INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team bang

Nonlinear Analysis for Biology and Geophysical flows

Paris - Rocquencourt

Theme : Observation, Modeling, and Control for Life Sciences

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2. Overall Objectives

2.1. Overall Objectives

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 dynamic of complex physical or biophysical phenomena can be represented efficiently either by the addition of many individual behaviours or by Partial Differential Equations which, under certain hypotheses, represent averages of large systems of cells or 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 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.
- Optimisation of cancer chemotherapy.
- Prion proliferation dynamics.

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 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 largee part of softwares currently in use in the project-team were initiated and developed within former projects (Menusin, M3N).

4.1.2. CellSys

Participants: Dirk Drasdo [correspondent], Stefan Höhme [PhD student, 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 [16].

5. New Results

5.1. Proliferation dynamics and its control

5.1.1. Cell division dynamics in structured cell populations

Participants: Annabelle Ballesta, Houda Benjelloun [INSA Rouen], Frédérique Billy, Catherine Bonnet [DISCO project-team, INRIA Saclay IdF], Jean Clairambault, Marie Doumic, Vladimir Flores [CONICET (OCSID), Beppo Levi Institute, Rosario, Argentina], Stéphane Gaubert [MaxPlus project-team], Germain Gillet [IBCP, Université Cl. Bernard Lyon 1], Peter Kim [University of Utah, Salt Lake City], Thomas Lepoutre [now in DRACULA project-team, INRIA Rhône-Alpes, Lyon], Pierre Magal [University Bordeaux II], 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, Univesità Sapienza, Rome, Italy], Thomas Ouillon [ENSTA, Paris], Hitay Özbay [Bilkent University, Ankara, Turkey], Benoît Perthame, Melina Rapacioli [CONICET, Argentina], Edmundo Rofman [CONICET, Argentina], Ruoping Tang [INSERM Paris (Team18 of UMR 872) Cordeliers Research Centre and St. Antoine Hospital, Paris], Rafael Verdes [CONICET, Favaloro University, Buenos Aires, Argentina], Vitaly Volpert [CNRS Lyon, UMR5208, Camille Jordan Institute, Lyon].

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 [44], 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 will be experimentally investigated by our biologist partners in the new European network ERASysBio+ *C5Sys*, coordinated by F. Lévi (Villejuif) and D. Rand (Warwick).
2. *Modelling haematopoiesis with applications to CML and AML.* A PDE model of haematopoiesis, physiologically structured in age and maturity, has been developed with applications to Chronic Myelogenous Leukaemia (CML) [11].

   The stability of another model, 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 adviser: J.-P. Marie) has been studied with possible therapeutic implications [33]. This model will be experimentally investigated, with the aim to identify its parameters in leukaemic cells, in the new DIGITEO project *ALMA* (cf. infra), coordinated by C. Bonnet (DISCO team, INRIA Saclay IdF).

   Systems combining PDEs and discrete representations in hybrid models, with applications to cancer growth and therapy, inn particular for AML, are the object of study of the new ANR program *Bimod*, coordinated by V. Volpert (Lyon), associating CNRS (V. Volpert, Lyon), Bordeaux II University (P. Magal) and the Bang project-team.
3. *Developmental model of the Optic Tectum in the chick embryo.* This joint work with an Argentinian team of mathematicians and experimentalist has been presented in a recent INRIA research report [34].
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 submitted article [37].

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, L. Dimitrio has begun her second PhD year by studying at INRIA nucleocytoplasmic transport with applications to p53 activity. Her PhD thesis work is designed 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.

5.1.2. Physiological and pharmacological control of cell proliferation

Participants: Annabelle Ballesta, Jean Clairambault, Sandrine Dulong [INSERM Villejuif (U 776)], Stéphane Gaubert [MaxPlus project-team], Thomas Lepoutre, 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 [9] with the collaboration of S. Gaubert (MaxPlus INRIA project-team, Saclay IdF) and will be investigated experimentally in the new *C5Sys* European network (cf. supra).
2. *Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs.* This theme is actively worked in collaboration, mainly with the teams of F. Lévi and J.-P. Marie (cf. supra). It has led to the presentation of a molecular PK-PD model for 5-FU+Leucovorin in a collaborative article [20], and it is also, for another drug, Irinotecan, the main subject of A. Ballesta's PhD thesis, recently resulting in a submitted article that reports a combination of mathematical modelling and experimentation in cell cultures.
3. *Whole body physiologically based model of anticancer drug pharmacokinetics.* This theme is also 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) 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.

5.1.3. Optimisation of cancer chemotherapy

Participants: Annabelle Ballesta, Jean Clairambault, Thomas Lepoutre, Francis Lévi [INSERM U 776, Villejuif].

Optimising cancer chemotherapy, especially chronotherapy, is the final aim of the activities mentioned above. This has been lately discussed in [9]. 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 [20], in A. Ballesta's PhD joint work with F. Lévi, and to a common European research position paper [26].

Another way to represent and overcome drug resistance in cancer from a Darwinian point of view using concepts of adaptive dynamics in proliferating cell populations is also being currently investigated.

5.1.4. Prion proliferation dynamics and protein polymerisation (ANR TOPPAZ)

Participants: Vincent Calvez [ENS Lyon], Frédérique Charles, Marie Doumic, Pierre Gabriel, Benoît Perthame, Leon Matar Tine [SIMPAF project-team, INRIA Lille Nord-Europe].

In collaboration with biologists from INRA/BCBP, Jouy-en-Josas (head H. Rezaei), a numerical scheme for protein polymerisation has been investigated by P. Gabriel and L. Matar Tine in [31].

The eigenvalue problem playing a major role in the representation of Prion proliferation dynamics and, in a more general way, in many fragmentation-coalescence phenomena, the article [41] investigates the dependency of the principal eigenvector and eigenvalue upon its parameters. V. Calvez and P. Gabriel are currently working on an optimal control viewpoint on this problem.

With H. Rezaei, a new and very complete PDE model for protein polymerisation has been designed. During her postdoc, F. Charles has applied this model to Huntington's disease and compared it with its ODE counterpart. This work is still in progress. 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 [41] investigates the dependency of the principal eigenvector and eigenvalue upon its parameters. V. Calvez and P. Gabriel are currently working on an optimal control viewpoint on this problem.

