INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Bang

Biophysique, Analyse Numérique et Géophysique

Paris - Rocquencourt

Theme : Observation, Modeling, and Control for Life Sciences

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BANG (Biophysique, Analyse Numérique et Géophysique) is a continuation of the former project M3N.

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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 and numerical methods for two kinds of problems involving Partial Differential Equations. Firstly problems from life sciences (cell movement, early embryonic development, tissue growth and regeneration, cancer modeling, pharmacology,...) are considered. Secondly models for complex fluid flows are studied (flows with a free surface, flows of holes and electrons in semiconductors).

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.

3. Scientific Foundations

3.1. Introduction

Partial Differential Equations are mathematical tools that allow to represent efficiently the evolution of complex physical phenomena. They represent averages of large systems of particles or cells.

Since the XIX$^{\text{th}}$ century this formalism has shown its efficiency and ability to explain both qualitative and quantitative behaviors. 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 Modeling

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 tumors 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.
- Mixed finite elements for problems with large density variations (semi-conductors, chemotaxis).
- Description of tumor growth and tissue regeneration are based on systems of stochastic equations of motion for individual cells or Monte-Carlo simulations of multi-cellular configurations.

4. Application Domains

4.1. Panorama

BANG has decided to develop new biomedical applications and focuses its know-how in these directions, while keeping more classical industrial relations. These are developed in relation with other INRIA projects: REO, CONTRAINTES, MAXPLUS, ESTIME, MACS, SIMPAF.

4.2. Proliferation dynamics and its control

- Cell division cycle and adaptive dynamics in structured cell populations.
- Physiological and pharmacological control of cell proliferation.
- Optimisation of cancer chemotherapy.
- Prion proliferation dynamics.

4.3. Tissue growth, regeneration and cell movements

This research activity aims at studying mathematical models related to tumor development and tissue organization. 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-organization in cell populations.

4.4. 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.

5. Software

5.1. Introduction

A major part of softwares were initiated and developped within former projects (Menusin, M3N) and are currently in use in the present project-team.

5.2. EMC2

Interactive 2D mesh generator (with Gamma project)

5.3. CellSys

Participants: Dirk Drasdo [correspondant], Stefan Höhme [PhD student, University of Leipzig], Nick Jagiella [PhD student].

Computer simulation software for individual cell (agent) -based models of tumor and tissue growth solved either by systems of coupled equations of motion for each individual cell or by Kinetic Monte Carlo methods.

6. New Results

6.1. Proliferation dynamics and its control

The part of this activity that is related to cell proliferation in health and cancer is organised according to 3 axes: (i) proliferation dynamics in physiologically structured cell populations, (ii) its physiological and pharmacological control at the level of cell populations and in a whole organism, and (iii) pharmacokinetic-phamacodynamic representation of drug control with application to optimisation of cancer chemotherapy.

A new activity has recently emerged in this field, related to neurodegenerative disorders: modelling amyloid protein (Alzheimer) and prion proliferation dynamics.

6.1.1. Cell division dynamics in structured cell populations

Participants: Mostafa Adimy [Anubis project-team], Annabelle Ballesta, Houda Benjelloun [INSA Rouen], Catherine Bonnet [DISCO project-team INRIA Saclay IdF], Jean Clairambault, Fabien Crauste [CNRS Lyon, UMR5208 Institut Camille Jourdan], Marie Doumic-Jauffret, Vladimir Flores [CONICET (OCSID) Institut Beppo Levi, Rosario -Argentina-], Stéphane Gaubert [MaxPlus project-team], Germain Gillet [IBCP, Université Cl. Bernard Lyon 1], Erwan Hingant [Université Rennes 1], Peter Kim [University of Utah, Salt Lake City], Thomas Lepoutre, Jean-Pierre Marie [INSERM Paris (Eq.18 de l'UMR 872) Hôtel-Dieu, Paris], Hitay Özbay [Bilkent University, Ankara, Turkey], Benoît Perthame, Melina Rapacioli [CONICET], Edmundo Rofman [CONICET], Rafael Verdes [CONICET, Université Favaloro, Buenos Aires, Argentine], Vitaly Volpert [CNRS Lyon, UMR5208 Institut Camille Jordan].

1. *Integrated model of the cell division cycle.* Starting from models designed in the Bang project-team from 2003 on, based on physiologically structured PDEs, a convergence model has been produced, coupling a linear cell division cycle model of the McKendrick type with a nonlinear proliferation/quiescence model. Exchanges between phases G0 and G1 are represented by nonlinear functions, allowing a rich behaviour (equilibria, exponential decay, exponential or polynomial increase) for the cell populations that can be either healthy or tumoral. This has been the object of E. Hingant's M2 internship in Spring 2009, and will be continued. This activity aims at representing simultaneously the proliferation dynamics of healthy and tumoral tissues that will subsequently be physiologically or pharmacologically controlled.
2. *Modelling haematopoiesis with applications to CML and AML.* A PDE model of haematopoiesis, physiologically structured in age and maturity, has been developed (M. Doumic-Jauffret, P. Kim) with applications to Chronic Myelogenous Leukaemia (CML) [19]. The stability of another 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 aviser: J.-P. Marie) has been studied with possible therapeutic implications (C. Bonnet, J. Clairambault, H. Özbay) in a conference paper that has been presented at the CDC conference in December 2008 in Cancun [55], and is presently the object of H. Benjelloun's internship and H. Özbay's visiting professor work. New developments about this stability analysis will be presented in 2010 in an IFAC conference (accepted paper, invited session in "Time Delay Systems 2010" in Prague).
3. *Molecular model of apoptosis.* With G. Gillet (prof. at IBCP/Lyon), we are currently designing a mathematical ODE model for the mitochondrial pathway of apoptosis, focused on the early phase of apoptosis (before the cytochrome c release). We aim to justify our modeling choices, analyse (theoretically and numerically) the behaviour of our system and compare numerically its results with experimental results obtained by G. Gillet, to answer biological issues such that: on which protein is it more efficient to act in order to reduce/induce apoptosis ? Which therapeutic strategy can result from this ?

