challenging and have a wide field of applications. On the other hand we want to test their efficacy on real data, thanks to an already well-established collaboration with a team of biophysicists. With such a continuing comparison with experiments, we aim at constantly aligning our mathematical problems to biological concerns.

7.4. International Initiatives

7.4.1. ECOS-CONICYT

B. Perthame and K. Vilches take part in the Franco-Chilean project 'Functional analysis, asymptotics and dynamics of fronts' headed by J. Dolbeault (University Paris-Dauphine) funded by ECOS-CONICYT.

7.4.2. EuroMed 3+3

M3CD, *Mathematical Models and Methods in Cell Dynamics*, a transmediterranean EuroMed3+3 program, has begun in January 2012 for 4 years, under the coordination of J. Clairambault. It associates 2 Inria teams: Bang and Dracula (Mostafa Adimy, Lyon) with the IAC-CNR in Rome (Roberto Natalini), the LMDP team in Marrakech (Hassan Hbid) and the MoMinBi team at Institut Pasteur, Tunis (Slimane BenMiled, Amira Kebir) to work on the general theme "Mathematical Models and Methods in Cell Dynamics". It has fostered in 2013 visits of students to Paris and Lyon, for Y. Bourfia, PhD student at Marrakech and UPMC, who works under the supervision of H. Hbid, M. Adimy and J. Clairambault and for Rym Jaroudi, M2 student at the University of Tunis, who works under the supervision of Slimane BenMiled and Amira Kebir.

A 2-day M3CD workshop, organised by Hassan Hbid, following a first one organised in November 2012 in Tunis, will take place in January 2014 (27-28) in Marrakech. Newcomers, researchers from the Northern side, who will be present in this workshop, will join the network in 2014: Marcello Delitala (Polito, Turin) and Oscar Angulo (University of Valladolid).

7.4.3. Xuguang Qi-Hubert Curien program

C. Emako-Kazianou and N. Vauchelet take part in a Xuguang Qi-Hubert Curien program funded by Campus-France in collaboration with Shanghai Jiao Tong university. This program no 30043VM entitled "PDE models for cell self-organization" is headed by N. Vauchelet and allows visits for both parts of the project. The chinese researchers involved in this program are Min Tang and Jie Lao.

7.4.4. 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 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. 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/about/).

7.5. International Research Visitors

7.5.1. Visits of International Scientists

- H.T. Banks (North Carolina State University), 2 weeks at UPMC (SKIPPER^{AD} project)
- Bard Ermentrout (University of Pittsburgh), 1 week at the Mathematical Neuroscience Team
- Miguel Escobedo (University of Bilbao, BECAM), 2 weeks at UPMC (SKIPPER^{AD} project)
- Thibaud Taillefumier (University of Princeton), 2 weeks at the Mathematical Neuroscience Team
- Jonathan Rubin (University of Pittsburgh), 3 days at the Mathematical Neuroscience Team
- Justyna Signerska (Polish Academy of Mathematics), 10 days at the Mathematical Neuroscience Team
- Suzanne Sindi (University of California MERCED), 1 week at UPMC (SKIPPER^{AD} project)
- Wei-Feng Xue (University of Canterbury), 2 days at UPMC (SKIPPER^{AD} project)
- Min Tang (Shanghai Jiaotong Univ.) , 1 month at BANG (Xu GuangQi Hubert Curien program no30043V M PDE models for cell self-organization, N. Vauchelet)

7.5.1.1. Internships

- Rym Jaroudi (University of Tunis) on the subject “Applying evolutionary game theory and adaptive dynamics to modelling cancer treatments”, supervised by S. Ben Miled, A. Kebir (Tunis) and J. Clairambault: October

7.5.2. Visits to International Teams

- 10 days at the University of Pittsburgh (J. Touboul)
- 1 week at the North Carolina State University (M. Doumic and C. Kruse)
- 3 weeks at the Biophysics Lab in Princeton (J. Touboul)
- 2 days at the Courant Institute (New-York) (J. Touboul)

- 3 days at BECAM Center (Bilbao) (M. Doumic)
- 4 weeks at the CEDOC center at Gulbenkian Science Institute (L. Almeida)
- 10 days at the CMM, University of Chile (B. Perthame)
- 10 days at MIT, USA (F. Bertaux)

8. Dissemination

8.1. Scientific Animation

B. Perthame is editor in various journals (CALCOLO, CPDE, DCDS(B), Mathematical Medicine and Biology).

D. Drasdo is in the editorial board of TheScientificWorldJOURNAL and ISRN Biophysics. He is a member of the leadership team of the large scale grant project Virtual Liver Network (VLN) and was invited speaker to the European Association for Study in Liver Conference 2013 (Luxembourg, Feb 2013).

M. Doumic represents Inria at the expert group of the Aviesan Institute "Molecular and structural bases of the living" (ITMO Bases moléculaires et structurales du vivant, head Thierry Meinnel) and was a plenary speaker at the SMB annual conference (Texas, June 2013).

