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Activity Report 2011

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 Modeling, Numerical Methods

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2. Overall Objectives

2.1. Presentation

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.

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 averages of large systems 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 the partial differential equation models are complemented by agent-based models which permit to capture phenomena on the spatial scale of the individual matter components.

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 improvments 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.
- Agent Based Models and Monte-Carlo simulations for multi-cellular configurations.

3.5. Proliferation dynamics and its control

- Cell division cycle in structured cell populations.
- Physiological and pharmacological control of cell proliferation.
- Intracellular spatiotemporal dynamics of genes and proteins: p53.
- Cell darwinism and drug resistance in cancer cells.
- Optimisation of cancer chemotherapy.
- Protein polymerization 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. 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. Software

4.1. Software

4.1.1. 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).

4.1.2. 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 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 [77].

5. New Results

5.1. Proliferation dynamics and its control

5.1.1. Cell division dynamics in structured cell populations

Participants: José Luis Avila Alonso [DISCO project-team, INRIA Saclay IdF], Annabelle Ballesta, Houda Benjelloun [INSA Rouen], 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], Faten Merhi [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.* A focus has been set on transitions between phases of the cell division cycle. The underlying biological question is: "Is desynchronisation between cells in proliferating cell populations a hallmark of cancer?". It has been considered by relating in a natural way transition kernels with the probability density functions of transition times in the cell population. It has been shown -which was expected, but never proved to our knowledge so far- that the more desynchronised cells are with respect to cell cycle phase transitions, the higher is the growth exponent of the cell population [48], otherwise said: desynchronised cell populations grow faster. This has been proven when transition kernels are time-independent, i.e., when no external controlled is exerted on transitions. The same question is currently experimentally investigated by our biologist partners in the European network ERASysBio+ *C5Sys*, coordinated by F. Lévi (Villejuif) and D. Rand (Warwick). Simulations using experimentally identified transition kernels in proliferating cell cultures controlled by theoretical time-dependent (circadian) control functions have verified the relevance of this mathematical result for theoretical cancer treatment optimisation (cf. infra "Periodic (circadian) control of cell proliferation in a theoretical model of the McKendrick type").
2. *Modelling haematopoiesis with applications to AML.* The stability of a delay system based on a PDE model designed by M. Adimy and F. Crauste, structured by a discrete differentiation variable and multiple delays, with applications to Acute Myeloblastic Leukaemia (AML, clinical advisers: J.-P. Marie and P. Hirsch; technical adviser: RP Tang) is studied with possible therapeutic implications [36]. This model is currently experimentally investigated, with the aim to identify its parameters in leukaemic cells, in the DIGITEO project *ALMA* (cf. infra "DIGITEO and Cancéropôle IdF" in "Regional initiatives"), coordinated by C. Bonnet (DISCO team, INRIA Saclay IdF) and in the recently launched DIGITEO project *ALMA2* (coordinated by J. Clairambault), that takes over the combined experimental-modelling activity in *ALMA*. Two INRIA postdocs, F. Merhi (in *ALMA*, 2010-2011) and A. Ballesta (in *ALMA2*, 2011-2013) have been devoted to this task. From a theoretical point of view, the Adimy-Crauste model has been modified so as a) to include quick self-renewal of cells in each stage of maturation and b) to represent each phase of the proliferating compartment (i.e., G_1, S, G_2 and M) separately. For the time being, only the M phase is supposed to have a fixed time duration as it is generally admitted that the short time (typically half an hour

if the total proliferating phase duration is normalised to 24 hours) necessary to perform mitosis is hardly submitted to any variation.

In a complementary manner, a new model for cell differentiation was introduced and analysed in [17], in collaboration with A. Marciniak and J.P. Zubelli. It assumed that differentiation of progenitor cells is a continuous process. From the mathematical point of view, it is based on partial differential equations of transport type. Specifically, it consists of a structured population equation with a nonlinear feedback loop. This models the signaling process due to cytokines, which regulate the differentiation and proliferation process. We compared the continuous model to its discrete counterpart, a multicompartmental model of a discrete collection of cell subpopulations recently proposed by Marciniak-Czochra et al. [Stem Cells Dev., 18 (2009), pp. 377–386] to investigate the dynamics of the hematopoietic system. We obtained uniform bounds for the solutions, characterized steady state solutions, and analyzed their linearized stability. We showed how persistence or extinction might occur according to values of parameters that characterize the stem cells' self-renewal. We also performed numerical simulations and discuss the qualitative behavior of the continuous model vis-à-vis the discrete one.

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 (prof. at IBCP/Lyon), we have designed a mathematical ODE model for the mitochondrial pathway of apoptosis, focused on the early phase of apoptosis (before the cytochrome C release). We have validated it with experimental data carried out in G. Gillet's lab and applied it to propose new therapeutic strategies against cancer. This work has led to a nearly submitted article [47].

5. *Molecular model of the activity of the p53 protein.* Following her first year of PhD in Rome with R. Natalini, working on cytoplasmic transport along microtubules presented in [38], L. Dimitrio has begun her third PhD year, going on studying at INRIA nucleocytoplasmic transport with applications to p53 activity. Her PhD thesis work is supervised in co-tutela between Sapienza University in Rome (R. Natalini) and INRIA (J. Clairambault). The protein p53 plays a capital part as "guardian of the genome", arresting the cell cycle and launching cell apoptosis or DNA repair in case of DNA damage. Results expected from this newly developed theme will provide a rational link between molecular pharmacokinetics-pharmacodynamics (cf. infra) of anticancer drugs and modelling of the cell division cycle in proliferating cell populations. L. Dimitrio has presented her ongoing work in different meetings in France and in Italy, and a paper in preparation will be submitted in 2012.

5.1.2. 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.* The impact of a periodic control exerted on cell cycle phase transitions has continued to be studied [16] with the collaboration of S. Gaubert (MaxPlus INRIA project-team, Saclay IdF) and T. Lepoutre (Dracula INRIA project-team, Lyon) and is currently investigated experimentally in the new *C5Sys* European network (cf. supra "Transition kernels in a McKendrick model of the cell division cycle" and "). Thanks to the work of Frédérique Billy (Postdoc in Bang) and Olivier Fercoq (PhD student in MaxPlus), together with permanent members of Bang, Dracula and MaxPlus teams, it has led to three publications [37], [39], [48].

2. *Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs.* This theme is actively worked on in collaboration, mainly with the teams of F. Lévi and J.-P. Marie (cf. supra " Transition kernels in a McKendrick model of the cell division cycle" and "Modelling haematopoiesis with applications to AML"). After a PK-PD model for 5-FU with folinic acid [86], it has led for the anticancer drug Irinotecan, the main object of A. Ballesta's PhD thesis [1], to an article published in PLoS Computational Biology [8], reporting a combined modelling and experimental approach to the effects of a combination of mathematical modelling and experimentation in cell cultures, and to another one [7], focusing on drug delivery optimisation.
3. *Whole body physiologically based model of anticancer drug pharmacokinetics.* This theme has also been studied in A. Ballesta's PhD thesis. The use of identification, in genetically different laboratory mouse strains, of parameters characterising an ODE model of the action of Irinotecan (cf. supra "Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs") in cell cultures, transposed at the whole-body level, has been designed as a proof of concept for individual adaptation of drug delivery in the context of (future) personalised medicine, a perspective sketched in [15] and among other collaborative contexts linking mathematics and medicine in [14], [3].