4. *Developmental model of the Optic Tectum in the chick embryo.* This work aims at validating a transport and diffusion system of PDEs as a model to describe the spatially organized operation of the proliferative neuroepithelial cells activity during the optic tectum corticogenesis. It is led in collaboration with 2 Argentinian teams, one at the Mathematics Institute Beppo Levi (Rosario), and another at the Favoloro University (Buenos Aires) and gathers theoreticians and experimentalists to produce a physiologically based model of neuroembryogenesis based on a transport equation with spatial diffusion. It has been presented by V. Flores and E. Rofman at the 24th IFIP TC7 conference held in July 2009 in Buenos Aires, and a common article (Verdes-Flores-Rapacioli-Rofman-Perthame-Clairambault) on this subject is in preparation.

6.1.2. Physiological and pharmacological control of cell proliferation

Participants: Annabelle Ballesta, Jean Clairambault, Sandrine Dulong [INSERM Villejuif (U 776)], Stéphane Gaubert [MaxPlus project-team], Erwan Hingant, Thomas Lepoutre, Francis Lévi [INSERM Villejuif (U 776)], Sylvain Soliman [Contraintes project-team].

This activity develops along 2 parallel axes: a theoretical (mathematical) one (J. Clairambault, S. Gaubert, T. Lepoutre) and a more experimental, or experimentally based, one. In the former are studied in a theoretical way the structural properties of periodic (circadian or pharmacological) controls on proliferation dynamics, measured by a Malthus-like exponent (first eigenvalue of the underlying differential operator). In the latter are examined, with experimental identification of parameters, the influence (pharmacodynamics) exerted by anticancer drugs on the cell division cycle; new developments include the representation of biological mechanisms of drug resistance in cancer cells.

1. *Periodic (circadian) control of cell proliferation in a theoretical model of the McKendrick type.* The influence exerted by a periodic function alternatively blocking and enhancing transition rates between phases of the cell division cycle, and similarly acting on apoptosis rates, that had been initiated by studies published in 2006, 2007 and 2008, has been continued, resulting in an article published in *Mathematical Modelling of Natural Phenomena* [11], to which must be added another one submitted [12], and T. Lepoutre's PHD thesis [2].
2. *Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs* This activity takes place within the framework of the European projects BioSim and Tempo (both ended at the end of 2009). New developments include a PK-PD model for 5FU+Leucovorin delivery (described in [26]), and an intracellular PK-PD model for Irinotecan, with identification of parameters on Caco2 cell cultures (A. Ballesta's PhD thesis work under J. Clairambault's supervision, working on experimental aspects with S. Dulong in F. Lévi's laboratory), both models having been presented in different conferences or workshops, including for A. Ballesta's a presentation at the SFBT annual meeting in Saint-Flour, for which she was granted the Delattre prize of the best PhD student presentation.
3. *Whole body physiologically based model of anticancer drug pharmacokinetics.* The application of molecular PK-PD principles to whole body modelling is necessary to make possible future optimisation of drug delivery schedules with respect to unwanted toxicity side effects in different physiological compartments, simultaneously with therapeutic effects on the tumour compartment. In an INRIA internship internal report, H. Gayrard had studied in 2008 such a whole-body model, structured in compartmental ODEs, for Irinotecan, from infusion in the general circulation until its delivery in the intracellular medium. A. Ballesta has taken over this subject as part of her PhD thesis.

6.1.3. Optimisation of cancer chemotherapy

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

Optimising cancer chemotherapy, especially chronotherapy, is the final aim of the activities mentioned above. This has been lately discussed in T. Lepoutre's PhD thesis [2] and in [12]. 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 [26] in A. Ballesta's PhD joint work with F. Lévi, to a review article on cell proliferation modelling for therapeutic optimisation in cancer [10] and a common European research position paper [33].

6.1.4. Prion proliferation dynamics and protein polymerization

Participants: Vincent Calvez [ENS Lyon], Marie Doumic-Jauffret, Pierre Gabriel, Thierry Goudon [SIMPAF project-team, INRIA Lille Nord-Europe], Thomas Lepoutre, Benoît Perthame.

In collaboration with biologists from INRA/BCBP, Jouy (H. Rezaei) and CEA/DSV (N. Lenuzza and F. Mouthon)

Since spring 2007, a collaboration with CEA/DSV has been initiated by B. Perthame and V. Calvez. It has first lead to two articles in 2008 [9], [8] and several ones in 2009 (two already accepted [17], [18], one submitted [21] and two in progress). Prion pathology (Bovine Spongiform Encephalopathy, commonly known as Mad-Cow Disease, or Creutzfeldt-Jakob Disease for instance) and Alzheimer Disease are both characterized by accumulation of large protein polymers, so-called *fibrils*, in the brain. The objective of our work is a mathematical modelling, numerical analysis, and comparison between simulations and experiments for prion and Alzheimer amyloid aggregation phenomena. It is a very promising field and can provide a deeper understanding of biological phenomena. It also adresses new and profound mathematical issues in the field of fragmentation equations (which are also found to describe the cell division cycle, see [17], [18]) and its inverse problem (see [20]).

6.1.5. Inverse problem in structured populations and fragmentation equations

Participants: Marie Doumic-Jauffret, Pedro Maia [IMPA, Brazil], Benoît Perthame, Jorge P. Zubelli [IMPA, Brazil], Frédérique Charles.