5.1.5. Inverse problem in structured populations and fragmentation equations

Participants: Marie Doumic, Léon Matar Tine.

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), we have explored a statistical viewpoint on the cell division problem, applying Lepski's method to find an optimal regularisation parameter. This work will be submitted very soon.

With L. Matar Tine, we have begun to work on a generalisation of the inverse techniques proposed in (Perthame, Zubelli, Inv. Prob., 2007) and (Doumic, Perthame, Zubelli, Inv. Prob., 2009), in order to adapt them to general fragmentation kernels and growth speeds. The potential applications of such a generalisation are numerous, ranging from polymerisation processes to the cell division cycle.

5.2. Tissue growth, regeneration and cell movements

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

Participants: Alexander R.A. Anderson [Moffitt Cancer Center, Tampa, USA], Augustinus Bader [Biotechnology Dept., Univ. Leipzig], Anne-Céline Boulanger [Ecole Centrale de Paris], Helen Byrne [Univ. of Nottingham, UK], Chadha Chettaoui, Mark Chaplain [Univ. of Dundee, UK], Dirk Drasdo, Rolf Gebhardt [Univ. of Leipzig, Germany], Jan G. Hengstler [Leibniz Research Center, Dortmund, Germany], Stefan Höhme, Isabelle Hue [INRA], Nick Jagiella, Ursula Klingmüller [German Cancer Center, Heidelberg], Axel Krinner, Emanuele Leoncini, Benoît Perthame, Ignacio Ramis-Conde, Alain Roche [Institut Gustave Roussy], Eckehard Schöll [Technical Univ. of Berlin, Germany], Luc Soler [IRCAD, Coordinator EU-project PASSPORT], Alain Trubuil [INRA], 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 both: 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.

In order to fill the existing gap we have studied intracellular regulation networks [63], [56], multi-scale IBMs where intracellular regulation and differentiation was explicitly represented within each individual cell [65], [62], [66], lattice-free IBMs [53] and continuum models that can capture their large scale behaviour [49], and cellular automaton (CA) models where each lattice site can be occupied either by at most one cell [47] or by many cells [64], [55] and their corresponding continuum equation [52].

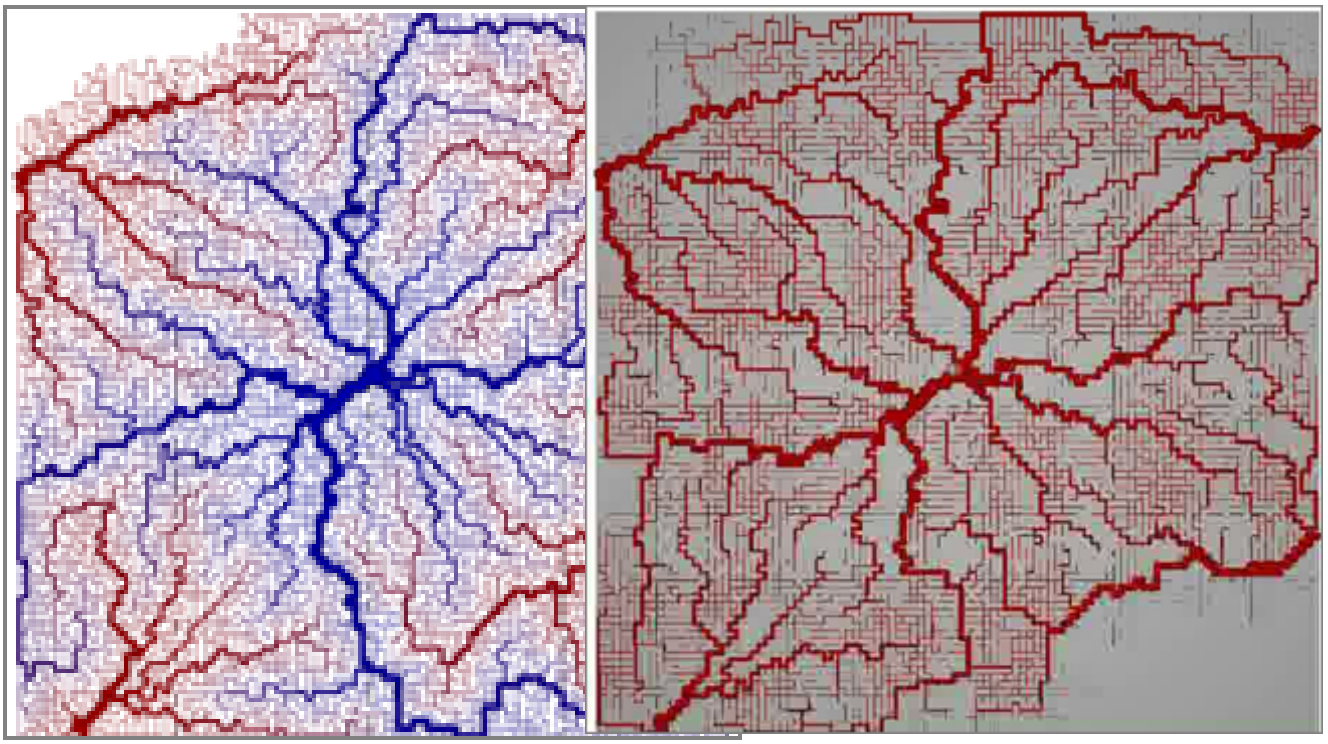

Figure 1. Left: Vessel network with arterial and venous branches. Right: Simulation of contrast agent in the vessel network.