5.1.3. 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, especially chronotherapy, is the final aim of the activities mentioned above. This has been lately discussed in [16] and also in works involving the *C5Sys* network [37], [48], and in the more general review [39] . Until now had been taken into account as constraints in optimisation strategies only the unwanted toxic side effects of anticancer drugs on healthy cells. More recently, another issue of anticancer treatment has been considered, namely the different mechanisms of resistance to drugs in cancer cells. This has led to include the effect of ABC transporters (active efflux pumps, as is the P-glycoprotein) in the intracellular PK-PD models mentioned above [86], in A. Ballesta's PhD joint work with F. Lévi's team [1], [8], [7], and to a perspective paper [15].

In project 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").

Another way to represent and overcome drug resistance in cancer from a cell Darwinian point of view using concepts of adaptive dynamics in proliferating cell populations is also currently being investigated along the line of other recent works [28] and is currently developed within the multidisciplinary GDR DarEvCan coordinated by M. Hochberg, Montpellier (cf. infra "GDR DarEvCan" in "National initiatives") and in a proposed ANR project also coordinated by M. Hochberg.

An open question that should have therapeutic implications consists of the interrogation: Is the emergence of drug resistance in cell populations a genetic (resulting from mutations at mitosis) or an epigenetic phenomenon (resulting from amplification of physiological mechanisms, such as ABC transport, which has nothing to do with genetic mutations)? And is it a reversible or irreversible phenomenon? These questions will be studied both theoretically and experimentally within the DarEvCan consortium and could result in new developments in the so-called *Darwinian medicine*.

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

Participants: Annabelle Ballesta, Vincent Calvez [ENS Lyon], Frédérique Charles, 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].

With H. Rezaei, a new and very complete PDE model for protein polymerisation has been designed. Following F. Charles' 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 fibrillization. This part is nearly submitted.

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 [11] investigated the dependency of the principal eigenvector and eigenvalue upon its parameters. We exhibited possible non-monotonic dependency on the parameters, conversely to what would have been conjectured on the basis of some simple cases.

5.1.5. Inverse problem in growth-fragmentation equations

Participants: Marie Doumic-Jauffret, Marc Hoffmann [ENSAE], Patricia Reynaud [CNRS, Nice Univ.], 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 [18] we have 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. This work is accepted in SIAM J. Num. Anal..

With L. Matar Tine, in [53] we have generalized the inverse techniques proposed in [88], [67] and [66], 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. This work is submitted.

5.2. Tissue growth, regeneration and cell movements

5.2.1. Chemotaxis, self-organisation of cell communities

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 [SJTU], Nicolas Vauchelet.

We have continued our analysis and simulation of models for large bacterial communities and more generally cells self-organisation as inititated several years ago [12], [31]. This is a rich domain because on the one hand several Partial Differential Equations arise, parabolic models, kinetic equations, hyperbolic systems and on the other hand complex patterns occur that are a sign of the complex underlying dynamics.
In their article [65], Y. Dolak and C. Schmeiser have proposed a mathematical model describing the individual behavior of bacteria responding to a chemical substance. Numerical simulations of this kinetic model have been investigated in [93]. In a macroscopic level of description, we perform a hydrodynamical limit which leads to an aggregation model, for which regular solutions blows up in final time [82]. The rigorous study of the behavior of the aggregates relies on a careful analysis of some non-linear scalar conservation laws in the framework of measures [24] and has been investigated in [55].

With the group of P. Silberzan in Curie Institute, in 2010 we have given an explanation of traveling bands first observed by Adler in the 80's for *E. coli* in microchannels. In a continuation of this work, based on analysis of individual trajectories, we have shown directional persistence which improves the efficiency of collective migration. Kinetic models with tumbling kernels that keep memory of the incoming velocity are able to reproduce accurately the wave parameters [35].
Computing effectively traveling wave can be difficult in unstable cases. An algorithm is proposed in [29] for the NonLocalFisher equation which catches the traveling wave and not the more stable pulsating wave.

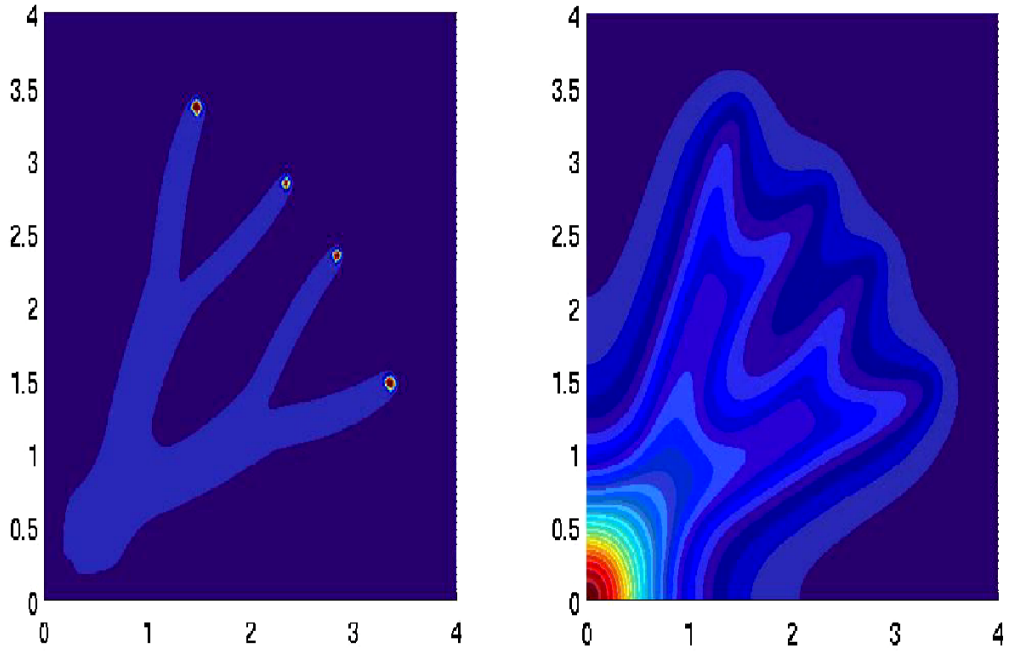

Figure 1. Dynamics of the swarmers and supporters $n + f$ concentration (left) and of the surfactin S (right) solving system