We have continued to investigate the identification of coefficients in the models used in structured populations modeling. With J. Zubelli (IMPA, Rio de Janeiro), we have shown that this is theoretically possible by regularization/denoising methods and have applied them to experimental data with Pedro Maia (IMPA, Rio de Janeiro). The comparison of various algorithms and their convergence analysis has been investigated, and has lead to a published article [20] and a submitted one [34].

We intend to apply and extend these methods for the study of prion proliferation equations, in order to recover parameter functions of the equations from aggregates size distribution. It will be studied by Frédérique Charles during her 18 months post-doctoral position, beginning in November 2009.

Moreover, 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 of Nice), we explore a statistical viewpoint on the cell-division problem.

6.2. Tissue growth, regeneration and cell movements

6.2.1. Single-cell-based models of tumor growth and tissue regeneration and 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, 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 mal-functions 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 increasing effort is made on the interface between both: individual cell based models (IBMs) which permit to include the molecular information on 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.

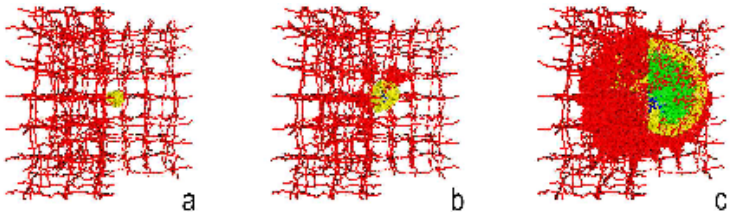

Figure 1. *Growth scenario of a tumor in a vascular network (red) that is remodelled by angiogenesis (c). Yellow: proliferating cells, green: quiescent cells, blue: necrotic region. (From [36])*

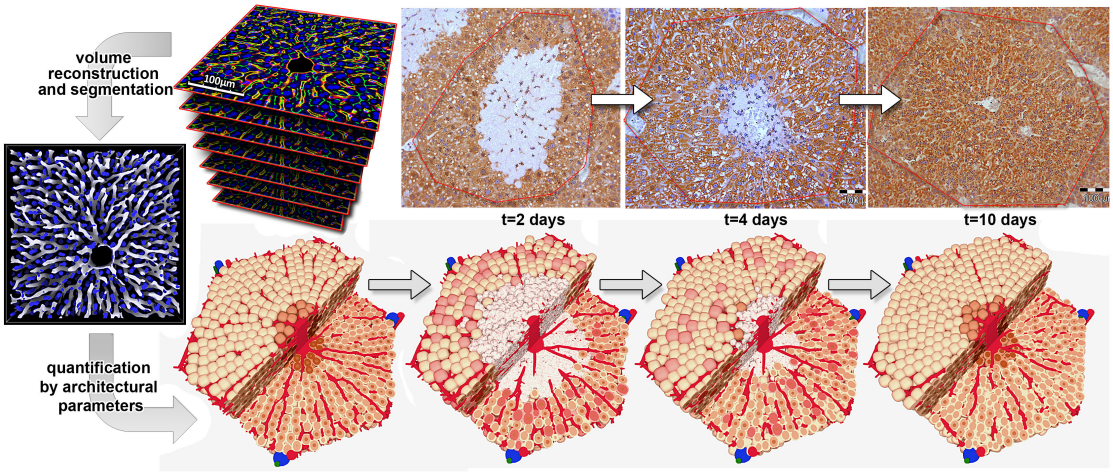

Figure 2. *Image processing of confocal and bright field microscopy (first line) was used to quantify the regeneration process of liver after intoxication with the drug CCl_4 and to set up a mathematical model. Simulations with this model were directly be compared with the experimental results (second line) (red: micro-vessels, brown: hepatocytes (dark: proliferating, light: quiescent), white: necrotic lesion).*

In order to fill the existing gap we have studied intracellular regulation networks [52], [47], multi-scale IBMs where intracellular regulation and differentiation was explicitly represented within each individual cell [53], [24], [29], lattice-free IBMs [45] and continuum models that can capture their large scale behavior [7], and cellular automaton (CA) models where each lattice site can be occupied either by at most one cell [40] or by many cells [28], [36] and their corresponding continuum equation [44].

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

- unstructured cell populations growing in monolayer [45], [48].
- multicellular spheroids [45], [46]
- vascular tumor growth (Fig. 1)
- regulatory and evolutionary aspects in tumor growth [23],
- cell differentiation and lineage commitment of mesenchymal stem cells [24], [35]
- complex tissue architectures in regenerative tissues such as the regeneration of liver lobules after toxic damage [51], [50] (also: Höhme et. al., PNAS, in revision). (Fig. 2; within the German BMBF-funded network "Systems Biology of the Hepatocyte"), liver regeneration after partial hepatectomy and cancer development in liver.
- early morphogenesis (trophoblast development)

The applications are guided by quantitative comparisons to experimental data either from published knowledge or 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 optimize 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 tumor shapes [54], and developed an image processing chain to quanitatively analyze liver regeneration processes in liver lobules [50] (also: Höhme et. al., PNAS, in revision).

Current and future directions include a stronger focus on models of in-vivo systems(within the German medical systems biology consortium "LungSys" (lung cancer treatment); in collaboration which Institut Gustave Roussy, and within the EU-network "CancerSys" (cancerogenesis in liver)). Modeling cancer development requires to take into account invasion, mutations and angiogenesis, three hallmarks of cancer and of linking the molecular to the multicellular scale [36]. Moreover, we extend the topic of liver regeneration to regeneration after partial hepatectomy (within the EU-project "Passport"), and extend our modeling activities to understand early embryonic development (Trophoblast development, collaboration with INRA).