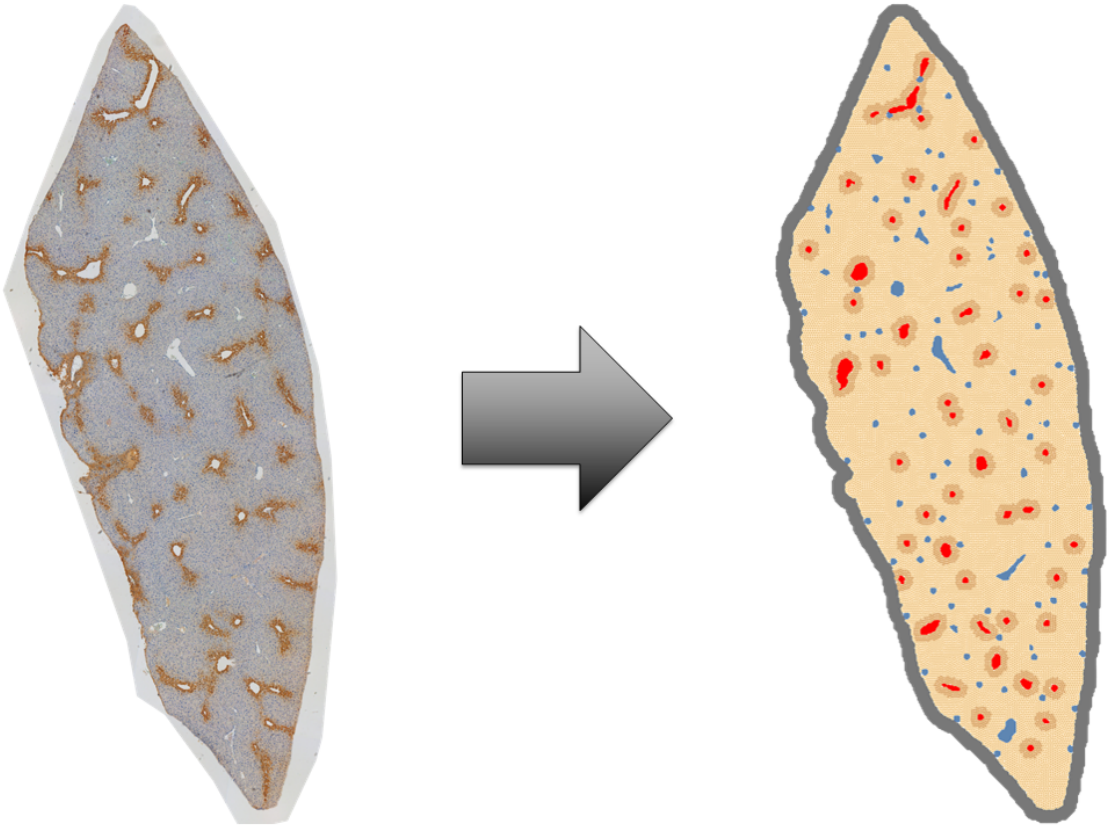

Figure 2. Left: Transfer of a bright field image in immunohistochemical staining (brown: cells with active glutamine synthetase) and (right) direct transfer in single cell (agent)-based mathematical model.

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

- Unstructured cell populations growing in a monolayer [53], [58].
- Multicellular spheroids [53], [54].
- Vascular tumour growth (Fig. 1).
- Regulatory and evolutionary aspects in tumour growth [2], [17].
- Cell differentiation and lineage commitment of mesenchymal stem cells [62], [57]. In our earlier work we have established a model of cell aging for in-vitro cultivated stem cell populations. Stem cell concepts developed earlier [62], [57] have been extended to include cell aging [19]. 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. [3].
- Complex tissue architectures in regenerative tissues, particularly in the liver.

Examples are:

- Regeneration of liver lobules after toxic damage [61], [60], [15]) within the German BMBF-funded network "Systems Biology of the Hepatocyte").
- Liver regeneration after partial hepatectomy (Fig. 2). 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.
- Cancer development in the liver. Within the project, mechanisms of cancer development in mice are studied. 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 [7]. Moreover, we managed to develop a new line of our program code to mimic liver cancerogenesis within a 3D model of groups of liver lobules. Simulations are very computer-time intense and are currently running to explain the observed phenotypes by our experimental partners. Recent results indicate that different phenotypes may emerge depending on the stiffness of the sinusoids, the blood micro-vessels within the lobule.
- Early morphogenesis (trophoblast development).

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 [67], and developed an image processing chain to quantitatively analyse liver regeneration processes in liver lobules [60], [15] 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) [2]. 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 [55]. 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).

Future directions will include cell-reprogramming with the ANR project Sine2Arti, detoxication in-vitro within the EU - project NOTOX, and multi-scale liver modelling of normal liver and diseases within the German Systems Biology Virtual liver network (VLN).

5.2.2. *Chemotaxis, self-organisation of cell communities*

Participants: Nikolaos Bournaveas [Univ. Edinburgh], Vincent Calvez [ENS Lyon], Thomas Lepoutre, Americo Marrocco, Benoît Perthame, Christian Schmeiser, Nicolas Vauchelet.

Our activity on the self-organisation of cell communities has been motivated by collaborations with a team of biologists (I. B. Holland, S. Séror, Institut de Génétique et Microbiologie, CNRS UMR 8621, Univ. Paris-Sud, F-91405 Orsay) and with a team of biophysicists (A. Buguin, J. Saragosti, P. Silberzan, Institut Curie, UMR CNRS 168 Physico-Chimie-Curie).
Most models explaining the dendritic patterns of cell colonies fundamentally use local depletion of nutrients, an explanation that biologists doubt for experimental devices with a large excess of nutrient. Therefore we have investigated other macroscopic models. They take into account the experimental observation that two types of cells are present in the dendrite : highly motile *swarmers* of population density n and *supporters* of population density f with smaller motility, that follow the swarmers. The model is written as

$$\left.\begin{aligned} &\partial_t n + \nabla\cdot[n(1-n)\nabla c - n\nabla S] = 0,\\ &-D_c\Delta c + \tau_c c = \alpha_c n,\\ &\partial_t S - D_s\Delta S + \tau_s S = \alpha_s m_{col} + \alpha_f f,\\ &\partial_t D_m = d_m n,\\ &\partial_t f - \nabla\cdot(D_m\nabla f) = B_f f(1-f) + B_n n, \end{aligned}\right\} \tag{1}$$

where c denotes the chemoattractant concentration and S is the surfactin concentration, a substance that plays a fundamental role during the motion of cells. The quantity D_m represents the trace left by the swarmers. Parameters D_c and D_S are diffusion coefficients, τ_S and τ_c are degradation rates and α_S, α_f, d_m, B_f, B_n represent birth rates.
Numerical simulations as well as qualitative properties of the solutions of model (1) are proposed in [42] (see also Figure 3); the mathematical analysis of travelling fronts is investigated in [35].