A. Lorz has studied a system consisting of the elliptic-parabolic Keller–Segel equations coupled to Stokes equations by transport and gravitational forcing. We show global-in-time existence of solutions for small initial mass in 2D. In 3D we establish global existence assuming that the initial $L^{3/2}$-norm is small. Moreover, we give numerical evidence that for this extension of the Keller–Segel system in 2D, solutions exist with mass above 8π, which is the critical mass for the system without fluid. The model is written as

$$\begin{cases} u \cdot \nabla c = \Delta c + n - a_1 c, \\ n_t + u \cdot \nabla n = \Delta n - \nabla \cdot (\chi n \nabla c), \\ a_2 u_t + \nabla P - \eta \Delta u + n \nabla \phi = 0, \\ \nabla \cdot u = 0. \end{cases} \tag{1}$$

Here c denotes the concentration of a chemical, n a cell density and u a fluid velocity field described by Stokes equations. The fluid couples to n and c through transport and gravitational forcing modelled by $\nabla\phi$. The pressure P can be seen as the Lagrange multiplier enforcing the incompressibility constraint. The chemical c diffuses, it is produced by the cells and it degrades. The cell density diffuses and it moves in the direction of the chemical gradient. The constant $a_1 \geq 0$ measures self-degradation of the chemical and the constants $a_2 \geq 0$, $\eta > 0$ determine the evolution undergone by u.

5.2.2. Single cell-based models of tumour growth, tissue regeneration, embryonic development

Participants: Annabelle Ballesta, Gregory Batt [CONTRAINTES project-team], François Bertaux, 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 Center, Dortmund, Germany and CANCERSYS consortium], Stefan Höhme, Elmar Heinzle [University of Saarbrücken and NOTOX consortium], Isabelle Hue [INRA], Nick Jagiella, Ursula Klingmüller [German

Cancer Center, Heidelberg and LungSys Consortium], Axel Krinner, Emanuele Leoncini, Johannes Neitsch, Benoît Perthame, Ignacio Ramis-Conde, Luc Soler [IRCAD, Coordinator EU-project PASSPORT and PASSPORT consortium], Irène Vignon-Clémentel [REO project-team], Juhui Wang [INRA], William Weens.

Structure formation in tissues as well as malfunctions on the multi-cellular level are inherently of multi-scale nature. Modifications on the molecular level by intrinsic or extrinsic factors affect the architecture and function on the multi-cellular tissue level. Much of the current research so far focuses on the analysis of intracellular pathways, genetic and metabolic regulation on the intracellular scale and on continuum equations for local densities of cells to capture multi-cellular objects on large spatial scales but only recently have increasing efforts been made at the interface between these two: individual cell based models (IBMs) which permit to include the molecular information on the one hand and to extrapolate to the multi-cellular tissue level on the other hand and hybrid models that combine continuum with individual-based models for different components.

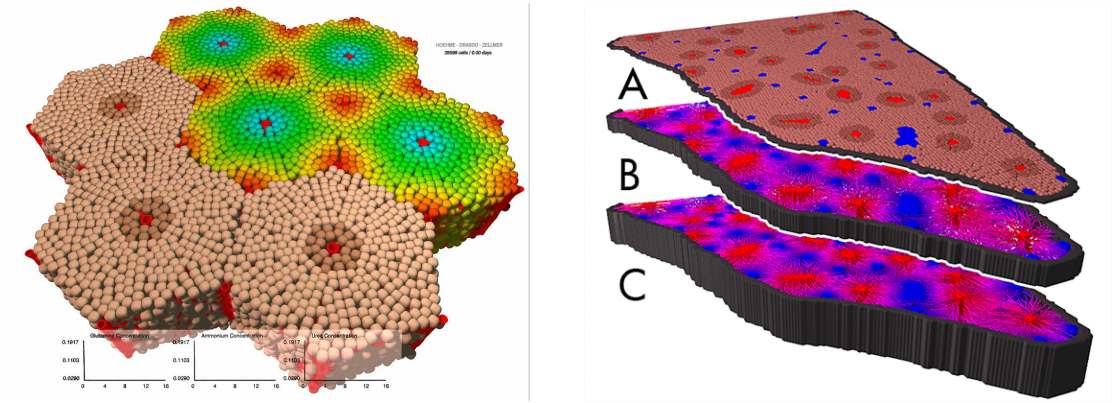

Figure 2. Left: Modeling ammonia detoxification during regeneration after drug-induced damage in a multi-lobule model. Here, a compartment model of ammonia detoxification has been coupled to the regeneration of liver mass. The colour indicates the gradient of ammonia after regeneration. The upper graphics indicate that our model directly calculates the blood concentrations of ammonia, urea and glutamine during the liver regeneration process. Right: In the meantime it is possible to simulate whole mice lobes up to 10 cells thick.

In order to fill the existing gap we have studied intracellular regulation networks [87], [72], multi-scale IBMs where intracellular regulation and differentiation was explicitly represented within each individual cell [90], [85], [91], lattice-free IBMs [69] and continuum models that can capture their large scale behaviour [63], and cellular automaton (CA) models where each lattice site can be occupied either by at most one cell [61] or by many cells [89], [71] and their corresponding continuum equation [68]. Moreover, for a simple, but for rigorous coarse graining not accessible, growth situation we were able to obtain quantitatively matching results with continuum and individual-cell-based models without any fit parameter.

Besides the methodical aspects we focus on a number of applications:

- Unstructured cell populations growing in a monolayer with free border [69], [74], or constraint by the presence of a granular or cellular embedding medium [19].
- Multicellular spheroids in liquid suspension [69], [70], and embedding granular or cellular matter [19]. For non-small-lung-cancer cell lines growing as multi-cellular spheroids, we could, starting with a complete parameterisation of the model by labelling experiments, simultaneously explain the proliferation, apoptosis, extracellular matrix and growth pattern of multi-cellular spheroids under different nutrient conditions within one consistent mathematical model.
- Vascular tumour growth.

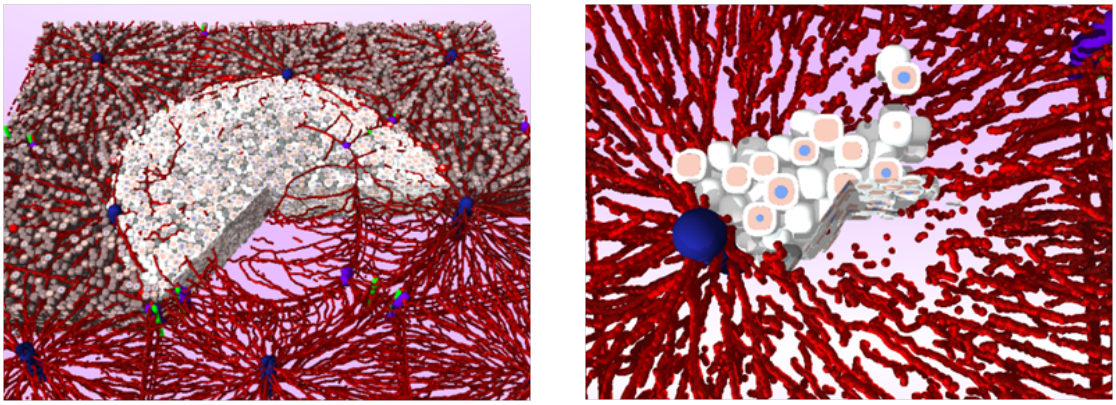

Figure 3. Left: Tumor growing in a liver lobule. Right: Tumor diggesting the vessels hence forming a tumor lacking blood vessels inside.