6.2.2. Cell communities self-organisation

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

Our activity on cell communities self-organisation 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-Chime-Curie).
We have continued to investigate macroscopic models at the scale of the full cell population taking into account cell motion and communications through chemo-attractant and repellent. Models which have been investigated are of the type

$$\left\{\begin{array}{rl} \dfrac{\partial}{\partial t}u - d_u\Delta u + \operatorname{div}[u(\dfrac{\alpha}{(1+c_a)^2}\nabla c_a - \eta\nabla c_r)] & = u[g(u,c_r) - f(u)], \\ \dfrac{\partial}{\partial t}w & = uf(u), \\ \dfrac{\partial}{\partial t}c_a - d_a\Delta c_a + \tau_a(u)c_a & = \rho_a u^2, \\ \dfrac{\partial}{\partial t}c_r - d_r\Delta c_r + \tau_r(u+w)c_r & = \rho_r w^2. \end{array}\right. \tag{1}$$

Here c_a and c_r represent the concentration of chemoattractant and chemorepellent respectively. These are assumed to diffuse according to Einstein's rule with coefficients d_a and d_r, they are degraded with the rates τ_a and τ_r (depending possibly on the cell population densities u and w), and they are secreted by the cells with rates ρ_a and ρ_r. Their actions are represented by Fokker-Planck terms in the equation for u, as in the classical Keller-Segel model. A critical comparison between the numerical solution to system (1) and experimental bacterial colonies of *B. subtilis* are described in [27].

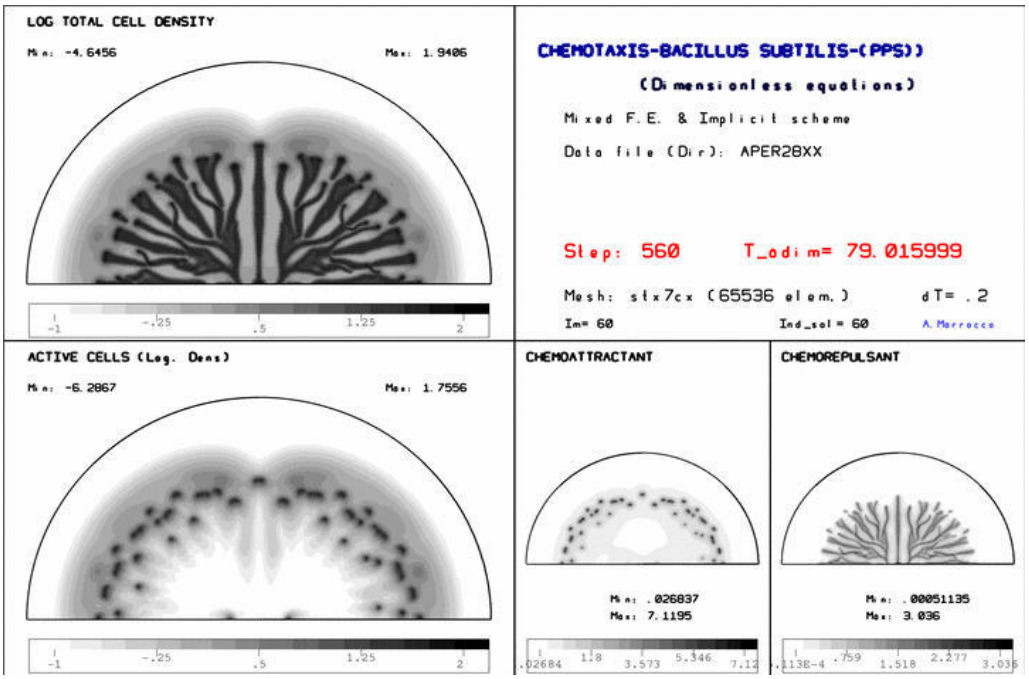

Figure 3. Typical result obtained for a numerical simulation with a system of type (1). Isovalues snapshots of various quantities during the evolution process. Total cell density ($u + w$), Active cells (u), Chemoattractant (c_a) and chemorepellent (c_r).

In order to improve these types of models it is necessary to consider the detailed behaviour of individual 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 [43]. The theory and the numerics of such models has been investigated by N. Vauchelet who shows that the blow-up patterns at the kinetic level are different from those of the Keller-Segel system. Blow-up bands are possible and not only pointwise blow-up.
The individual based kinetic models also lead to macroscopic extensions of the Keller-Segel system that we are currently using to reproduce several experimental observations for *E. coli* at Institut Curie, UMR CNRS 168, and in particular traveling pulses with asymmetric profiles.

6.3. Free surface geophysical flows

Participants: Emmanuel Audusse [Université Paris 13, Institut Galilée], 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 [42] with a moving mesh. However for efficiency reasons, vertically averaged models such as the Saint-Venant system [49] are often used.

We have developed extensions of the Saint-Venant system where the basic Saint-Venant solver [38] 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. These extensions are derived from the free surface Navier-Stokes equations:

- 1D section-averaged Saint-Venant model,

- Multilayer Saint-Venant model with mass exchanges,

- Multilayer Saint-Venant system with varying density,

- Vertically averaged models for the free surface Euler system.

The Multilayer Saint-Venant model with varying density is compared with the Navier-Stokes solver “Ophélie” developed at EDF/LNHE and generalized by M. Pelanti.

One of the applications of the Saint-Venant solvers concerns overland flows.

6.3.1. 1D section-averaged Saint-Venant model

Even if efficient 2D Saint-Venant solvers are available, in many studies of natural rivers hydraulics on large domains, the 1D Saint-Venant equations are used. However for these rivers, it is important to take into account the width variations. So the section-averaged Saint-Venant system is derived asymptotically from the 3D incompressible Navier-Stokes system for free surface flows and some additional source terms are induced by the cross section shape.

