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Activity Report 2012

Project-Team BANG

Nonlinear Analysis for Biology and Geophysical flows

IN COLLABORATION WITH: Laboratoire Jacques-Louis Lions

RESEARCH CENTER
Paris - Rocquencourt

THEME
Observation, Modeling, and Control for Life Sciences

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Project-Team BANG

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

Creation of the Project-Team: February 01, 2004 .

1. Members

Research Scientists

Luís Lopes Neves de Almeida [DR, HdR]
Jean Clairambault [DR, HdR]
Marie Doumic-Jauffret [CR, detached from ENPC]
Dirk Drasdo [DR, HdR]
Yohan Penel [CR, CETMEF (ministry of Ecology)]
Jacques Sainte-Marie [CETMEF (ministry of ecology), HdR]
Jonathan Touboul [CR, detached from Corps des Mines]

Faculty Members

Emmanuel Audusse [Paris-Nord, Assistant Professor]
Edwige Godlewski [Professor, UPMC, HdR]
Anne Mangeney [Professor, Univ. Paris-Diderot, HdR]
Benoît Perthame [Team Leader, Professor, UPMC, HdR]
Nicolas Seguin [UPMC, Assistant Professor, HdR]
Nicolas Vauchelet [UPMC, Assistant Professor]

External Collaborators

Marie-Odile Bristeau [ex-team member, DR, retired September 2010]
Irène Vignon-Clémentel [Reo project-team]

Engineers

Raouf Hamouda
Tim Johann [Univ. Leipzig]
Paul van Liedekerke [Contrat européen]
Stéphanie Prigent [ERC]

PhD Students

François Bertaux [Inria & UPMC]
Anne-Céline Boulanger [UPMC]
Thibault Bourgeron [UPMC]
Géraldine Cellière [UPMC]
Chadha Chettaoui [Université Paris-Diderot]
Luna Dimitrio [Inria, UPMC]
Ján Eliaš [Inria & UPMC]
Adrian Friebel [Univ. Leipzig]
Hadjer Wafaâ Haffaf [UPMC]
Nick Jagiella [ENS-DMA, Dease]
Johannes Neitsch [Univ. Leipzig]
Adélaïde Olivier [Univ. Paris Dauphine]
Cristóbal Quininao [UPMC]
Philippe Ung [EDF & CNRS]
William Weens [UPMC]
Karina Vilches Ponce [CNRS]

Post-Doctoral Fellows
Sakina Ayata
Annabelle Ballesta
Frédérique Billy
Ibrahim Cheddadi
Stefan Hoehme [Univ. Leipzig]
Yi Yin

Administrative Assistant
Nathalie Bonte

2. Overall Objectives

2.1. Introduction

BANG (Biophysique, Analyse Numérique et Géophysique) is a continuation of the former project M3N. It aims at developing models, simulations and numerical algorithms for two kinds of problems involving dynamics or Partial Differential Equations. Firstly problems from life sciences (cell movement, early embryonic development, tissue growth and regeneration, cancer modelling, pharmacology,...) are considered. Secondly models for complex fluid flows are studied (shallow water models, flows with a free surface).

The common scientific features behind these 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 application to life sciences, data analysis, agent-based, ODE and PDE approaches are combined.

2.2. Highlights of the Year

The ERC Starting Grant allocated to M. Doumic-Jauffret in 2012 will sustain a long term programme in mathematical biology. The many faces of the subject imply modelling of biopolymer size repartition, applications to prion (and other neurodegenerative) diseases, inverse problems, numerical simulations in biology and a strong interaction with biologists.

3. Scientific Foundations

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 XIX$^{\text{th}}$ 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, medical doctors). These are usually based on Navier-Stokes system for fluids (as in free surface fluid flows), on parabolic-hyperbolic equations (Saint-Venant system for shallow water, 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. 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 movement from the individual to the collective scales.
- Reduction of full 3d Navier-Stokes system to 2d or 1d hyperbolic equations by a section average (derivation of Saint-Venant system for shallow water).

3.4. Numerical Algorithms

Various numerical methods are used in BANG. They may be based on finite elements or finite volume methods, or stochastic methods for individual agents. Algorithmic improvements are needed in order to take into account the specificity of each model, of their coupling, or their 3D features. Among them we can mention

- Well-balanced schemes for shallow water system.
- Free-surface Navier-Stokes solvers based on a multilayer St-Venant approach.
- Deterministic and stochastic agent based models for the simulation of multi-cellular systems.

3.5. Proliferation dynamics and its control

- Cell division cycle in structured cell populations.
- Physiological and pharmacological control of cell proliferation.
- Physical mechanisms and constraints in cell proliferation.
- Intracellular spatiotemporal dynamics of genes and proteins: p53.
- Cell darwinism and drug resistance in cancer cells.
- Optimisation of cancer chemotherapy.
- Protein polymerisation and application to amyloid diseases.
- Inverse Problem for growth-fragmentation equations.

3.6. 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 interaction.
- Chemotaxis, self-organisation in cell populations.

3.7. 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 equation used to analyze 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.