- Regulatory and evolutionary aspects in tumour growth [81], [78], recently with resolution of intracellular signal transduction pathway variants found in normal vs. malignant cells [33].
- Cell differentiation and lineage commitment of mesenchymal stem cells [85], [73]. In our earlier work we have established a model of cell aging for in-vitro cultured stem cell populations. Stem cell concepts developed earlier [85], [73] have been extended to include cell aging [83]. By this extension it is possible to explain the clonal heterogeneity that was not captured by the previous model. The cell age was coupled with the generation number. It is published in ref. [84] and [56].
- Complex tissue architectures in regenerative tissues, particularly in the liver.

Examples are:

- Regeneration of liver lobules after toxic damage [80], [79], [76]), [40], [41], [42] within the German BMBF-funded network "Systems Biology of the Hepatocyte"). As extension of this project we linked the regeneration of liver architecture after toxic damage to a model of ammonia detoxification by the individual hepatocyte and the liver as a proof of concept to study the link between architecture and function. The comparison of experimental findings by our collaboration partners with our model results suggests that the detoxification during regeneration after drug-induced damage is mainly determined by the total population size of healthy hepatocytes (Fig. 2). Adjustments of enzymatic activities of the individual hepatocytes seem to have only minor effects.
- Liver regeneration after partial hepatectomy ([44]). Based on the work on regeneration of a liver after toxic damage where we focused on a single liver lobule, we within the EU project CANCERSYS set up a model on liver regeneration after partial hepatectomy enabling us to model up to the whole liver lobe scale of a mouse, 4 cells thick. This models permits to bridge the gap between the single-cell-model scale and the whole-liver organ scale. Calibrating this model with mouse data we were able to predict the proliferation pattern in pig as a proof of principle that modelling can be used to bridge the gap between different animals. Experiments performed so far confirm the prediction. This is a fundamental issue as it is a longstanding unsolved question in how far experiments in animal models can be used to predict therapeutic responses in the Human. We also expanded the software towards whole liver lobe bright field image analysis.
  Being able to use a mathematical model calibrated with data from a model animal, for example, mouse to predict tissue organisation processes in another animal, for example, human opens new possibilities to assess drug toxicity [43].

- The fundamental objective is to move towards modelling from the molecular up to the whole organ scale. A conceptual framework for this was presented in ref. [23].
- Cancer development in an environment of granular particles and cells. For the first part we studied how an embedding medium such as granular particles or cells modify the spatial and temporal growth pattern of expanding cell populations [19]. The model could explain the growth kinetics found by Helmlinger et. al. (1997) for growing tumor spheroids embedded in agarose gel. If the friction between the embedding objects and the environment is larger than the friction between the growing clone and its environment we found a fingering instability reminiscent of a Saffman-Taylor instability observed in a Hele-Shaw cell. We systematically studied which model parameters promote the instability. The motivation for this project was to analyse in how far invading tumour fronts can be explained by physical mechanisms alone as in some tumour phenotypes invasive fronts can be observed.
  In order to extend this project towards carcinoma development mechanisms of liver cancer development in mice were studied [42]. Within systematic sensitivity analyses we were able to identify parameters explaining the experimentally found tumor phenotypes (Fig. 3). The critical parameters were stiffness of sinusoids, the micro-blood vessels within the liver lobules, tumor cell - sinusoidal adhesion, tumor cell polarity, and the ability of tumour cells to digest neighbouring vessels. As part of the project, in close collaboration with experimental partners, critical differences between liver in normal and transgenic mice have been studied by image analysis [62].
- Synthetic biology. By multi-scale simulations including intracellular pathways in our single-cell-based simulation framework we were able to mimic conditions under which tissue homeostasis and tissue location could be achieved in monolayer culture.

The applications are guided by quantitative comparisons to experimental data either from published knowledge or - in most cases - generated by experimental partners. One main focus is on the understanding of mechanisms that control the growth dynamics and growth phenotypes of multi-cellular systems and use these later to predict and optimise therapy or biotechnological growth processes.

The adjustment of the models developed to applications requires data analysis both, of molecular data such as gene expression profiles and of image data such as spatial-temporal growth pattern. For this purpose we recently considered the geometric and topological measures to quantify tumour shapes [92], and developed an image processing chain to quantitatively analyse liver regeneration processes in liver lobules [79], [76], [44], [40], [41]. As a further step we published executables and descriptions of important elements of our code to spread our model as it turns out that agent-based cell modelling enjoys increasing interest in different communities (engineering, mathematical biology, systems biology, physics) [81]. Current directions moreover include a stronger focus on models of in-vivo systems (within the German medical systems biology consortium “LungSys” (lung cancer treatment); and within the EU-network “CancerSys” (cancerogenesis in liver)). Within LungSys we recently developed a realistic 2D and 3D spatial temporal model of blood flow in xenografts to compare to DCE MRI images visualising the tumour perfusion. Modelling cancer development requires to take into account invasion, mutations and angiogenesis, three hallmarks of cancer and of linking the molecular to the multicellular scale [71]. Moreover, we extend the topic of liver regeneration to regeneration after partial hepatectomy (within the EU-project “Passport”), and extend our modelling activities to understand early embryonic development (Trophoblast development, collaboration with INRA).
Almost each of our projects is in close collaboration with experimental partners within grant projects performing experiments to permit parameterisation and validation of our models.

5.3. Modeling in computational neurosciences

Participants: Maria Caceres [Univ. Granada], Jose Carrillo [ICREA Barcelona], Benoît Perthame, Jonathan Touboul.

Networks of interacting neurons can be well described by nonlinear PDEs like the Noisy Integrate and Fire model. These are Fokker-Planck-Kolmogorov equations on the probability density of neurons, the main parameters in the model being the connectivity of the network and the noise. In [10], we analyse several aspects of the NNLIF model: the number of steady states, a priori estimates, blow-up issues and convergence toward equilibrium in the linear case. In particular, for excitatory networks, blow-up always occurs for initial data concentrated close to the firing potential. These results show how critical is the balance between noise and excitatory/inhibitory interactions to the connectivity parameter.
At a larger scale, neurons form large-scale spatially extended populations receiving similar input and interconnected in a specific way. Each neuron receives noisy inputs, and as such their membrane potential is adequately described as the solution of stochastic network equations. In [58] we study the asymptotic regimes of such spatially extended networks with delays and obtain a complex mean-field equation the dynamics of which is analyze in [57]. We observe that noise induces transitions from stationary spatially homogeneous solutions to oscillatory solutions, and the transition is characterized by chaotic Turing patterns of activity.

5.4. Free surface geophysical flows

Participants: Emmanuel Audusse [LAGA - Université Paris 13, Institut Galilée], Sakina Ayata, Anne-Céline Boulanger, Marie-Odile Bristeau, Benoît Perthame, Jacques Sainte-Marie [CETMEF and MACS project-team].