In order to improve these types of models it is necessary to consider the individual behaviour of cells in response to external stimuli. This is the purpose of kinetic models of cell populations and in particular the variants proposed recently by Y. Dolak and C. Schmeiser [51]. Theoretical results and numerical simulations of such models has been investigated by N. Vauchelet in [27]. It is noteworthy that the blow-up patterns at the kinetic level can be very different from those of the Keller-Segel system. These individual-based kinetic models also lead to hydrodynamical models usually referred to as aggregation equations. The mathematical analysis of such systems induces several difficulties due to the finite time blow-up of solutions. We propose a first approach in [18]; the extension of these results is a work in progress.
Another typical behaviour of cell colonies, first observed by Adler in the 80's are travelling bands for E. coli that are not well explained by the present macroscopic models, as the famous Keller-Segel system. In [25] we propose an explanation which again uses the same methodology; the individual behaviour of cells is described by a kinetic equation and the macroscopic model for the colony follows by asymptotic analysis.

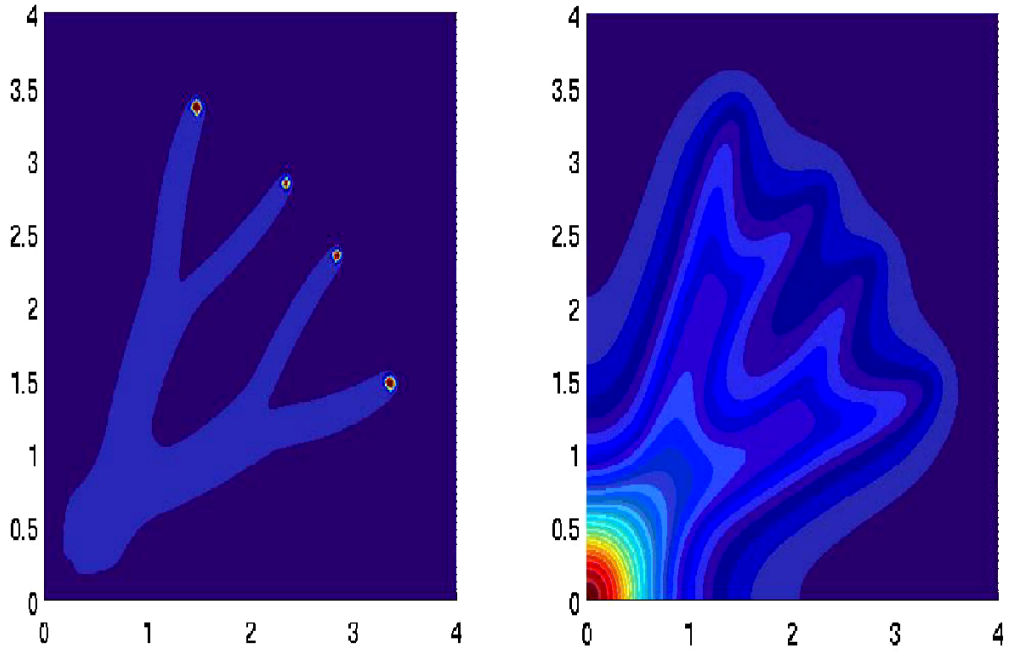

Figure 3. Dynamics of the swarmers and supporters $n + f$ concentration (left) and of the surfactin S (right) solving system (1).

5.3. Free surface geophysical flows

Participants: Emmanuel Audusse [Université Paris 13, Institut Galilée], Sakina Ayata, Anne-Céline Boulanger, Marie-Odile Bristeau, Marica Pelanti, Benoît Perthame, Jacques Sainte-Marie [Saint-Venant Laboratory-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 [50] with a moving mesh. However for efficiency reasons, vertically averaged models such as the Saint-Venant system [59] 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 [46] 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 are beginning to couple the hydrodynamics of free surface flows with other phenomena such as biology (phytoplankton culture) or erosion.

Many of the works presented here are included in the "Habilitation à diriger des recherches" of J. Sainte-Marie [4].

5.3.1. A non-hydrostatic shallow water model

The classical Saint-Venant is well suited for the modelling of dam breaks or hydraulic jumps, but in a lot of cases among which are the propagation of gravity waves on a varying bottom the hydrostatic assumption becomes too restrictive. In [48] we have proposed an extended version of the Saint-Venant where the hydrostatic assumption is dropped and the pressure depends on the vertical acceleration in order to take into account dispersive effects. This model is obtained going one step further in the asymptotic development proposed by Gerbeau and Perthame [59], we show that it admits an energy balance. We have defined a numerical scheme [40] for this non-hydrostatic model, it is based on an extension of any finite volume solver of the Saint-Venant system. Several numerical results are given (undular bore, swelling, soliton) and especially comparisons between simulations and experimental measurements. They correspond to situations where the influence of the convective part of the vertical velocity is small, actually the non-hydrostatic terms added here vanish in stationary regimes.

5.3.2. A multilayer Saint-Venant system with varying density for the simulation of stratified flows.

Considering flows with large friction coefficients, with significant water depth or with important wind effects, the horizontal velocity can hardly be approximated – as in the Saint-Venant system – by a vertically constant velocity. We have developed a multilayer approximation that allows the fluid to circulate from one layer to the connected ones [6].

We are now interested in applications to geophysical water flows such as lakes and estuarine waters, which typically exhibit a significant density stratification related to vertical variations of temperature and chemical composition. In these water bodies effects related to small density gradients may strongly affect the hydrodynamics. We are considering free surface flows with a varying density (related to salinity or temperature) in order to simulate stratifications and upwelling phenomena.

We start with the free surface hydrostatic Euler equations and a transport equation for a tracer T, typically salinity or temperature in the applications considered. The density is given by $\rho = \rho(T)$ (this means that the flow remains incompressible).

The vertical discretisation of the horizontal velocity u and tracer T consists in a Galerkin approximation (P_0 type) in Lagrangian formulation. After dividing the flow domain in a given number of layers, the vertically discretised system is obtained by integrating the continuous equations on each layer. Then, using the Leibnitz rule, we introduce the averaged values of the variables and the exchange terms.

A kinetic interpretation of this system is also proposed leading to a numerical scheme. Due to the density coupling, non linear systems have to be solved on each water column. This model is well suited to simulate stratified flows and upwellings, it is able to treat as well dry areas as hydraulic jumps and variable density effects (see Fig.4 and 5). It is an important milestone for the coupling with bio-dynamics.