3.8. Free surface flows

Several industrial applications require to solve fluid flows with a free surface. BANG develops algorithms in two directions. Firstly flows in rivers and coastal areas using the Saint-Venant model with applications to dam break and pollution problems in averaged shallow water systems. Secondly, 3D hydrostatic flows by a multilayer Saint-Venant approach and 3D Navier-Stokes flows.

4. Application Domains

4.1. Biology and medicine

The team is mostly involved in applications to biology and medicine. More precisely it aims at understanding biophysical mechanisms that sustain cell proliferation of malfunction. The main examples are biopolymers size repartition, cell self-organisation, tissu growth and cancer development or treatment.

4.2. Geophysical flows and environment

The team will split and give rise to another team ANGE specialised in complex geophysical flows in interaction with environment. Free surface flows as tsunamis, flows in river and costal areas and their ecological consequences are typical examples of applications developed in the team based on algorithms for the free-surface Navier-Stokes equations.

5. Software

5.1. Software

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: Dirk Drasdo [correspondent], Stefan Höhme [Research Associate, University of Leipzig], Adrian Friebel [PhD student, University of Leipzig], Tim Johann [Software Engineer, University of Leipzig], Nick Jagiella [PhD student].

Computer simulation software for image analysis of tissue samples at histological scales, as well as individual cell (agent)-based models of tumour and tissue growth solved either by systems of coupled equations of motion for each individual cell or by Kinetic Monte Carlo methods [56].
The software CellSys is currently been completely reorganised to permit easier use by external and internal researchers. The idea is to perspectively go open-source and offer consultancy for potential users.

6. New Results

6.1. Proliferation dynamics and its control

6.1.1. Cell division dynamics in structured cell populations

Participants: José Luís Avila Alonso [DISCO project-team, Inria Saclay IdF], Annabelle Ballesta, Frédérique Billy, Frédéric Bonnans [Commands project-team, Inria Saclay IdF], Catherine Bonnet [DISCO project-team, Inria Saclay IdF], Jean Clairambault, Luna Dimitrio, Marie Doumic-Jauffret, Xavier Dupuis [Commands project-team], Olivier Fercoq [MaxPlus project-team, Inria Saclay IdF], Stéphane Gaubert [MaxPlus project-team, Inria Saclay IdF], Germain Gillet [IBCP, Université Cl. Bernard Lyon 1], Philippe Gonzalo [IBCP, Université Cl. Bernard Lyon 1], Pierre Hirsch [INSERM Paris (Team18 of UMR 872) Cordeliers Research Centre and St. Antoine Hospital, Paris], Thomas Lepoutre [now in DRACULA project-team, Inria Rhône-Alpes, Lyon], Jonathan Lopez [IBCP, Université Cl. Bernard Lyon 1], 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, 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 has continued to be developed with identification of model parameters by FUCCI imaging in collaboration with G. van der Horst's team in Amsterdam and with F. Delaunay's team in Nice, within the C5Sys European network, coordinated by F. Lévi (Villejuif) [10], [11], [12], [39], [42], [43]. Main young researchers on this theme, F. Billy has concluded her 2-year Inria postdoc at Bang, leaving for an industrial company in November 2012, and 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 (JL Avila, C. Bonnet), 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 March 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.
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 the activity of the p53 protein.* This work, the object of Luna Dimitrio's PhD thesis [1], co-supervised by J. Clairambault and R. Natalini (Rome), has led to her PhD defence in September 2012 at UPMC, and to a first publication [18], that should be followed by others. After L. Dimitrio's leave for the pharmaceutic industry, a new PhD student, Ján Eliš, has taken over this theme in September 2012 in a new PhD thesis at UPMC, under the supervision of J. Clairambault and B. Perthame

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 [39], [11], [12], [10], [42], [43]. Whereas transition kernels between cell cycle phases without control have been experimentally identified in cell cultures by FUCCI imaging [12], 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.
2. *Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs.* This theme has continued to be developed with new publications for the drugs irinotecan [40], [44], 5-fluorouracil and oxaliplatin [43].

6.1.3. Optimisation of cancer chemotherapy

Participants: Annabelle Ballesta, Frédérique Billy, Frédéric Bonnans [Commands project-team], Jean Clairambault, Sandrine Dulong [INSERM Villejuif (U 776)], Xavier Dupuis [Commands project-team], Olivier Fercoq [MaxPlus project-team], Stéphane Gaubert [MaxPlus project-team], Thomas Lepoutre [Dracula project-team], Alexander Lorz, Francis Lévi [INSERM U 776, Villejuif], Michael Hochberg [ISEM, CNRS, Montpellier], Benoît Perthame.

Optimising cancer chemotherapy, in particular chronotherapy, is the final aim of the activities mentioned above. This theoretical activity has been continued, using the McKendrick paradigm in works involving the *C5Sys* network [12], [42], [43], with numerical optimisation algorithms for the toxicity constraint, and 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. 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 [10], [27], [39]. The time scales under investigation, much shorter than in ecology, are still much longer than in microbiology, and are those of clinical treatments.

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 [40], [44].