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 Navier-Stokes system leading to a 3D solver [64] with a moving mesh. However for efficiency reasons, vertically averaged models such as the Saint-Venant system [75] 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 [60] 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.

5.4.1. Hydrodynamics and biology coupling

Cultivating oleaginous microalgae in specific culturing devices is seen as a potential source of biofuel for the future. The complexity of this process coupling non linear biological activity to hydrodynamics makes the optimization problem very delicate. The large amount of parameters to be taken into account paves the way for a useful mathematical modeling. Due to the high heterogeneity of raceways along the depth dimension regarding temperature, light intensity or nutrients availability, we adopt a multilayer approach for hydrodynamics and biology. For hydrodynamics, we use a multilayer Saint-Venant model that allows mass exchanges, forced by a simplified representation of the paddlewheel. Then, starting from an improved Droop model that includes light effect on algae growth, we derive a similar multilayer system for the biological part. A kinetic interpretation of the whole system results in an efficient numerical scheme. We show through numerical simulations in two dimensions that our approach is capable of discriminating between situations of moving water or calm pond and show the influence of light intensity. Moreover, in this paper [49] we exhibit

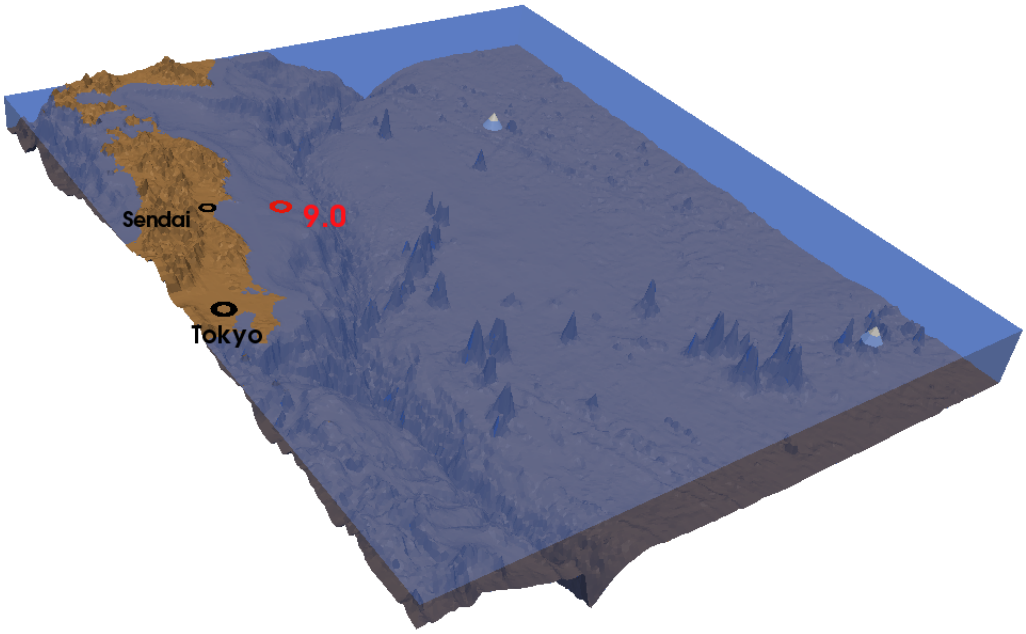

Figure 4. Map of Japan with the seism epicentre and the DART buoys 21418 and 21413.

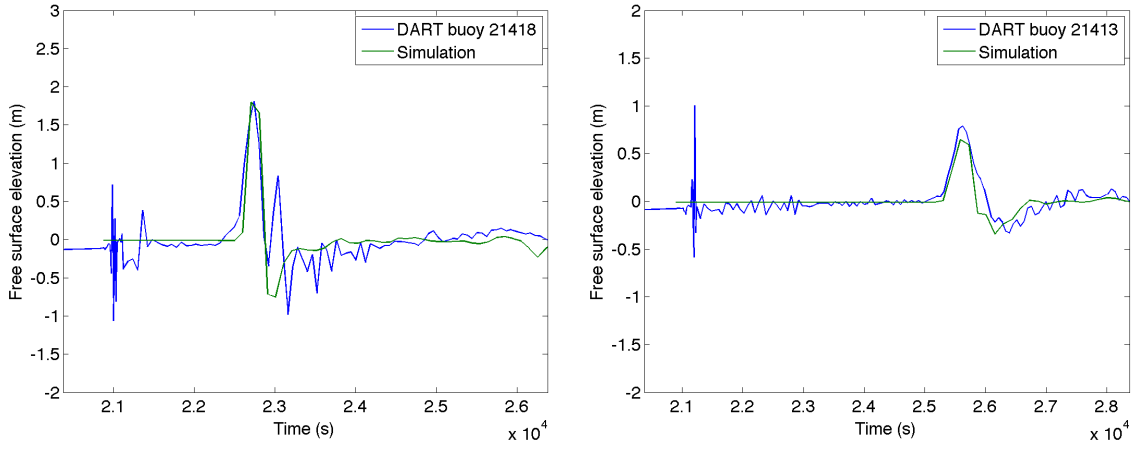

Figure 5. Free surface elevation of the sea, comparison between the recorded data by the buoys 21418 and 21413 and the simulation obtained with our 3d Navier-Stokes code.

that a posteriori treatment of our velocity fields can provide lagrangian trajectories which are of great interest to assess the actual light pattern perceived by the algal cells and therefore understand its impact on the cell factory.

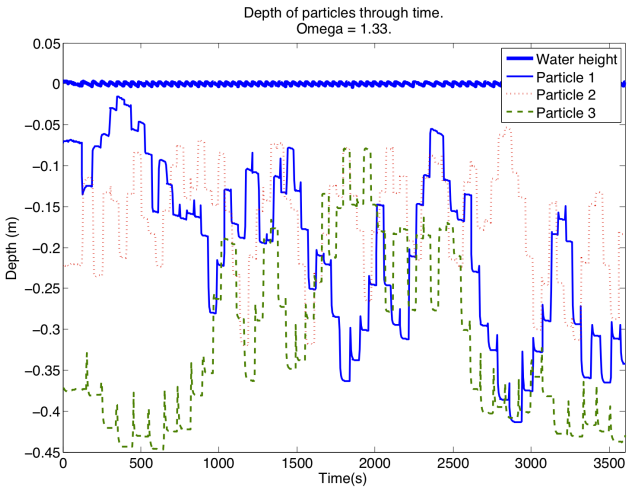

Figure 6. Trajectories of three particles during the simulations. In every figure, the large curve represents the water height at the middle of the pool. The other plot is the height of a given particle through time. The algae undergo sudden changes of depth every time it meets the wheel.

5.4.2. Analytical solutions for the free surface hydrostatic Euler equations

In this paper [50] we propose a large set of analytical solutions for the hydrostatic incompressible Euler system in 2d and 3d. These solutions mainly concern free surface flows but flows with partially free surface or in a deformable pipe are also considered. These analytical solutions that can admit entropic shocks can be especially useful for the validation of numerical schemes.