Besides this work on the multilayer system, the collaborative research project between BANG and EDF has led to an upgraded and extended version of OPHÉLIE, a thermo-hydrodynamic model for lakes and reservoirs developed in the late Eighties at the National Laboratory of Hydraulics and Environment (LNHE) of EDF R&D (see M.-J. Salençon and J.M. Simonot [68]).

The OPHÉLIE code is based on the two-dimensional laterally averaged hydrostatic incompressible Navier–Stokes equations, with Boussinesq approximation and rigid lid upper boundary condition hypothesis.

Simulations of the response of density-stratified water flows to wind forcing have shown good agreement of the numerical results obtained with the new version of OPHÉLIE with theoretical studies and field observations reported in the literature. Examples of numerical experiments include simulations of upwelling phenomena and wind-induced internal waves (see Fig. 6 and 7).

This study is done in collaboration with M.J. Salençon (EDF/LNHE) and is the object of a grant.

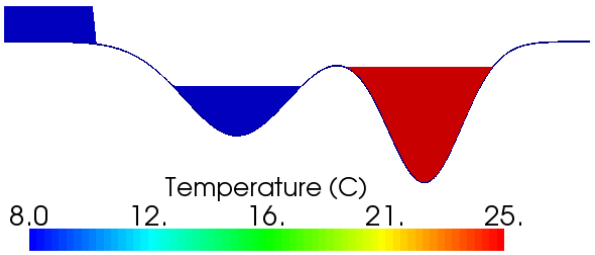

Figure 4. Test case with dry areas, shocks and variable densities effects. Initial condition.

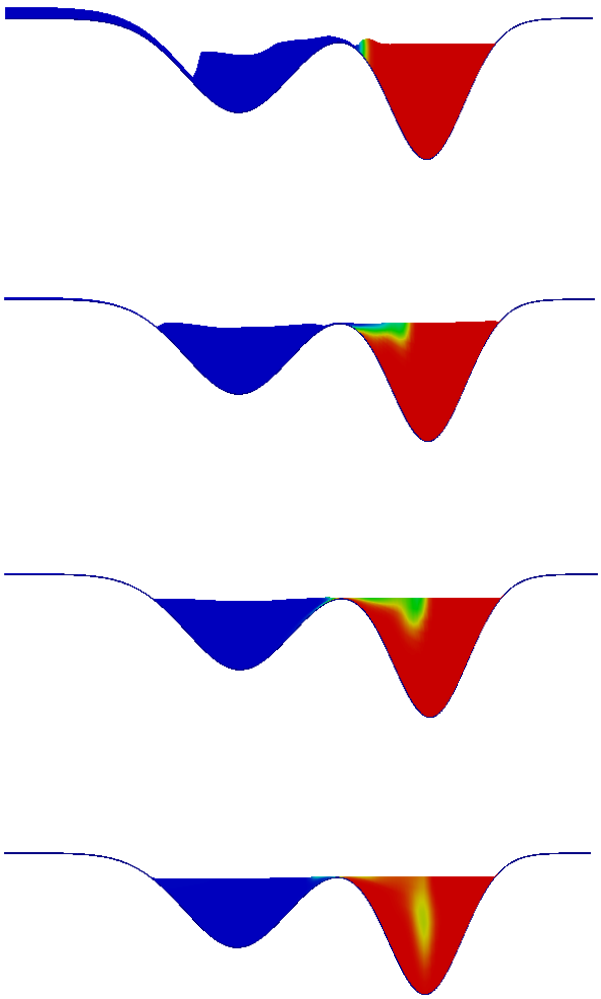

Figure 5. Test case with dry areas, shocks and variable densities effects. Flow dynamics at four different times, $t_1 = 2.5s$*,* $t_2 = 7.5s$*,* $t_3 = 12.5s$*, and* $t_4 = 27.5s$*.*