Underway is also the use of methods of optimal control developed by the Commands project-team (F. Bonnans, X. Dupuis) to optimise therapies in the treatment of Acute Myeloblastic Leukaemia (AML, cf. supra "Modelling haematopoiesis with applications to AML").

6.1.4. Protein polymerisation and application to amyloid diseases (ANR grant TOPPAZ)

Participants: Annabelle Ballesta, Vincent Calvez [ENS Lyon], Marie Doumic-Jauffret, 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 biologists' team of H. Rezaei [29], 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 [15] published in J. de Math. Pur. Appl. investigated the dependency of the principal eigenvector and eigenvalue upon its parameters. We exhibited possible nonmonotonic dependency on the parameters, conversely 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-Jauffret, 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 [19] 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 [49], in collaboration with N. Krell, M. Hoffmann and L. Robert.

In [20], published in J. Math. Biol. with L. Matar Tine, we generalised the inverse techniques proposed previously in [53], [57], 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 is in progress with M. Escobedo and T. Bourgeron.

6.2. Tissue growth, regeneration and cell movements

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

Participants: Nikolaos Bournaveas [Univ. Edinburgh], Axel Buguin [UPMC, Institut Curie], Vincent Calvez [ENS Lyon], 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. Numerical simulations have been performed and blow-up is also observed, which differs highly from pointwise blow-up in parabolic models. Representing them leads to various theoretical questions and amounts to define measure solutions [25], [24] or to develop an existence theory.

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 [32].

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

Participants: Gregory Batt [CONTRAINTES project-team], François Bertaux, 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, Elmar Heinzle [University of Saarbrücken and NOTOX consortium], Isabelle Hue [INRA], Nick Jagiella, Ursula Klingmüller [German Cancer Centre, Heidelberg and LungSys Consortium], Axel Krinner, Johannes Neitsch, Benoît Perthame, Ignacio Ramis-Conde, Luc Soler [IRCAD, Coordinator EU-project PASSPORT and PASSPORT consortium], Jens Timmer [University of Leipzig, Germany], Irène Vignon-Clémentel [REO project-team], Juhui Wang [INRA], William Weens.

6.2.3.1. A Multi-scale model for clonal competition in growing tumours

In this work we set up a multi-scale model testing the impact of three experimentally found variants of a signal transduction pathway controlling cell-cell adhesion on multi-cellular growth as well as the possible consequences of inhomogeneous populations where each of the three phenotypes competed [30].

6.2.3.2. Growth of cell populations in embedding granular and cell-like matter

In this work simulations of growing 2D and 3D clones embedded in granular and cell-like matter were mimicked [21]. The influence of active directed cell motion vs. passive pushing triggered by cell proliferation, as well as of various parameters of the embedding matter, such as the friction of embedding objects with its environment, adhesion strength, size of objects, elastic modulus etc. on the growth kinetics and the spatial pattern has been studied. The emerging patterns are strongly reminiscent of a fingering instability (a type of a Saffman-Taylor instability) occuring if a viscous fluid is injected into a more viscous fluid constrained between two plates (Hele Shaw cell).

6.2.3.3. Quantitative modelling of multi-cellular spheroids

Nick Jagiella in his thesis has worked out how stepwise and iteratively mechanisms controlling the spatial-temporal growth dynamics can be inferred by combining information from bright field micrographs stained for proliferating, dying cells, cell nuclei and extra-cellular matrix with the macroscopic growth kinetics.
This thesis, pursued within the German network project LUNGSYS was defended in September 2012. The thesis work was mainly supervised by Dirk Drasdo, PI for this part within the LUNGSYS project. Main collaborators were Margareta Mueller (previously DKFZ, Heidelberg) and Ursula Klingmueller, (DKFZ Heidelberg).
Moreover, Géraldine Cellière has worked out a model to mimic the aggregation of cells in the hanging drop method, a standard method to generate 3D multi-cellular aggregates. The kinetics and final configuration give information on multicellular aggregates. This work is pursued within the EU NOTOX project. Main collaborators are Fozia Noor and Elmar Heinzle (Univ. of Saarbruecken).

6.2.3.4. Image reconstruction of 3D liver architecture at subcellular level

In order to permit simulation liver function we started to set up an image processing pipeline resolving liver at subcellular scale. This will enable us to mimic all flows in liver, which comprises of blood flow through the micro-vessels (sinusoids), of blood plasma through the space between micro-vessel wall and hepatocytes, the main type of liver cells (called space of Disse), and of the bile through a network of bile canaliculi. Besides image analysis, also setting up the models of the flows has been started.

This work is conducted by the PhD student Adrian Friebel (IZBI, University of Leipzig) co-supervised by Dirk Drasdo and Stefan Hoehme (IZBI, University of Leipzig) within the Germany funded grant project Virtual Liver Network (VLN; PI from IZBI, Leipzig: Dirk Drasdo). Main collaborator is Jan G. Hengstler from the IfADo (directeur at the Leibniz Institute in Dortmund, Germany).