5.4.3. Phytoplankton growth in marine ecosystem

Four different phytoplankton growth models have been implemented. The simplest model assumes constant chlorophyll/carbon and carbon/nitrogen ratios. The more complex ones take into account photoadaptation through a variable chlorophyll/carbon ratio and they also assume a variable carbon/nitrogen cellular quota (non-redfieldian stochiometry). These models have been coupled to a 1D ecosystem model at BATS, a station located in an oligotrophic area of the North-Western Atlantic Ocean. The different models have been calibrated from in situ data recorded at BATS using a micro-genetic algorithm to optimize the parameter values. The models with optimized parameters were then compared with each others. The results highlighted the necessity to take into account photoadaptation and variable cellular quotas to simulate the seasonal dynamics of chlorophyll and primary production in oligotrophic areas. They also demonstrated that the chlorophyll did not have to be represented by a prognostic variable and could be represented by a diagnostic variable instead, see [46].

5.4.4. Erosion processes : modelling and simulation

We are interested in the modelling of sediment transport phenomena. We mostly focus on bedload transport and we do not consider suspension sediment processes. We first propose a coupled numerical scheme for the

classical Saint-Venant – Exner model. It is based on a relaxation approach and it works with all sediment flux function. We exhibit that this coupled approach is more stable than the splitting approach that is mostly used in industrial softwares. Then we derive an original three layers model in order to overcome the difficulties that are encountered when using the classical Exner approach and we write a related relaxation model, see [45].

6. Contracts and Grants with Industry

6.1. Grants with Industry

Grant EDF-LNHE Grant with **EDF-LNHE** (2010-2011) "Modélisation hydraulique des milieux naturels." Simulation of free surface stratified flows (the density stratification being due to temperature and/or salinity), effect of the wind, upwellings.
Comparison of the variable density multilayer code developed at Inria and the rigid lid hydrostatic Navier-Stokes code (Ophélie) of EDF.

7. Partnerships and Cooperations

7.1. Regional Initiatives

7.1.1. DIGITEO and Cancéropôle IdF

The DIGITEO IdF LSC *ALMA* program, 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, postdoc of Bang (Dec. 2010-Nov. 2011), 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. Tang (INSERM-UPMC) to supervise biological experiments on leukaemic cells. ALMA has been granted for 3 years, beginning in December 2010.

More recently, the Cancéropôle IdF *ALMA2* program has taken over the experimental identification part in St. Antoine Hospital, together with further model design in Bang - and Disco with the continuation of J.L. Avila's PhD thesis -, for 18 months (Oct. 2011-March 2013) with the postdoc of A. Ballesta, shared between J.-P. Marie's team and Bang. With this postdoc project will also be developed the theoretical and experimental - in leukaemic cell cultures - study of combined therapies by classical cytotoxics (anthracyclins, aracytin) and recently available targeted therapies (anti-Flt-3). A possible emergence of drug resistance to these drugs is also a question that will be studied both theoretically and experimentally in leukaemic cell cultures, in relation with the interdisciplinary French consortium DarEvCan (cf. supra "Optimisation of cancer chemotherapy") in which both Bang and J.-P. Marie's team participate.

7.1.2. INRA.

Collaboration with INRA (Isabelle Hue, Juhui Wang, Alain Trubuil) on Trophoblast development. One PhD student position in Bang (Chadha Chettaoui) is funded within the Doctoral School *Ecole du Vivant*, Paris.

7.2. National Initiatives

7.2.1. 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.

7.2.2. ANR TOPPAZ

(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 5.1.4 and 5.1.5.

7.2.3. ARC Nautilus

Participation in the ARC Nautilus on the coupling between hydrodynamics and biology (phytoplankton) in collaboration with the EPI COMORE, LOCEAN, LOV.

(http://www-sop.inria.fr/comore/ARC_Nautilus/index.html)

7.2.4. ANR METHODE

Participation in the ANR project "METHODE" (Modélisation de l'Ecoulement sur une Topographie avec des Hétérogénéités Orientées et des Différences d'Echelles / Modelling of the flow on a topography with oriented heterogeneities and different scales) in collaboration with Orléans University, BRGM, CEMAGREF, CERMICS, INRA.

7.2.5. ANR Sine2Arti

Participation in the ANR project Sine2Arti. The project considers tissue homeostasis and cell reprogramming.

7.2.6. ANR PhysCancer

Participation in the ANR project Physics of Cancer. The project studies the impact of a constraining extracellular material on the growth and division of cells and cellular aggregates.

7.2.7. 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. It has held its first national meeting in December in Paris. The Bang team takes an active part in its development.

(http:///www.darevcan.univ-montp2.fr/)

7.3. European Initiatives

7.3.1. ERASysbio+ C5Sys European network.

This European program (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) works on this subject.

7.3.2. EU-project PASSPORT

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

7.3.3. EU-project CANCERSYS

Participation in the European network CANCERSYS on modelling tumour genesis in liver. This project includes also collaborators from the Paris region. A PhD student (William Weens) works on this subject.

- Title: CANCERSYS
- Type: COOPERATION (SANTE)
- Instrument: Specific Targeted Research Project (STREP)
- Duration: November 2008 - October 2011
- Coordinator: Univ. Dortmund (Leibniz Research Centre for Working Environment and Human Factors) (Germany)

7.3.4. EU-project NOTOX

Participation in the European network NOTOX on modelling drug detoxication by liver cells cultivated in bioreactors.

- Title: NOTOX
- Type: COOPERATION (SANTE)
- Instrument: Integrated Project (IP)
- Duration: January 2011 - December 2015
- Coordinator: UNIVERSITAET DES SAARLANDES (Germany)

7.3.5. INRIA Associate Team QUANTISS

Title: Towards quantitative tissue simulations

INRIA principal investigator: Dirk Drasdo

International Partner:

Institution: University of Leipzig (Germany)