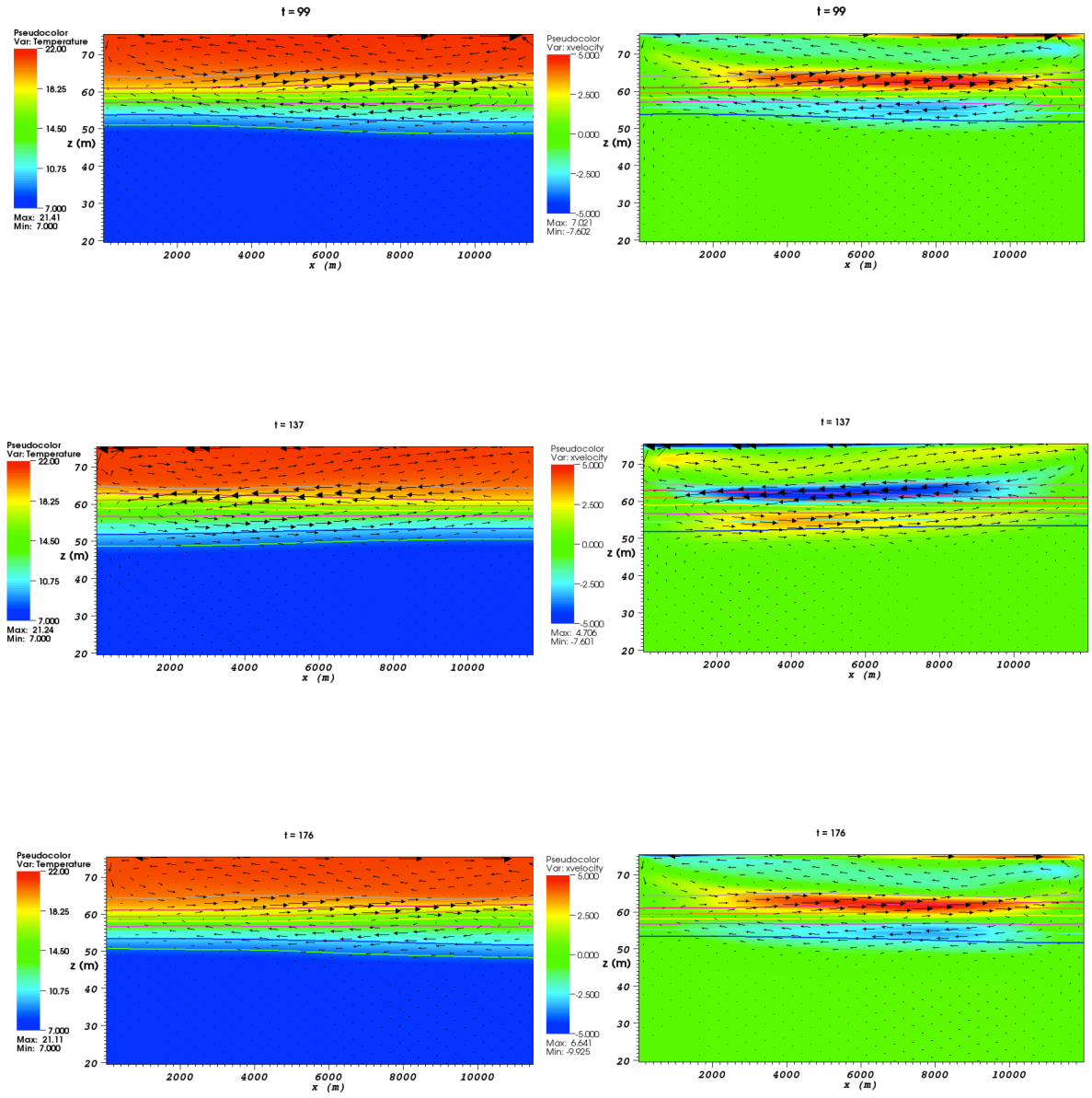

Figure 6. Simulation of vertical-mode internal waves induced by periodic wind forcing in a stratified lake. Temperature and horizontal velocity at times $t = 99$ *h,* $t = 99 + T_{V3}/2 = 137$ *h,* $t = 99 + T_{V3} = 176$ *h.*

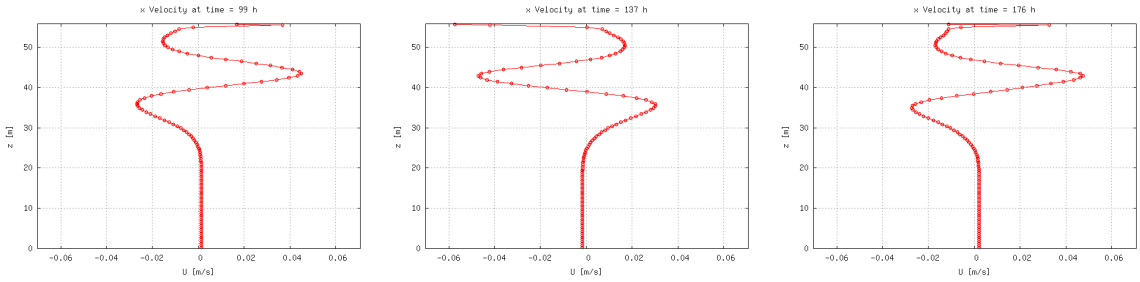

Figure 7. Simulation of vertical-mode internal waves induced by periodic wind forcing in a stratified lake. Horizontal velocity profile at the middle of the basin at times $t = 99$ *h,* $t = 99 + T_{V3}/2 = 137$ *h,* $t = 99 + T_{V3} = 176$ *h.*

5.3.3. Hydrodynamics and biology coupling

In order to extend the use of the hydrodynamics models developed in the team, we started a project about hydrodynamics and biology coupling in a raceway (ARC Nautilus between BANG and COMORE (INRIA Sophia-Antipolis)). A raceway designates a small pond built for the intensive culture of algae. This is an accurate topic for both researchers and industrialists. While the former want to optimise the algae growth and oil production with the purpose of transforming it into biofuel, they need mathematical modelisation in order to make their raceway efficient. Since many parameters come into account : raceway depth, paddlewheel agitation, temperature, wind, nutrients concentration... experimental determination of the optimal combination would be too costly.

Anne-Céline Boulanger's internship was defined in this context: trying to make a first evaluation, in two dimensions, of the possibilities of the models used in both INRIA teams to tackle the problem of hydrodynamics and biology coupling in a raceway. It needed to emphasise the problems that could occur, the dynamics involved, biologically and physically speaking and how we could improve our models such that they can reproduce the real phenomena as close as possible. The first results have been obtained by the coupling of the multilayer Saint-Venant system described above and a Droop model (Anne-Céline Boulanger's internal report). The results are encouraging and will be pursued in a PhD thesis (started in October 2010).

5.3.4. Multilayer shallow water equations and bedload processes

We are interested in the coupling of hydrodynamics and bedload evolution. This question naturally appears in several applications in coastal engineering or in river dynamics. There exists a large amount of models for the hydrodynamic part, from free surface Navier-Stokes equations to shallow water system. Here we consider the multilayer shallow water model [6] that formally approximates the free surface hydrostatic Navier-Stokes equations. These fluid models have been used for a long time and have been widely validated. For the bedload dynamics people often use what is known as Exner models with some closures due to Grass, Meyer-Peter, etc... These models are quite empirical and have a restrictive range of validity. Some preliminary numerical results [5] have already been obtained by coupling our kinetic scheme for multilayer model with a very simple numerical discretisation of the Exner equation. The results look qualitatively good. We have now two main goals for our studies :

- To study the bedload model : we would like to investigate the derivation of Exner equation and we hope to be able to give a rigorous derivation of the equation and maybe to propose some new models. In particular these models are generally coupled with classical shallow water fluid models and we would like to use new information that comes from our more detailed multilayer models.
- To adapt the numerical scheme to this new application : the characteristic times of fluid and bedload

processes can be very different. Then it would be interesting to construct numerical schemes that handle this information.

5.3.5. Other applications

Other applications related to geophysical flows are also treated:

- **1D section-averaged Saint-Venant model.**

  We have proposed a kinetic interpretation of the 1D section-averaged Saint-Venant system and derived an associated numerical scheme [14]. This work has been done in collaboration with N. Goutal (EDF/LNHE).

- **Overland flows.**

  We have continued the study concerning the simulation of overland flows. Particularly, we have compared the results obtained with the multilayer model and the experimental measurements for the flow on a corrugated panel. This work is a participation to the ANR project "METHODE" (url http://methode.netcipia.net).