J. Clairambault represents Inria at the expert group of the Aviesan Cancer Institute (ITMO Cancer, head Fabien Calvo) and is also a member of the "Conseil des Partenaires de l'IUC" (Institut Universitaire de Cancérologie, UPMC, founded November 2012) as (nominated) representative of UPMC.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Licence: Jean Clairambault, 2 h "Croissance tissulaire" lecture to P2-L2 students at CHU St Antoine, January

Master: Jean Clairambault, (1) 1 h lecture Toulouse, April; (2) 9h lectures M2 mathbio, UPMC, September

Master: Marie Doumic, Méthode des Éléments Finis, M1 ENSTA, Paris: 12 h (TD, professeur en cours magistral: P. Ciarlet et S. Fliss)

Master: Dirk Drasdo, M2, Mathematical Biology, UPMC: "Towards systems biology of multi-cellular tissues.": 24h

International schools: Jean Clairambault, 2 h tutorial "PK-PD models for chronotherapeutic optimisation in cancer treatments", Systems Medicine of Multifactorial Disorders workshop and tutorial, CASyM, Ljubljana, June

8.2.2. Supervision

HDR: Marie Doumic, Etudes de modèles de croissance et fragmentation et applications en biologie, Habilitation thesis, UPMC, June [2]

PhD in progress: Aurora Armiento, Inverse Problems for aggregation models, since September 2013, supervision by M. Doumic and P. Moireau

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

PhD in progress: Noémie Boissier, "Flows in organs on histological scales" (since November 2013), supervision by Dirk Drasdo and Irene Vignon-Clémentel

PhD in progress: Youssef Bourfia, UPMC (since September 2011), supervision by Jean Clairambault, Mostafa Adimy (Dracula team, Lyon) and Hassan Hbid (UCAD, Marrakech)

PhD in progress: Thibault Bourgeron, UPMC, since September 2012, supervision by M. Doumic and B. Perthame

PhD in progress: Tanguy Cabana, started in 2013, supervision by Jonathan Touboul and Raphaël Krikorian

PhD in progress: Géraldine Cellière, UPMC (since October 2011), supervision by Dirk Drasdo, Andrei Zinovyev and Emmanuel Barillot (Institut Curie)

PhD in progress: Ján Eliaš, UPMC (since September 2012), supervision by Jean Clairambault and Benoît Perthame

PhD in progress: Casimir Emako-Cazianou, UPMC (since December 2012), supervision by Luís Almeida and Nicolas Vauchelet

PhD in progress: Sarah Eugène, Stochastic Models for Nucleated Polymerization, since September 2013, supervision by M. Doumic and P. Robert

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

PhD in progress: Luis Carlos García del Molino, "Heterogeneous networks and their dynamics", supervision by J. Touboul and K. Pakdaman

PhD in progress: Hadjer Wafaâ Haffaf, UPMC (since September 2011), supervision by Marie Doumic

PhD in progress: Tommy Heck, on development of cell models and interaction with ECM. (since April 2013), co-supervised by Paul Van Liedekerke

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

PhD in progress: Tim Odenthal (KULeuven), computational framework for individual cell-based models. Degree obtained December 2013. Co-supervision by Paul Van Liedekerke

PhD in progress: Adélaïde Olivier, Univ. Paris Dauphine, since September 2012, supervision by M. Doumic and M. Hoffmann

PhD in progress: Cristóbal Quiñinao, "McKean-Vlasov equations and neurosciences", supervision by J. Touboul and S. Mischler

PhD in progress: Karina Vilches, (since September 2010), supervision by C. Conca and B. Perthame

8.2.3. Juries

Luís Almeida: Member of the Interdisciplinary Committee 51 of the Comité National de la Recherche Scientifique.

Luís Almeida: as PhD thesis jury president: Magali Tournus (UPMC).

Luís Almeida: as member of a University position application jury: Lyon 1 - 26 MCF 2626/4178, May-June

Jean Clairambault: as PhD thesis examiner: Jonathan Pascalie (Toulouse), October

Jean Clairambault: as PhD thesis reporter and examiner: (1) Marc Sturrock (Dundee), May; (2) Tommaso Lorenzi (Turin), June; (3) Anne-Cécile Lesart (Grenoble), November

Jean Clairambault: as president of a University position application jury: MC UPMC 1244/4178, April-May

Marie Doumic: selection committee member for the CR2 position at Inria Paris-Rocquencourt (2013). PhD thesis examiner: Peipei Shang (supervision by J-M. Coron), Erwan Hingant.

Dirk Drasdo: as PhD thesis reporter and examiner: Kevin Alessandri (Inst. Curie, 2.12.2013), Physics

Dirk Drasdo: as PhD thesis reporter, examiner and President of jury: Julien Delile, Univ. Paris VI, 14.2.2013, Computer Science

DIrk Drasdo: as PhD thesis reporter and examiner: Tim Odenthal, Univ. Leuven, 13.12.2013, Engineering.

Jonathan Touboul: selection committee member for the NSF-ANR call on computational neurosciences (CRCNS).

8.3. Popularization

- Jean Clairambault: (1)1 h Forum des métiers UPMC, September; (2) 2 h Exposé “Animath” lycée St Laurent, Lagny, November
- Marie Doumic: movie on the ERC grants for "Horizon 2020", http://www.horizon2020.gouv.fr/cid75865/video-lancement-horizon-2020-decembre-2013.html

9. Bibliography

Major publications by the team in recent years

[1] B. PERTHAME. *Transport equations in biology*, Frontiers in Mathematics, Birkhäuser Verlag, Basel, 2007, x+198.

Publications of the year

Doctoral Dissertations and Habilitation Theses

[2] M. DOUMIC. *Etudes de modèles de croissance et fragmentation et applications en biologie*, Université Pierre et Marie Curie (Paris VI), June 2013, Habilitation thesis (HDR)., http://hal.inria.fr/tel-00844123

Articles in International Peer-Reviewed Journals

[3] JUAN CARLOS L. ALFONSO, N. JAGIELLA, L. NÚÑEZ, MIGUEL ANGEL. HERRERO, D. DRASDO. *Estimating dose painting effects in radiotherapy: a mathematica model*, 2014, PloS One (accepted for publication).

[4] A. BALLESTA, J. CLAIRAMBAULT. *Physiologically Based Mathematical Models to Optimize Therapies Against Metastatic Colorectal Cancer: a Mini-Review*, in "Current Pharmaceutical Design", March 2013, Epub ahead of publication., http://hal.inria.fr/hal-00849018

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