We have proposed a kinetic interpretation of this section-averaged Saint-Venant system and derived an associated numerical scheme. The numerical treatment of the source terms related to the cross section has to preserve the equilibrium of the “lake at rest”, it is based on an extension of the hydrostatic reconstruction technique [37] developed for the topography source term. So the numerical scheme -formally 2^{nd} order in space and time- is stable and well-balanced. We also have studied the computation of the friction term either by a centered implicit scheme or using the apparent topography approach. The accuracy of the proposed method has been proved by comparison with analytic solutions and also with experimental measures.

This work [22] has been done in collaboration with N. Goutal (EDF/LNHE).

6.3.2. Multilayer Saint-Venant system with mass exchanges

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.

To drop this limitation, a first multilayer Saint-Venant model has been introduced in [39] where the interfaces are advected by the flow and so there is no mass exchange between the layers. A new multilayer approximation has been proposed that allows the fluid to circulate from one layer to the connected ones. The total water height is divided at each time step in a given distribution, then there is only one continuity equation for the total height and a momentum equation for each layer.

We have studied the derivation of this model, its main properties (energy equality, kinetic interpretation,...) and proved its validity through numerical simulations [4]. The basic tool remains the Saint-Venant solver [38] with a kinetic scheme and an hydrostatic reconstruction [37] to take into account the bottom topography. A formally 2^{nd} order extension has been done for the 1D code and has to be done in the 2D code.

These multilayer models give a precise description of the vertical profile of the horizontal velocity while preserving the computational efficiency of the classical Saint-Venant system. The interest of the second approach is that it allows to simulate recirculating area as, for instance, the effect of the wind on a lake. We are now validating this application by comparison with the Navier-Stokes solver "Mistral" developed at Cermics.

This multilayer solver is also the basic tool for the system with varying density presented in the following section.

6.3.3. Multilayer Saint-Venant system with varying density. Comparison with a Navier-Stokes solver.

We are now considering a free surface flow 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 discretization 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 discretized 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.

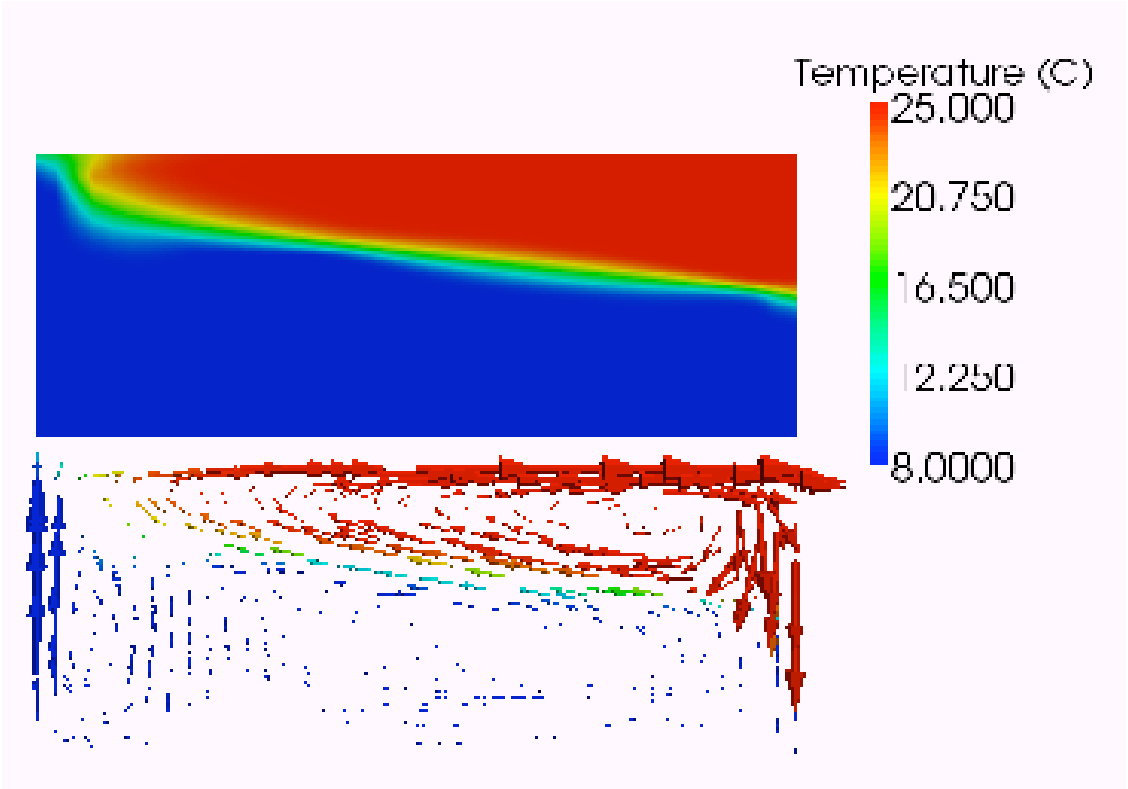

Figure 4. *Upwelling due to wind effect in a stratified lake.*

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 (see Fig.4), it is an important milestone in view of the coupling with bio-dynamics.

Besides this work on the multilayer system, we are working on the generalization of the code "Ophélie" initially developed at EDF/LNHE. This code is based on the hydrostatic Navier-Stokes solver with the Boussinesq approximation for the density variations. For the free surface, the rigid lid assumption is done.