- **Debris flows.**

  Marica Pelanti has pursued his study concerning the simulation of geophysical gravitational flows such as avalanches which typically contain both solid granular components and an interstitial fluid phase [23]. This work has been done in collaboration with F. Bouchut (CNRS/Université Paris-Est - Marne-la-Vallée) and A. Mangeney (IPGP).

6. Contracts and Grants with Industry

6.1. Grants with Industry

6.1.1. 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. Other Grants and Activities

7.1. Regional Initiatives

7.1.1. DIGITEO

The DIGITEO IdF *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 experimental parameter identification by F. Merhi, postdoc of Bang, working at St. Antoine Hospital (Paris), under the supervision of J. Clairambault to link experimental and theoretical aspects and of J.-P. Marie and R. Tang (INSERM-UPMC) to supervise biological experiments on leukaemic cells. It has been granted for 3 years, beginning in December 2010.

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

(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.

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.

(url 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.

(url http://methode.netcipia.net)

7.2.5. ANR Sine2Arti

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

7.3. European Initiatives

7.3.1. 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.

7.3.2. 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)

7.3.3. 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.

7.3.4. EU-project NOTOX

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

7.4. International actions

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 University of Dundee, UK, on cell models that take into account the role of key molecules that control cell invasion in cancer by representing the intracellular scale, 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. Some of the former collaborations are now continued within the different EU projects enumerated above.

8. Dissemination

8.1. Animation of the scientific community

Benoît Perthame is Editor-in-chief of M2AN and editor in various journals (CALCOLO, CPDE, SIAM J. Math. Analysis, DCDS(B)).

Dirk Drasdo is member of the VPH FET advisory board for the EU.

Organisation of a weekly informal, interactive seminar by Marie Doumic, 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 (since June 2007) by Jean Clairambault and Francis Lévi. Supervision of Anne-Céline Boulanger's PhD thesis by Marie-Odile Bristeau and Jacques Sainte-Marie. 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 Pierre Gabriel's PhD thesis by Marie Doumic and Benoît Perthame. Supervision of Nick Jagiella's PhD thesis (since July 2007) by Dirk Drasdo, Benoît Perthame, and Irène Vignon-Clémentel (REO project-team). Supervision of William Weens's PhD thesis (since September 2008) by Dirk Drasdo. Supervision of Houda Benjelloun's M2 internship (until February 2010) by Jean Clairambault (Bang), Catherine Bonnet and Hitay Özbay (DISCO team, Saclay IdF). Supervision of Emanuele Leoncini's M2 internship by Dirk Drasdo. Supervision of Thomas Ouillon's M1 internship (May-August 2010) by Jean Clairambault.

8.2. Scientific popularisation

Jean Clairambault has written a popularisation article (in French) for the December issue of La Recherche, Les cahiers de l'INRIA [30].

Dirk Drasdo has written with Christine Leininger (Multimedia team, INRIA) a popularisation article (in French) in the issue # 13 of *DocSciences* http://www.docsciences.fr/Au-coeur-du-foie .

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): 18 h (Jean Clairambault)
- M2 Pharmacology (Rennes 1): 3 h (Jean Clairambault)
- M2 Pharmacology & Oncology (Paris XI): 2 h (Jean Clairambault)
- Doctoral school "Innovation thérapeutique" (Paris XI): 2 h (Jean Clairambault)
- M2, Mathematics ("Growth, reaction movement and diffusion from biology") (Paris VI): 18 h (Dirk Drasdo)
- European biomathematics summer school on mathematical modelling of cancer growth and treatment, Dundee, August 2010: 5 h + 3 h (Dirk Drasdo and Jean Clairambault)
- Course on Finite Elements (professor: P. Ciarlet), ENSTA, Paris: 12 h (Marie Doumic, assistant professor)

8.4. Participation in congresses, workshops,...

- Perthame Benoît: Neurosciences, CIRM, Marseille, January 2010
- Perthame Benoît: Winter school on PDE and Math Biology, Habana, Cuba, February 2010
- Perthame Benoît: ANR Mica, Tours, February 2010
- Perthame Benoît: Spatio-temporal patterns, Geneva, March 2010
- Perthame Benoît: Workshop on travelling waves, Banff, Canada, March 2010
- Perthame Benoît: ICMS (organiser) PDEs in math. biology (cell migration and tissue mechanics), Edinburgh, April 2010
- Perthame Benoît: Arc Nautilus, Villefranche-sur-Mer, France, April 2010
- Perthame Benoît: French-Egyptian Conf., Cairo, May 2010
- Perthame Benoît: Computational and math. methods in sc. and engineering, Madison, Wisconsin, May 2010
- Perthame Benoît: OCCAM, Modelling at different scales in biology, Oxford, June 2010
- Perthame Benoît: Short course, Mathematics in life sciences, Granada, Spain, July 2010
- Perthame Benoît: Workshop on kinetics and fluids, Beijing, July 2010
- Perthame Benoît: Frontiers of mathematics and applications, short course, Santander, Spain, August 2010
- Perthame Benoît: PDEs in Math. Biology, Bedlevo, Poland, September 2010
- Perthame Benoît: Newton Institute, Cambridge, October2010
- Perthame Benoît: JMK2, Kairouan, Tunisia, November 2010
- Perthame Benoît: ICMS Conf. on kinetic PDEs, Edinburgh, November 2010
- Perthame Benoît: Short course and Conf. on nonlinear PDE: math. theory, computation and applications, Singapore, November 2010