6.2.3.5. Ammonia metabolism during liver regeneration

Based upon the paper on liver regeneration after drug-induced damage (Hoehme et. al. PNAS 2010 [55]) we in a next step investigated the change of ammonia metabolism during the regeneration process. Ammonia is toxic for the body. We linked our spatial-temporal liver lobule model with a compartment model for the ammonia, glutamine and urea metabolism. In the latter we consider a compartment (the peri-central compartment) in which glutamine synthetase, a strongly ammonia-detoxifying enzyme, is degraded efficiently and a (peri-portal) compartment, in which this is not the case. By testing different hypotheses on the chemical reactions taking place during the degradation process and quantitatively comparing to time-space data of the regeneration process including data on the activity of glutamine synthetase we were able to propose a potentially missing chemical reaction. Validation experiments have been started and suggest that the original reaction scheme was indeed incomplete.

This work is conducted by Dirk Drasdo and Stefan Hoehme (IZBI, University of Leipzig) partly within the Germany funded grant project Virtual Liver Network (VLN; PI from IZBI, Leipzig: Dirk Drasdo) and the EU project NOTOX. Main collaborators are Rolf Gebhardt (chair for Biochemistry, University of Leipzig), Jan G. Hengstler from the IfADo (Leibniz Institute in Dortmund, Germany) and BioControl Jena GmbH, a company in Jena, Germany.

6.2.3.6. Multi-scale simulation of cell cycle progression during liver regeneration

In previous work on liver regeneration after drug induced damage (Hoehme et. al. PNAS 2010 [55]) the experimentally observed spatial-temporal proliferation pattern has been used as an input parameter. We have now started to study the molecular control of cell cycle progression by hepatocyte growth factor (HGF). Based on model predictions with a hypothesized model linking the downstream activation of the HGF-pathway with cell cycle progression, experiments were performed which now led to a validated intracellular model of cell cycle progression by HGF. Moreover, based on model simulations predicting that two sources of HGF are necessary to explain the experimentally observed proliferation pattern, experiments detecting the potential sources of HGF have been initiated. The models are multi-scale in that the precise spatial architecture of a piece of liver tissue is modelled representing each individual hepatocyte as well as the blood micro-vessels. A system of ODE's mimicking the HGF signalling and its impact on cell cycle progression is solved inside each individual cell. The project works out a systematic strategy to stepwise identify multi-scale multi-level processes in tissue organisation extending the lines pursued in Hoehme et. al. [55] and Holzhuetter et. al. [23].
This work is conducted by Dirk Drasdo and Stefan Hoehme (IZBI, University of Leipzig) within the Germany funded grant project Virtual Liver Network (VLN; PI from IZBI, Leipzig: Dirk Drasdo). Main collaborators are Ursula Klingmueller and Lorenza D'Alessandro (UK is Professor at Heidelberg University and department head at German Cancer Research Centre (DKFZ), Heidelberg, Germany) as well as Jens Timmer and Andreas Raue (JT is Professor University of Freiburg, Germany).

6.2.3.7. Phenotypes in early liver cancer

The model of a liver lobule, the smallest functional unit of liver (Hoehme et. al., PNAS 2010 [55]) has been used as a starting point to explain the experimentally observed early tumour phenotypes. We made a sensitivity analysis to identify the parameters that influence the tumour phenotype. Each simulation mimicked a monoclonal tumour. We could show that the observed early phenotypes could be explained by only a few sensitive parameters which are the direction of cell division, cell-micro-vessel adhesion, and destruction of micro-vessels by the tumour cells.
This work has been taken over from the previous PhD student William Weens by the PhD student François Bertaux who is co-supervised by Dirk Drasdo and Gregory Batt. Main collaborator is Jan G. Hengstler from the IfADo (directeur at the Leibniz Institute in Dortmund, Germany).

6.2.3.8. Regeneration of liver after partial hepatectomy

We continued this earlier activity by initiating experiments on pigs to test the model prediction that the 2nd wave of proliferation during regeneration after partial hepatectomy in pig should occur only close to the Glisson capsule, that encloses the liver, while in mouse proliferation occurs homogeneously and isotropically distributed over the whole liver lobe.
This work is conducted by Dirk Drasdo and Stefan Hoehme (IZBI, University of Leipzig) within the Germany funded grant project Virtual Liver Network. Main collaborators are Jan G. Hengstler from the IfADo (Leibniz Institute in Dortmund, Germany) and Eric Vilbert, Centre Hépato-Biliaire (CHB)- INSERM U785, Hospital Paul Brousse, Villejuif.

6.2.3.9. High resolution model for eukaryotic cells

In order to permit simulations directly out of 3D reconstructions of confocal laser scanning micrographs at subcellular resolution we developed a model that is capable to resolve complex cell shapes. The model parameters were calibrated by comparison with experiments probing the material properties of cells. Moreover, the cell division was implemented. The model was integrated into the CellSys software.
This work is conducted by the PhD student Johannes Neitsch (IZBI, University of Leipzig) co-supervised by Dirk Drasdo and Stefan Hoehme (IZBI, University of Leipzig) within the Germany funded grant project Virtual Liver Network (VLN). Main collaborators are Jan G. Hengstler from the IfADo (directeur at the Leibniz Institute in Dortmund, Germany) and Josef Kaes (Prof. for Experimental Physics, Univ. Leipzig).