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

6.3.4. Vertically averaged models for the free surface Euler system

To deal with small amplitude waves (swell, waves induced by a rapid opening or closing of a gate,...), the Saint-Venant system is not sufficient, actually these equations rely on the assumption that the vertical velocities are negligible and the resulting pressure is hydrostatic.

To improve the model, from the free surface Navier-Stokes system, a first non-hydrostatic Saint-Venant system (pressure depends of the vertical acceleration) including friction and viscosity has been derived [41]. The interest of this model has been proved by comparison of numerical results with experiments.

Then we have considered the full Euler system with free surface (keeping all the terms related to vertical velocity). In a first step, we use the shallow water assumption and the associated small parameter ϵ that is the ratio between two typical characteristic lengths (horizontal and vertical) of the fluid domain. We obtain a single layer averaged system approximating the Euler system up to $\mathcal{O}(\epsilon^2)$ terms. Secondly, we drop the assumption $\epsilon \ll 1$ and we decompose the water height H into N layers with N possibly large. This means we have shallow layers instead of a global shallow water assumption. Using this multilayer approach, we derive a system approximating the Euler system up to $\mathcal{O}(1/N)$ terms. For the proposed model, we also give a kinetic type interpretation based on a Boltzmann transport coupled with a reaction term.

From this complex kinetic interpretation, a numerical scheme should be deduced leading to a free surface Euler solver for deep flows without a moving mesh to deal with.

6.3.5. Overland flows

Overland flows on agricultural soils induce problems of environmental resources preservation (decrease of soil thickness by erosion, nutrients losses, decrease in water quality). To improve watershed management, a good prediction of the surface flow network is needed.

For agricultural areas, empirical works showed that the interaction between furrows and topography strongly controls the geometry of the flow network: at low flux, overland flow follows the furrow direction, while, at high flux, overland flow follows the topographic slope too. We intend to model this type of flow in order to better understand and predict the effect of surface morphology on overland flow.

As a first step, we have compared numerical simulations with different friction terms (Darcy-Weisbach, Manning) to laboratory measurements. This example which has been developed at Inra (Orléans) concerns the overland flow due to some rain on a sloping channel with different roughnesses.

This work is a participation in the ANR project "METHODE" (url http://methode.netcipia.net).

7. Other Grants and Activities

7.1. Actions at region level

Participation in the GDR-CNRS "CHANT"(équations Cinétiques et Hyperboliques : Aspects Numériques, Théoriques, et de modélisation). (url http://chant.univ-rennes1.fr)

Participation in the GDR-CNRS "MABEM" (Modélisation mathématique en biologie et médecine) (url http://gdr-mabem.math.cnrs.fr)

Active ongoing collaboration with U 776 INSERM “Rythmes biologiques et cancers" (Francis Lévi, Villejuif). A work program INRIA-INSERM has begun, relying on 1 INSERM post-doc, 1 INRIA PhD student, 1 appliance (Lumicycle luminometer, Actimetrics Inc.) acquired by INRIA for use at INSERM U 776.

A Collaboration is going on with team 18 of the INSERM Unit 872 “Resistance and survival of tumour cells” (Centre des Cordeliers, Paris) and Département d’hémato-oncologie de l’Hôtel-Dieu (Jean-PierreMarie, Paris), on mathematical modelling for Acute Myeloblastic Leukaemia (AML) and its treatment.

We can also mention a collaboration on Trophoblast development with INRA (Isabelle Hue, Alain Trubuil, Juhui Wang) with a common Phd student (Chadha Chettaoui), starting collaborations with UPRES 4040 (Institut Gustave Roussy (IGR), Paris) on prediction of therapy using ultrasound imaging of blood perfusion and with the departments of Stem Cells & Development (Shahradim Taijbakhsh), of Molecular Genetics of Development (Margaret Buckingham) at the Institut Pasteur, Paris.

7.1.1. ANR TOPPAZ

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

TOPPAZ (Theory and Observations of Polymerization processes in Prion and Alzheimer diseases) is a 3-year (2009-2012) research project financed by ANR grant “programme blanc” and head 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 head by J. Zubelli) and a biophysicist team head by H. Rezaei.

It started in August 2009 by the project “PRION” in CEMRACS.

The general goal is to develop new mathematical and numerical tools for polymerization processes, in strong link with experimentalists and with direct application to experimental datas designed by the biologists team.

7.1.2. EDF-LNHE

A grant with EDF-LNHE (2009-2010) “Modélisation hydraulique des milieux naturels” has led to the simulation of free surface stratified flows (the density stratification being due to to temperature and/or salinity), taking into account the effect of wind ad upwelling phenomena. This work allows comparing the variable density multilayer code developed at INRIA with the rigid lid hydrostatic Navier-Stokes code of EDF.

7.2. European actions

7.2.1. NoE Biosim

Biosimulation,a new tool in drug development. J. Clairambault takes part with F. Lévi (INSERM U 776) in workpackage 13, *Modeling circadian drug effects in anti-cancer treatment*. Participation (J. Clairambault) in technical meetings of WP13 in Villejuif, Brussels and Berlin. Biosim has come to an end in October 2009.

7.2.2. Strep Tempo

Temporal genomics for tailored chronotherapeutics. (url http://www.chrono-tempo.org/) J. Clairambault is head of workpackage 2 *Integration and modeling*, which involves the Bang and Contraintes projects at INRIA and also the SME Physiomics PLC (Oxford). Participation of J. Clairambault and A. Ballesta at the concluding conference of Tempo in Paris (November 19-20). Tempo has come to an end in December 2009.

7.2.3. Submitted European projects

New European FP7 projects have recently been submitted, two with F. Lévi (Villejuif) and D. Rand (Warwick Systems Biology Centre) as coordinators, on systems biology for cancer and circadian clocks, another one with M. Kimmel (Warsaw) as coordinator, on modelling drug resistance in cancer therapies.