- Clairambault, Jean: Several meetings of the Paris region competitivity pole Medicen, Systematic, Cap Digital for IT and health: Paris January 2010, Palaiseau February 2010, Levallois March and April 2010, Villejuif September 2010
- Clairambault, Jean: Séminaire de Mathématiques du Vivant, Bordeaux, March 2010
- Clairambault, Jean: Séminaire de mathématiques appliquées, Collège de France, Paris, May 2010
- Clairambault, Jean: 8th AIMS-DSDEA Conference, Dresden, May 2010
- Clairambault, Jean: CMPD3, Bordeaux, June 2010
- Clairambault, Jean: RIMM (co-organiser), Paris, June 2010
- Clairambault, Jean: ESOF, Turin, July 2010
- Clairambault, Jean: 16th WorldPharma Conference, Copenhague, July 2010
- Clairambault, Jean: DIEBM, Samos, Greece, September 2010
- Clairambault, Jean: Functional genomics towards personal healthcare, Santorini, Greece, September-October 2010
- Clairambault, Jean: Mathematics seminar, Jiao Tong University, Shanghai, November 2010
- Clairambault, Jean: 1st Congress on molecular medicine, Shanghai, November 2010
- Clairambault, Jean: GdR STIC-Santé, Paris, workshop on modelling and imaging, December 2010
- Drasdo Dirk: Riken Symposium Tokyo, April 2010 (invited speaker)
- Drasdo Dirk: Workshop on Mathematical Modeling of Biological Systems, Leuven, Belgium, April 2010 (invited)
- Drasdo Dirk: ICBME 2010, Singapore, August 2010 (two talks)
- Drasdo Dirk: ICSB 2010 Workshop, Edingburgh, September 2010 (invited speaker)
- Drasdo Dirk: Workshop on physics and mechanics in biological systems, ESPCI, Paris, December 2010 (invited speaker)
- Drasdo, Dirk: GdR STIC-Santé, workshop on modelling and imaging, Paris, December 2010
- Drasdo Dirk: Various talks in workshops within the EU and national grant network projects: Virtual Liver Network, LungSys, CancerSys, Passport (about 10 talks in 2010)
- Doumic, Marie: CRSC - HT Banks seminar, Raleigh, USA, February 2010
- Doumic, Marie: 9th ICOR, Habana, Cuba, February 2010
- Doumic, Marie: Nonlinear PDE, Edinburgh, April 2010 (not attended due to volcanic eruption)
- Doumic, Marie: Alzheimer projects workshop, Paris, June 2010
- Doumic, Marie: Non Linear days / Venakides days, Paris, June 2010
- Doumic, Marie: PDE in Mathematical Biology, Bedlewo, Poland, October 2010
- Audusse Emmanuel: International Conference on Microfluidics and Complex Flows (ECM 09), Polytechnic School of Tunisia, Tunis, November 2009
- Audusse Emmanuel: Numerical Methods for Interactions between Sediments and Water, Paris 13 University, September 2010
- Sainte-Marie Jacques: Numerical Methods for Interactions between Sediments and Water, Paris 13 University, September 2010
- Sainte-Marie Jacques: Séminaire d'Analyse Numérique et Calcul Scientifique, Besançon, France, November 2010
- Ballesta, Annabelle: MMSB, Tel Aviv, January 2010
- Ballesta, Annabelle: RIMM, Paris, June 2010
- Ballesta, Annabelle: SFBT, Tunis, June 2010

- Ballesta, Annabelle: SM2A, Rabat, June 2010
- Ballesta, Annabelle: SFC, La Colle sur Loup, France, September 2010
- Ballesta, Annabelle: Functional genomics towards personal healthcare, Santorini, September-October 2010
- Ballesta, Annabelle: Cancer pharmacogenomics, Madrid, November 2010
- Ballesta, Annabelle: GdR STIC-Santé, workshop on modelling and imaging,Paris, December 2010
- Billy, Frédérique: Functional microscopy in biology (MiFoBio), Seignosse, France, September 2010
- Billy, Frédérique: GdR STIC-Santé, workshop on modelling and imaging, Paris, December 2010
- Gabriel, Pierre: Rencontres Numériques, Lille, March 2010
- Chettaoui Chadha: Workshop IZBI, University of Leipzig, 2010
- Chettaoui Chadha: Summer school, Computational Cell Biology, Cold Spring Harbor Laboratory, New York, 2010
- Chettaoui Chadha: Société Francophone de Biologie Théorique, Institut Pasteur, Tunis, 2010
- Chettaoui Chadha: Morphogenesis in Living Systems 2010, RNSC, Centre Universitaire des Saints-Pères, Université René-Descartes, Paris, 2010
- Chettaoui Chadha: Modelling actions in Phase department, INRA, Paris, 2010
- Chettaoui Chadha: 9th International Symposium, Computer Methods in Biomechanics and Engineering, Valencia, Spain, 2010
- Dimitrio, Luna: 8th AIMS-DSDEA Conference, Dresden, May 2010
- Dimitrio, Luna: Functional microscopy in biology (MiFoBio), Seignosse, France, September 2010
- Dimitrio, Luna: GdR STIC-Santé, workshop on modelling and imaging, Paris, December 2010
- Gabriel, Pierre: Rencontres Numériques, Lille, March 2010
- Gabriel, Pierre: Workshop PDEs in math. biology (cell migration and tissue mechanics), ICMS, Edinburgh, April 2010
- Gabriel, Pierre: 8th AIMS-DSDEA Conference, Dresden, May 2010
- Gabriel, Pierre: 3rd CMPD Conference, Bordeaux, June 2010
- Gabriel, Pierre: Workshop Fluid-kinetic modelling, Newton Institute, Cambridge, September 2010
- Pelanti Marica: Thirteenth International Conference on Hyperbolic Problems, Beijing, June 2010
- Pelanti Marica: Symposium on Mathematical Models and Numerical Methods for Hazardous Geophysical Mass Flows, NTU, Taipei, Taiwan, June 2010 (invited talk)
- Pelanti Marica: Seminar at the Research Centre "Physics of Geological Processes", Oslo University, September 2010

9. Bibliography

Major publications by the team in recent years

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Publications of the year

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[2] S. HÖHME. *Agent-based modeling of growing cell populations and the regenerating liver based on image processing*, Doctoral School, Faculty of Mathematics and Computer Science, University of Leipzig, April 2010.

[3] A. KRINNER. *Multi-scale individual-based models*, Doctoral School, Faculty of Mathematics and Computer Science, University of Leipzig, June 2010.

[4] J. SAINTE-MARIE. *Models and numerical schemes for free surface flows. Beyond the Saint-Venant system*, Université Pierre et Marie Curie, November 2010, Habilitation à diriger des recherches.

Articles in International Peer-Reviewed Journal

[5] E. AUDUSSE, F. BENKHALDOUN, J. SAINTE-MARIE, M. SEAID. *Multilayer Saint-Venant Equations over movable beds.*, in "DCDS-B", 2011, to appear.

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