6.2.3.10. Yeast cells playing the Game of Life

Within a collaboration with a synthetic biology lab at MIT, we work on the multicellular modelling of engineered yeast cell populations. Those cells secrete a messenger molecule (IP) which diffuse in the medium, bind to other cells, and trigger a signalling cascade which finally induce expression of lethal genes. A model has been established based on our single-cell-based model framework associated with PDE's simulations, and it is currently used to explain and guide experiments obtained at MIT.
This work is conducted within the project Sine2Arti by François Bertaux co-supervised by Gregory Batt and Dirk Drasdo, and by Szymon Stoma. Main collaborator is Ron Weiss, MIT, Boston, USA.

6.2.3.11. Stochastic modelling of extrinsic apoptosis

Here we extended a well-established ODE model of TRAIL-induced apoptosis developed by Sorger's group in Harvard by the possible effect of cell-to-cell variability due to stochasticity of rare events in the cascade.
This work is conducted within the project Sine2Arti by François Bertaux co-supervised by Gregory Batt and Dirk Drasdo, and by Szymon Stoma as well as Xavier Duportet for the experimental part.

6.2.3.12. Artificial Homeostasis in HeLa cells

The aim is to genetically engineer human cancer cells (HeLa cell line) such that they perform population control in a petri dish. To do so, it is made use of extrinsic apoptosis by forcing cells to produce a messenger molecule able to trigger apoptosis above a certain threshold concentrations in the medium. We developed a mathematical model which integrates both PDEs and intracellular components into a single-cell-based model framework. Such model allows to help designing the genetic system that should be integrated into cells as well as guiding experiments.
This work is conducted within the project Sine2Arti by François Bertaux who is co-supervised by Gregory Batt and Dirk Drasdo. Moreover Szymon Stoma for the modelling part, as well as Xavier Duportet for the experimental part from the CONTRAINTES team are included.

6.2.4. Modelling flow in tissues

Participants: 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].

6.2.4.1. Flow and perfusion scenarios in cancer

In this subject we simulated typical flow and perfusion scenarios in tumour and tissue including, how the spatial-temporal pattern look like on the scale of non-invasive medical image modalities currently applied, to infer parameters that are used to or may permit to evaluate the perfusion of tumors in patients. The simulations use Poiseuille flow and Kirchhoff rule in 3D blood network representing typical architectures.
The work was part of the PhD thesis of Nick Jagiella, defended in September 2012 co-supervised by Dirk Drasdo and Irene Vignon-Clementel, and conducted within the grant funded network projects LUNGSYS and LUNGSYS II. Main collaborators were Oliver Sedlaczek, DKFZ Heidelberg and University of Heidelberg, Fabian Kissling, Technical University of Aachen and Hendrik Laue, Fraunhofer Mevis, Bremen (all in Germany).

6.2.4.2. Flow in liver lobules

The aim of this project is to simulate realistically the flow of matter within liver lobules from images generated with different image modalities at histological scales. So far we have established a model of blood flow and perfusion in liver lobules based upon 3D reconstruction of confocal micrographs.
This work is conducted by collaboration of different groups within the Germany funded grant project Virtual Liver Network. From our group Nick Jagiella, Adrian Friebel, and Stefan Hoehme, Dirk Drasdo are involved, main collaborators are Irene Vignon-Clementel (REO project team Inria), Marino Zerial and Ivo Sbazarini (Max-Planck Institute for Molecular Cell Biology and Genetics, Dresden, Germany), Lutz Brusch (Technical University of Dresden) and Jan G. Hengstler from the IfADo (Leibniz Institute in Dortmund, Germany).

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

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

Contraction of actin structures (in one, two or three dimensions) plays an important role in many cellular and tissue movements, both at a multicellular tissue level and at a cellular (and even intracellular) one: from muscle contraction to neural tube closure, epiboly in zebrafish embryo, the contractile ring in cytokinesis, cell crawling,... examples are everywhere in the living world. These structures consist of meshworks of actin filaments (which are like fibers) that are cross-linked by molecular motors (Myosin II) which can make the actin filaments slide relative to each other, thus generating deformation movements.

In [4] we are particularly interested in modelling the contraction of acto-myosin cables in morphogenesis and tissue repair. The experiments done in collaboration with A. Jacinto's lab show that the local curvature (and in particular its sign) plays an important role in the contractile behaviour of the acto-myosin cables. These experimental results led us to develop some of these ideas in [6] and to do a more abstract study of flows by the positive part of the curvature in [5].

6.3. Neurosciences

Participants: M. Galtier, G. Hermann, M. Magnasco, T. Taillefumier, Jonathan Touboul.