Laboratory: IZBI

Duration: 2010 - 2012

See also: http://www.msysbio.com/ea

In a recent joint work including members of the BANG and IZBI-teams we were able to predict a novel, so far unrecognized mechanism that is fundamental for a correct regeneration process during liver regeneration by a mathematical hybrid agent-based simulation model (Hoehme et. al., PNAS, 2010) . To identify the model assumptions and the start configuration in the simulation model we combined quantitative information from experimental images on a regenerating liver prior and during regeneration after drug intoxication from animal data with experimental observations of isolated cell-cell-interaction processes from in-vitro (outside the living organism) cell cultures. The model was able to mimic the regeneration process quantitatively. The key mechanism predicted by our mathematical model could subsequently be validated experimentally. It was one of a very few cases in tissue organization where an important mechanism could be correctly predicted by a mathematical model. The modeling work was jointly performed by researchers in INRIA and IZBI. A similar strategy is now performed in other modeling applications to tissue organization included in this collaboration. For this purpose image processing and analysis tools as well as simulation software, developed at IZBI and INRIA, are being extended. The collaboration pursues three major topics (T): T1: Simulation of liver disease and regeneration. This includes liver regeneration after partial hepatectomy (partial removal of liver tissue), steatosis, fibrosis, and liver cancerogenesis (development of liver cancer). Partial hepatectomy is applied after severe lesions, for example caused by liver cancer. Many projects aim at developing multi-scale models including various cell types,

spatial tissue architecture, metabolism, cell-cell signaling and signal transduction. The project T1 includes many experimental partners within national and EU projects, most of them in Germany. T2: Simulation of tumor growth and therapy. The role of erythropoietin in Lung cancer therapy should be evaluated and improved therapy schedules should be developed. The model will be multi-level spanning the molecular scale up to the centimeter-scale. This project includes about 15 partner teams in Germany, 11 of them experimental teams and includes the German Cancer Center, a few years ago with a nobel price. T3: Simulation of cell differentiation and lineage specification in multi-cellular aggregates and structured tissues and the role of cell aging. This project addresses the hot topic of stem cell organization in normal and cancer tissues with a special focus on the processes of stem cell transformation and cell re-programming. T4: tumor development and cell aging.

7.3.6. Others

The German part of the BANG project-team and associated team in Leipzig takes part in the Germany-wide Virtual Liver network (VLN) on Systems Biology of the liver (funded by the BMBF) from the molecular level up to the whole organ and body levels. This network is the follow-up of the former Systems Biology network on the "Hepatocyte" through which two PhD students (S. Höhme and A. Krinner) were funded, having recently graduated.

The project includes collaborations within about 10 subprojects with many research groups within Germany (including our main partners from Hepatosys, J.G. Hengstler, Leibniz Research Center, Dortmund, and R. Gebhardt, Univ. of Leipzig).

Key running collaborations exist with the Leibniz Research Center in Dortmund and with the Biochemistry-department of the University of Leipzig on liver regeneration after drug-induced damage and partial hepatectomy. Several other collaborations within the German Consortium on LungCancerSys (BMBF) on the role of Erythropoitin on Lung Cancer must also be mentioned and with the University of Saarbrücken in modelling drug toxicity to hepatocytes in-vitro. Some of the former collaborations are now continued within the different EU projects enumerated above.

7.4. International actions

7.4.1. M3CD

A new EuroMed3+3 program, M3CD *Mathematical Models and Methods in Cell Dynamics* has been accepted in December for 2 [+ 2: renewal] years. 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 in Tunis (Slimane BenMiled) to work on the general theme "Mathematical Models and Methods in Cell Dynamics".

7.4.2. INRIA-Conicyt

INRIA-Conicyt 'MULTISPECIES CELL COMMUNITIES AUTO-ORGANIZATIONS AND TISSUE GROWTH', C. Conca, B.Perthame.

7.4.3. Visits of International Scientists

7.4.3.1. Professors

- H.T. Banks (april, 2011, 1 week)
  - Subject: Mathematical modelling of intracellular negative feedback systems
  - Institution: NC State University (Raleigh)(USA)
- Carlos Pares (from march 14th to 18th, 2011)
  - Subject: Modeling and simulation of hyperbolic systems
  - Institution: University of Malaga (Spain)

7.4.3.2. Internship

- Karina VILCHES (from Feb 2011 until Dec 2011)
  - Subject: Modeling and control of multidrug therapy
  - Institution: University of Chile (Santiago) (Chile)

8. Dissemination

8.1. Animation of the scientific community

Benoît Perthame is editor in various journals (CALCOLO, CPDE, SIAM J. Math. Analysis, DCDS(B)).

Dirk Drasdo is in the editorial board of TheScientificWorldJOURNAL and ISRN Biophysics. He is member of the VPH FET advisory board for the EU and an expert team for Mathematics for health care.

Organisation of a weekly informal, interactive seminar by Marie Doumic-Jauffret, Dirk Drasdo and Irène Vignon-Clémentel (REO project-team).

Benoît Perthame represents INRIA at the expert group of the INSERM Institute "Molecular and structural bases of the living" (ITMO Bases moléculaires et structurales du vivant, head Thierry Meinnel).

Jean Clairambault represents INRIA at the expert group of the INSERM Cancer Institute (ITMO Cancer, head Fabien Calvo).

Supervision of Annabelle Ballesta's PhD thesis (June 2007-June 2011) by Jean Clairambault and Francis Lévi.
Supervision of François Bertaux's PhD thesis (since September 2011) by Dirk Drasdo and Gregory Batt.
Supervision of François Bertaux's M2 internship (until August 2011) by Dirk Drasdo and Gregory Batt.
Supervision of Anne-Céline Boulanger's PhD thesis by Marie-Odile Bristeau and Jacques Sainte-Marie.
Supervision of Youssef Bourfia's PhD thesis (since September 2011) by Jean Clairambault, Mostafa Adimy and Hassan Hbid (UCAD, Marrakech).
Supervision of Chadha Chettaoui's PhD thesis (since September 2008) by Dirk Drasdo and Juhui Wang (INRA).
Supervision of Luna Dimitrio's PhD thesis (since March 2010) by Jean Clairambault and Roberto Natalini (University Sapienza, Rome).
Supervision of Adrian Friebels PhD thesis (since June 2011) by Dirk Drasdo and Stefan Hoehme.
Supervision of Pierre Gabriel's PhD thesis (until June 2011) by Marie Doumic-Jauffret and Benoît Perthame.
Supervision of Hadjer Wafaâ Haffaf's PhD thesis (from September 2011) by Marie Doumic-Jauffret.
Supervision of Nick Jagiella's PhD thesis (since July 2007) by Dirk Drasdo, Benoît Perthame, and Irène Vignon-Clémentel (REO project-team).
Supervision of Emanuele Leoncini's M2 internship by Dirk Drasdo.
Supervision of Johannes Neitsch's PhD thesis (since June 2011) by Dirk Drasdo and Stefan Hoöhme.
Supervision of William Weens's PhD thesis (since September 2008) by Dirk Drasdo.

8.2. Scientific popularisation

B. Perthame has given a public talk 'Interactions entre mathématiques et sciences du vivant', CentreSciences, Chartres, May, 2011.

Participation in the "Fête de la science" in Paris (ESPCI, October 2011) : A. Ballesta, F. Billy, J. Clairambault, S. Dulong, F. Lévi in a joint INRIA-INSERM booth dedicated to chronotherapy.

A. Ballesta, J. Clairambault, F. Lévi, A. Langlois (direction), C. Mistral (graphisme) "La chronothérapie des cancers", video/animation of scientific popularisation, producted in collaboration with the multimedia team of INRIA Paris-Rocquencourt, November 2011

A. Ballesta has presented chronotherapy, illustrated by her popularisation movie on the subject in various lycées of the Paris region in 2011.

D. Drasdo has written an article on simulated liver regeneration in the popular journal systembiologie.de (in English and German, printed and under http://www.systembiologie.de) (Issue 03, 2011).