7.2.4. EU-project PASSPORT

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

7.2.5. EU-project CANCERSYS

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

7.3. International actions

Collaboration with South America (INRIA-CONICYT, Math. Am.Sud, France-Brésil) with IMPA (Rio de Janeiro, Brazil). The relations are old and include various aspects. Several conferences in mathematical biology have been organized in Rio di Janeiro with a participation of BANG. This has allowed close collaborations (with papers published) on the inverse problem in structure population modeling and on numerial schemes for diffusive conservation laws, with Concepción (Chile) a research axis on cross-diffusions has been launched.

Collaboration with South America (INRIA-CONICET, Math. Am.Sud) with the Mathematics Institute Beppo Levi (Rosario) and the Favoloro University (Buenos Aires), Argentina. A developmental model of the Optic Tectum in the chick embryo has been designed, presented at the 24th IFIP TC7 conference held in July 2009 in Buenos Aires, and a joint article (Verdes-Flores-Rapacioli-Rofman-Perthame-Clairambault) on this subject is in preparation.

German part of the BANG-group takes part in the Germany-wide network on the Systems Biology of the ”Hepatocyte” from which currently two PhD-students (S. Höhme and A. Krinner) are funded (collaboration with several partners in German network, particularly J.G. Hengstler, Leibniz Research Center, Dortmund, and R. Gebhardt, Univ. of Leipzig).

Key running collaborations 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 Max-Planck-Institute for ”Dynamik Komplexer Technischer Systeme” in Magdeburg, Germany on the modelling and optimization of cell growth in Vaccine production, with the Leibniz Research Center in Dortmund and the Biochemistry-department of the University of Leipzig on liver regeneration after drug-induced damage. Starting collaboration within the German Consortium on LungCancerSys (official confirmation of German ministry grant proposal acceptance expected in Jan. 2009). Some of the former collaborations are now continued within accepted EU projects. Papers are published, submitted and in preparation.

8. Dissemination

8.1. Scientific community

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

Organization of a weekly informal, interactive seminar by Marie Doumic-Jauffret, Dirk Drasdo and Irène Vignon-Clémentel (REO project-team). The seminar intends to bring people of those projects together that work on Biology-related topics (e.g. Bang, Contraintes, Gamma, Macs, Reo, Sisyphe) to gain a better understanding of each other's work, interset and expertise. Since biological problems are very complex and often require expertise on very different research fields we could in this way obtain feedback on state-of-art data analysis and modeling methods at the interface of our work to neighboring fields and eventually use the synergetic potential present in the different groups.

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

Supervision of Annabelle Ballesta's PhD thesis (since June 2007) by Jean Clairambault. Supervision of Chadha Chettaoui's PhD thesis (since September 2008) by Dirk Drasdo and Juhui Wang (INRA). Supervision of Nick Jagiella's PhD thesis (since July 2007) by Dirk Drasdo and Benoît Perthame. Supervision of Thomas Lepoutre's PhD thesis (September 2007-November 2009) by Jean Clairambault, Benoît Perthame and Stéphane Gaubert (Maxplus). Supervision of William Weens's PhD thesis (since September 2008) by Dirk Drasdo and Irène Vignon-Clémentel (REO project-team). Supervision of Houda Benjelloun's internship (September 2009-February 2010) by Jean Clairambault and Catherine Bonnet (DISCO future project-team). Supervision of Anne-Céline Boulanger's internship (February-March) by Dirk Drasdo and Irène Vignon-Clémentel (REO project-team). Supervision of Erwan Hingant's M2 internship (February-June 2008) by Jean Clairambault.

8.2. Scientific popularization

Annabelle Ballesta has designed entirely by herself a short on principles of mathematical modelling for cancer chronotherapeutics: "Soyez sympas, synchronisez !" that has been presented on different occasions to non specialized audiences, in particular in Lycées of the Paris region, but also to a "Fête de la Science" in November in Cité des Sciences, Paris.

Jean Clairambault has given a conference in March in the Lycée Talma (Brunoy, Essonne, France) on the subject "Des modèles mathématiques pour la médecine : représentation de processus biologiques et optimisation de traitements médicamenteux".

8.3. Teaching

1. Modélisation dans le domaine biomédical: Introduction à la biologie mathématique (Cours en 2e année dans le tronc commun "Physiologie et biotechnologies"). École Centrale de Paris (Chatenay-Malabry): 15 h; (Jean Clairambault)
2. M2 Pharmacology (Rennes 1): 3 h; (Jean Clairambault)
3. M2 Pharmacology & Cancerology (Paris XI): 2 h; (Jean Clairambault)
4. École Doctorale "Innovation thérapeutique" (Paris XI): 2 h; (Jean Clairambault)
5. M2, Mathematics ("Growth, reaction movement and diffusion from biology") (Paris VI): 8 h; (Dirk Drasdo)

8.4. Participation in congresses, workshops,...

- Perthame Benoît: Séminaire à l'université de Chicago (Etats Unis), janvier 2009
- Perthame Benoît: Minicours -adaptive dynamics, a population view-, Barcelone (Espagne), février 2009
- Perthame Benoît: Conférence à l'IHP sur la division cellulaire, Paris , mars 2009
- Perthame Benoît: Minicours -Turing instabilities, Turing patterns- Rio de Janeiro (Brésil) mars 2009
- Perthame Benoît: Distinguished Visitor Course "Cell communities selforganization", Bloomington (Etats Unis), avril 2009
- Perthame Benoît: Organisateur du workshop mathematical biology, Oberwolfach (Allemagne), 3-9 mai 2009
- Perthame Benoît: SMAI2009, plenary speaker, Nice (France), mai 2009
- Perthame Benoît: Séminaire, Barcelone (Espagne), juin 2009
- Perthame Benoît: Organisateur du workshop "selforganisation", Banff, juillet 2009
- Perthame Benoît: IMA Minneapolis Conference (Etats Unis), juillet 2009
- Perthame Benoît: Plenary speaker at French-Brazil meeting, Rio de Janeiro (Brésil), septembre 2009