We pursued the analysis of the dynamics of networks of neurons in the presence of noise. Limit theorems in simple cases were treated in [9], and more refined models including space, delays and heterogeneities were analysed in [34], [35], touboulde lays:12,touboulNeuralFieldsDynamics:12. In all these contributions we analysed the eminently important role of noise and heterogeneity on the qualitative dynamics of networks. Mathematical results were obtained for representation of the solutions to linear functional differential equations [22] that were motivated by plasticity phenomena in the cortex.

6.4. Free surface geophysical flows

Participants: Emmanuel Audusse [LAGA - Université Paris 13, Institut Galilée], Anne-Céline Boulanger, Marie-Odile Bristeau, Benoît Perthame, Jacques Sainte-Marie, Nicolas Seguin, Edwige Godlewski, Anne Mangeney, Yohan Penel, Raouf Hamouda, Philippe Ung.

The ANGE team has been created in november 2012. This new team (led by J. Sainte-Marie) resumes the activities of the BANG team concerning geophysical flows.

We are involved in research concerning the numerical simulation of free surface geophysical flows such as rivers, lakes, coastal areas and also overland flows. Many applications related to environmental problems are concerned : floodings, dam breaks, swell, transport and diffusion of pollutants, water quality, upwellings, sustainability of aquatic ecosystems, ...

The basic model for these problems is the 3D free surface Stokes system leading to a 3D solver [52] with a moving mesh. However for efficiency reasons, vertically averaged models such as the Saint-Venant system [54] are often used.

The Saint-Venant equations are deduced of the Navier-Stokes system with two main assumptions:

- the pressure is hydrostatic,
- the horizontal velocity is represented by its average.

We have developed extensions of the Saint-Venant system where the basic Saint-Venant solver [51] is still used and, in that way, the robustness, the efficiency and the easiness to treat the free surface are preserved while the domain of validity is larger.

In these extensions, we relax the two above assumptions. Actually, we have derived a non-hydrostatic shallow water model and a multilayer Saint-Venant system.

We have coupled the hydrodynamics of free surface flows with other phenomena such as biology (phytoplankton culture) or erosion.

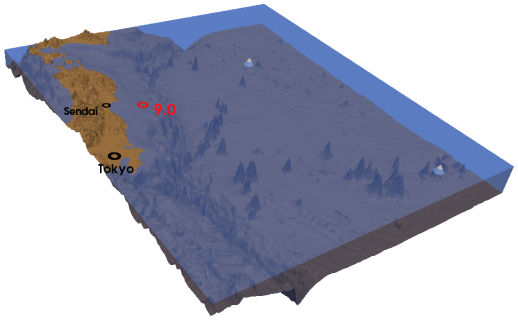

Figure 1. Map of Japan with the seism epicentre and the DART buoys 21418 and 21413.

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, a postdoc has been recruited, student scholarships have been provided and 3 PhD students have started their research in the laboratory (J. Scher, C. Quininao and L. C. García del Molino).

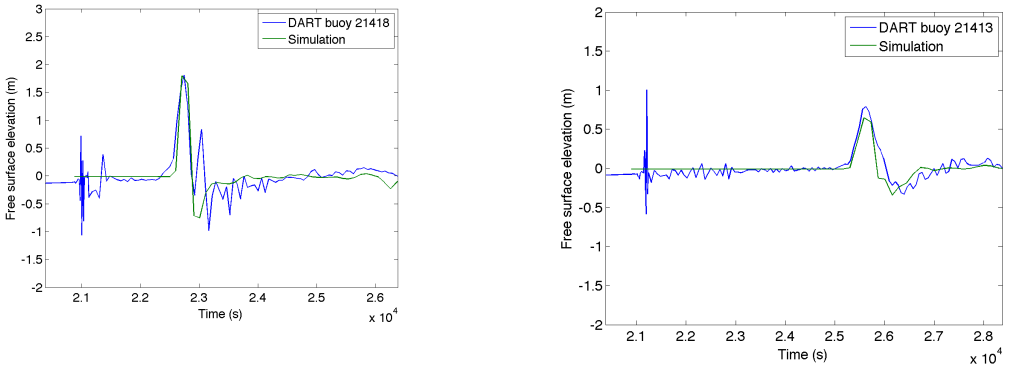

Figure 2. Free surface elevation of the sea, comparison between the recorded data by the buoys 21418 and 21413 and the simulation obtained with our 3d Navier-Stokes code.

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 RP. 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").

7.1.3. INRA

Collaboration with INRA (Isabelle Hue, Juhui Wang, Alain Trubuil) on Trophoblast development. One PhD student position in Bang has been funded within the Doctoral School *Ecole du Vivant*, Paris for Chadha Chettaoui), who has defended her thesis in July 2012.

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. ANR TOPPAZ

(url http://www-roc.inria.fr/bang/TOPPAZ/index.html)

TOPPAZ (Theory and Observations of Polymerisation processes in Prion and Alzheimer diseases) is a 3-year (2009-2012) research project financed by ANR grant "programme blanc" and headed by Marie Doumic-Jauffret.

It involves two teams, a mathematical and numerical team (B. Perthame, V. Calvez, P. Gabriel, T. Lepoutre, P. Michel, and a team in Brazil headed by J. Zubelli) and a biophysicist team headed by H. Rezaei. It has allowed to finance the post-doctoral contract of F. Charles and the 1-year grant of L. M. Tine.