D. Drasdo was also interviewed by Kai Kraemer for the article Virtuelle Heilung (Laborjournal, 3/2011), in German and by Richard Grant for an article in The Scientist, also on liver regeneration (accessible by internet 2011).

J. Clairambault has published an article in Acta Biotheoretica [14]: "Commitment of mathematicians in medicine. A personal experience, and generalisations", following an international workshop organised in 2010 in Paris on "The role and impact of mathematics in medicine", on which a collective report has been published independently [3].

8.3. Teaching

- "Modélisation dans le domaine biomédical: Introduction à la biologie mathématique". Lectures in 2nd school year in the common course "Physiology and biotechnologies"). École Centrale de Paris (Chatenay-Malabry): 9 h (Jean Clairambault)
- M2 Pharmacology (Rennes 1): 4 h (Jean Clairambault)
- M2 Pharmacology & Oncology (Paris XI): 2 h (Jean Clairambault)
- Doctoral school "Innovation thérapeutique" (Paris XI): 2 h (Jean Clairambault)
- M2, Mathematical Biology, UPMC: "Agent-based models of tissue organisation": 24h (Dirk Drasdo)
- School on Cancer modelling at IRCC (Institute for Cancer Research and Treatment) in Candiolo, Italy, March 2011: "Individual-cell-based models for tumor growth and tissue regeneration": 6h (Dirk Drasdo)
- Course on Finite Elements (professor: P. Ciarlet), ENSTA, Paris: 12 h (Marie Doumic-Jauffret, assistant professor)
- TP atelier LM220 "Arithmétique" (Paris VI): 26 h (Luna Dimitrio, PhD student)
- L2 "Biology, Health & Environment" at university P. M. Curie, 21 h : S. Ayata
- M2 "Oceanography and marine environments" at university P. M. Curie, 9 h : S. Ayata
- Course "Wave propagation", ENSTA, Paris: 16 h : J. Sainte-Marie
- Ecole d'Ingénieur SupGalilée (Univ. Paris 13) Finite Elements, 48 h : E. Audusse
- Numerical methods, UAM (Universidad Autonoma Madrid, Spain), 10 h : E. Audusse

8.4. Participation in congresses, workshops,...

- Audusse Emmanuel: SMAI congress, Guidel, France.
- Audusse Emmanuel: Finite Volumes and Complex Analysis (6th conference), Prague (presentation)
- Audusse Emmanuel: Conference "Numerical methods for Hyperbolic Equations Theory and Applications", Santiago de Compostela, Spain.
- Audusse Emmanuel: NumHyp ("Numerical Approximations of Hyperbolic Systems with Source Terms and Applications."), Roscoff, France. (organizer)
- Ayata, Sakina: Comparison of biogeochemical models with increasing complexity in photosynthesis formulation : the importance of taking into account photoadaptation in marine ecosystem models. Advances in Marine Ecosystem Modelling Research Symposium AMEMR III, Plymouth, England (poster).
- Ayata, Sakina: Comparison of biogeochemical models with increasing complexity in photosynthesis formulation. Joint TANGGO/Green-Mercator Workshop, Paris. (presentation)

- Ballesta, Annabelle: "Mathematical Oncology: new challenges for systems biomedicine", - 57th Workshop of the International School of Mathematics "G. Stampacchia": Mathematical oncology: new challenges for systems biomedicine, Erice, Italy, Sept. 2011.
- Ballesta, Annabelle: European Conference on Mathematical and Theoretical Biology (ECMTB) Kraków, Poland, July 2011 (poster).
- Ballesta, Annabelle: "Young Investigators International Workshop", Rouen, France, April 2011.
- Billy, Frédérique: "Mathematical modeling of the control of proliferation in cycling cell population" - 57th Workshop of the International School of Mathematics "G. Stampacchia": Mathematical oncology: new challenges for systems biomedicine, Erice, Italy, Sept. 2011
- Billy, Frédérique: "Modélisation mathématique de mécanismes de la croissance tumorale", Seminar talk, Laboratory of Applied Mathematics, Le Havre University, Le Havre, France, April 2011.
- Billy, Frédérique: "Mathematical modeling of interactions between cell cycle and circadian rhythms" - Mathematics and Biology: Young investigators international workshop, Rouen, France, April 2011.
- Boulanger Anne-Céine: Conference "Numerical methods for Hyperbolic Equations Theory and Applications" at Santiago de Compostela, Spain (presentation).
- Boulanger Anne-Céline: SMAI congress, Guidel, France. (presentation)
- Bristeau Marie-Odile: NumHyp ("Numerical Approximations of Hyperbolic Systems with Source Terms and Applications."), Roscoff, France.
- Cheddadi ibrahim: Towards quantitative individual-based and continuum models of cells aggregates, *ECMTB 2011*, Kraków, Poland, June 2011.
- Cheddadi, Ibrahim: *Modélisation visco-élasto-plastique d'écoulements de mousse*, seminar of Laboratory Matière et Systèmes Complexes, Paris 7, November 2011
- Cheddadi, Ibrahim: *Modélisation visco-élasto-plastique d'écoulements de mousse*, seminar of Institut Navier, Rhéophysique team, Marne-la-Vallée, November 2011.
- Chettaoui, Chadha: Towards a single-cell-based model of early development in ruminants, 8th European Conference on Mathematical and Theoretical Biology, Kraków, Poland, June 2011.
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- Drasdo Dirk: Workshop on integrated liver modelling, Berlin, Germany
- Drasdo Dirk: ECMTB 2011 Kraków (invited to three minisymposia), June-July 2011.
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- Perthame Benoît: Singularities in Nonlinear Problems, Kyoto, short course 2-5/12 2011
- Perthame Benoît: San Diego SIAM PDE (conf. and short course) 14-16th nov. 2011
- Perthame Benoît: Sapporo, short course in the conference “Front propagation, biological problems and related topics”, 6th to 9th sept. 2011
- Perthame Benoît: Vancouver ICIAM plenary speaker, July 18-22 2011
- Perthame Benoît: Spain (Granada) Conference BIOMAT 6-8 June 2011
- Perthame Benoît: USA Providence (Conference for the 70th birthday of C. Dafermos) 11th-12 May 2011
- Perthame Benoît: Nice (Conf. en l’honneur de C. Bardos) 21-24/2 2011
- Perthame Benoît: Santiago (Chile) Seminar 3-12/1/2011
- Sainte-Marie Jacques: NumHyp (“Numerical Approximations of Hyperbolic Systems with Source Terms and Applications.”), Roscoff, France. (invited speaker)
- Sainte-Marie Jacques: Conference “Numerical methods for Hyperbolic Equations Theory and Applications” at Santiago de Compostela, Spain (invited speaker).
- Sainte-Marie Jacques: SMAI congress, Guidel, France (presentation)
- Sainte-Marie Jacques: invited speaker in various seminars (Orléans, INRA Montpellier, univ. Paris XIII,...)
- William Weens: Invited talk, INRIAbcd, Lyon, France, March 2011.
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