The general goal is to develop new mathematical and numerical tools for polymerisation processes, in a strong link with experimentalists and with direct application to experimental data designed by the biologists' team. The achievements of ANR TOPPAZ are described in Sections 6.1.4 and 6.1.5.

7.2.1.4. 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 [27]. It has held its first national meeting in December 2011 in Paris, and another one in April 2012 in Montpellier. The Bang team takes an active part in its development, which relies mainly on applying methods from evolutionary theory to cancer biology [33]. (url http:///www.darevcan.univ-montp2.fr/)

7.2.1.5. GdR EGRIN

The CNRS supports the creation of a "research group" called EGRIN, starting in january 2013 and devoted to the modelling, analysis and simulation of gravity driven flows. J Sainte-marie is the head of the scientific committee of this research group.

(url http://gdr-egrin.math.cnrs.fr/)

7.2.1.6. Green Stars

Participation in the Green Stars project ("Investissement d'avenir") on the production of biofuel using microalgae in collaboration with the EPI COMORE, LOCEAN, INRAA, LOV.

7.2.1.7. 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.

7.2.1.8. 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).

7.3. European Initiatives

7.3.1. FP7 Projects

7.3.1.1. ERASysbio+ C5Sys European network.

This European program (url http://www.erasysbio.net/index.php?index=272) has begun in April 2010, with the title "Circadian and cell cycle clock systems in cancer". Coordinated by F. Lévi (Villejuif) and D. Rand (Warwick), it studies 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. It has been granted for 3 years. A postdoctoral fellow (F. Billy) has been hired at Inria-Bang until November 2012 on this funding, giving rise to various publications in 2012 [10], [11], [12], [39], [42].

7.3.1.2. NOTOX

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. EU-project PASSPORT

Participation in the European network PASSPORT on modelling liver regeneration after partial hepatectomy (url http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/50-passport-strep)

7.3.1.4. ERC Starting Grant SKIPPERAD

The ERC Starting Grant allocated to M. Doumic-Jauffret in december 2012 will last for five years. The acronym standing for *Simulation of the Kinetics and Inverse Problem for protein Polymerisation in Amyloid Diseases* (Prion, Alzheimer's), its main goal is to contribute to the design of new methods for protein polymerisation simulation and prediction, a major issue in amyloid diseases.

7.4. International Initiatives

7.4.1. Inria Associate Teams

7.4.1.1. QUANTISS, with BMBF

Title: Towards quantitative tissue simulations
Inria principal investigator: Dirk Drasdo
International Partner (Institution - Laboratory - Researcher):
University of Liepzig (Germany) - IZBI
Duration: 2010 - 2012
See also: http://www.msysbio.com/ea

The scientific achievements addressed tissue organisation processes such as tissue regeneration, degeneration and growth. Our main contribution was the development of concepts, a process chain, and software suite to permit quantitative simulations of tissue organisation processes on histological scales. Our main applications were multiple projects on liver, lung cancer and mesenchymal stem cell differentiation. The results of the main projects for 2012 have briefly been summarised the results section (liver regeneration, multiscale liver modelling, blood flow modelling, software generation CellSys, etc. most based on the grant projects LUNGSYS and Virtual Liver network).

7.4.2. 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.

7.4.3. EuroMed 3+3

M3CD, *Mathematical Models and Methods in Cell Dynamics*, a transmediterranean EuroMed3+3 program, has begun in January 2012 for 2 [+ 2: renewal] 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) to work on the general theme "Mathematical Models and Methods in Cell Dynamics". It has fostered visits of students (in particular 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 researchers, participation in the international SM2A conference in Marrakech (June 2012, url http://sm2a-2012.ucam.ac.ma/en/), and a M3CD 2-day workshop in Tunis (Institut Pasteur, November 2012, (url http://euromedbiomaths.org/atelier-M3CD-Tunis/)) organised by Amira Kebir (MoMinBi).

7.4.4. Inria International Partners

7.4.4.1. 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 ($http://www.lungsys.de/$)

7.4.4.2. 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.
($http://www.virtual-liver.de/about/$)

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 member of the leadership team of the large scale grant project Virtual Liver Network (VLN).

B. Perthame 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).

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.

Luís Almeida was in 2012 a member of the Scientific Advisory Board of CIRB (Centre of Interdisciplinary Research in Biology), Collège de France (UMR CNRS 7241/ INSERM U1050).

8.2. Teaching - Supervision

8.2.1. Teaching

Master: Jean Clairambault, (1) M2 pharmacologie Rennes (cours magistral, 4h/an) et (2) ED Innovation thérapeutique, Université Paris-Sud (cours magistral, 2 h/an): "Modélisation chronothérapeutique du schéma d'administration"; (3) M2 Paris-Descartes "Croissance tissulaire" (2012, cours magistral, 1 h 30)

Master: Marie Doumic-Jauffret, 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: "Agent-based models of tissue organisation": 24h

Master: Jonathan Touboul, Master Science of Complex Systems (Erasmus Mundus, Ecole Polytechnique, U. Chalmers, Warwick and Gothenburg), M2, 40h, cours magistral "Stochastic Calculus and Limit Theorems"

International schools: Dirk Drasdo, (1) Evry 2012 Thematic Research School "Modelling complex biological systems in the context of genomics" (1.5hrs); (2) DPG - Physics School "Forces and Flow in Biological Systems" (1.5hrs)

8.2.2. Supervision

HdR: Luís Lopes Neves de Almeida, "Quelques problèmes liés à l'étude d'équations aux dérivées partielles issues de la physique, de la géométrie et de la biologie", UPMC, April 2012

PhD: Chadha Chettaoui, "Physical-Based Modelling and Analysis of Animal Tissue Growth and Morphogenesis", ENS Paris, July 2012, Supervisors Dirk Drasdo, Juhui WANG (Unité MIA, INRA, Jouy-en-Josas and, Isabelle HUE (INRA/ENV Alfort/CNRS)

PhD: Luna Dimitrio,"Modelling nucleocytoplasmic transport with application to the intracellular dynamics of the tumour suppressor protein p53" [1], UPMC, September 2012, Supervisors Jean Clairambault and Roberto Natalini (University Sapienza, Rome)

PhD: Nick Jagiella, "Parameterisation of Lattice-Based Tumor Models from Data", UPMC, September 2012. Supervisors Dirk Drasdo, Benoît Perthame, and Irène Vignon-Clémentel (REO)

PhD: William Weens,"Mathematical Modeling of Liver Tumor", UPMC, September 2012. Supervisor Dirk Drasdo

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

PhD in progress: Anne-Céline Boulanger, supervision by Marie-Odile Bristeau and Jacques Sainte-Marie

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

PhD in progress: Luís 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-Jauffret

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

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

PhD in progress: Justine Scher, "Growth-Fragmentation equations in neurosciences", supervision by J. Touboul and S. Mischler

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

M2: Alban Lévi, "Complexity of Random Neural Networks", ENS Cachan et Collège de France, April-August 2012, supervision by G. Wainrib and J. Touboul

M1: Quan Shi, "Self-Organized criticality in random neural networks", École Polytechnique et Collège de France, April-August 2012, supervision by J. Touboul

M1: Flavio de Souza Serra de Pinho Cabeca, "Collective Oscillations in excitable networks", École Polytechnique et Collège de France, April-August 2012, supervision by J. Touboul

8.3. Popularisation

Participation in the "Fête de la science" at Inria-Rocquencourt (October 2011) involving F. Billy, J. Clairambault, V. Roche (Villejuif), in a joint Inria-INSERM booth dedicated to chronotherapy: presentation of a movie and of a video game, both designed by Annabelle Ballesta, and of 2 posters by A. Ballesta and by F. Billy.

J. Clairambault has written a short "Perspective in Mathematical Biology": "Can theorems help treat cancer?" in the Journal of Mathematical Biology [17], contributed by the European Society for Mathematical and Theoretical Biology.

D. Drasdo gave a general presentation on multiscale tissue modelling in the "2e Forum international de Prospective de Recherche et Traitement pour le cancer" in September 2012.

J. Touboul has written a chapter: "A mathematician's view of simplexity in the brain" in the book by A. Berthoz, "Simplexity", to be published by Editions Odile Jacob, Paris.

9. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] L. DIMITRIO. *Modelling nucleocytoplasmic transport with application to the intracellular dynamics of the tumor suppressor protein p53*, Université Pierre et Marie Curie - Paris VI and Università degli studi di Roma I, September 2012, http://hal.inria.fr/tel-00769901.

[2] N. JAGIELLA. *Parameterization of Lattice-Based Tumor Models from Data*, Université Pierre et Marie Curie - Paris VI, September 2012, http://hal.inria.fr/tel-00779981.

[3] W. WEENS. *Mathematical modeling of liver tumor*, Université Pierre et Marie Curie - Paris VI, September 2012, http://hal.inria.fr/tel-00779177.

Articles in International Peer-Reviewed Journals

[4] L. ALMEIDA, P. BAGNERINI, A. HABBAL. *Modeling actin cable contraction*, in "Comput. Math. Appl.", 2012, vol. 64, n^{o} 3, p. 310–321, http://dx.doi.org/10.1016/j.camwa.2012.02.041.

[5] L. ALMEIDA, A. CHAMBOLLE, M. NOVAGA. *Mean curvature flow with obstacles*, in "Annales de l'Institut Henri Poincaré (C) Non Linear Analysis", 2012, vol. 29, n^{o} 5, p. 667 - 681 [*DOI :* 10.1016/J.ANIHPC.2012.03.002], http://www.sciencedirect.com/science/article/pii/S0294144912000297.

[6] L. ALMEIDA, J. DEMONGEOT. *Predictive Power of "A Minima" Models in Biology*, in "Acta Biotheoretica", 2012, vol. 60, p. 3-19, http://dx.doi.org/10.1007/s10441-012-9146-4.

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