- Perthame Benoît: Ciudad Real Prix SEMA, septembre 2009
- Perthame Benoît: Conference, Cornaldo (Italie), octobre 2009
- Perthame Benoît: SAMSI workshop, octobre 2009
- Perthame Benoît: Plenary speaker at ECM09 Conference Tunis (Tunisie), novembre 2009
- Perthame Benoît: International workshop on biomathematics ans biomechanics, Tozeur (Tunisie), 19-23 novembre 2009
- Perthame Benoît: "Darwin's legacy" conference , Lisbon (Portugal), novembre 2009
- Perthame Benoî : Minicours "Adaptive dynamics", Varsovie (Pologne), décembre 2009
- Clairambault Jean: Workshop "Recent developments in medical mathematics in cancerology: modelling and mathematical analysis", Marseille, February 2009
- Clairambault Jean: Journée sur la division cellulaire (V. Bansaye, organisateur), Institut Henri-Poincaré, Paris, March 2009
- Clairambault Jean: Workshop 'Mathematical methods and modelling of biophysical phenomena", Angra dos Reis, Brazil, March 2009
- Clairambault Jean: Workshop "Mathematical modelling in biology and medicine", Dubrovnik, April 2009
- Clairambault Jean: 2nd NIH-INRIA workshop, Rocquencourt, June 2009
- Clairambault Jean: XXIXe séminaire de la SFBT, Saint Flour, June 2009
- Clairambault Jean: Séminaire "Syndromes myéloprolifératifs" (J.-P. Marie et W. Vainchenker, organisateurs), Chantilly, June 2009
- Clairambault Jean: XIth Congress of the EBRS, Strasbourg, August 2009
- Clairambault Jean: Conférence aux élèves de 3e année du "Programme d'approfondissement de mathÂmatiques appliquÂes", École Polytechnique, Palaiseau, October 2009
- Clairambault Jean: Tempo final conference, Paris, November 2009
- Clairambault Jean: Workshop on biomathematics, Tozeur (Tunisia), November 2009
- Clairambault Jean: Entretiens du Centre Jacques Cartier "Santé et systèmes complexes", Lyon, November 2009
- Doumic-Jauffret Marie: Workshop on mathematical biology, Oberwolfach (Allemagne), 3-9 mai 2009
- Doumic-Jauffret Marie: CEMRACS, projet PRION, Luminy (France), 2-5 août 2009
- Doumic-Jauffret Marie: Workshop of ANR project ATLAS, Nice (France), 14-17 septembre 2009
- Doumic-Jauffret Marie: Workshop on mathematical biology, Bonn (Allamagne), 4-6 octobre 2009
- Doumic-Jauffret Marie: International workshop on biomathematics and biomechanics, Tozeur (Tunisie), 19-23 novembre 2009
- Doumic-Jauffret Marie: Séminaire modélisation mathématique et calcul scientifique, Université Lyon I (France), 1er décembre 2009
- Drasdo Dirk: Experimental Biology EB2009, New Orleans, April 2009 (invited speaker)
- Drasdo Dirk: v-tissue international expert workshop, Durham, USA, April 2009 (invited speaker)
- Drasdo Dirk: School on Cancer Systems Biology and Expert meeting, Rostock, June 2009 (invited speaker)
- Drasdo Dirk: NIH-INRIA meeting, Rocquencourt, June 2009
- Drasdo Dirk: Summer school: CEMRACS 2009, Mathematical modeling in medicine, Marseille, July 2009 (invited speaker)

- Drasdo Dirk: INRIA Colloquium, Paris, October 2009
- Drasdo Dirk: Other talks in German Cancer Center, Heidelberg; Institut Curie, Paris; Brussels
- Lepoutre Thomas: Advanced course on Mathematical Biology -Modeling and Differential Equations-, février 2009
- Lepoutre Thomas: Conference on Mathematical Biology -Modeling and Differential Equations-, février 2009
- Lepoutre Thomas: Workshop on mathematical biology, Oberwolfach (Allemagne), 3-9 mai 2009
- Lepoutre Thomas: Multiscale Analysis of Self-Organization in Biology, 12-17 juillet 2009
- Lepoutre Thomas: Présentation d'un poster à "Banff International Station for Mathematical Innovation and Discovery", Banff (Canada), juillet 2009
- Lepoutre Thomas: Participation au CEMRACS, Luminy (France), août 2009
- Lepoutre Thomas: Séminaire sur la diffusion croisée, Université Pierre et Marie Curie, juillet 2009
- Jagiella Nick: ANNUAL MEETING 2009 -"DEASE Summer School"-, Heraklion (Crete), mai 2009
  Titre de la présentation: Biomechanical versus nutrient control, what controls the growth kinetics of cell aggregates in-vitro and in-vivo?
- Jagiella Nick: Transatlantic Summer School "Cancer Systems Biology, Molecular Mechanisms and Mathematical Modelling", Rostock-Warnemuende, (Allemagne), juin 2009
  Présentation d'un poster en commun avec Weens William, Vignon-Clémentel Irène et Drasdo Dirk
- Ramis-Conde Ignacio: Transatlantic Summer School "CancerSystems Biology, Molecular Mechanisms and Mathematical Modelling", Rostock-Warnemuende, (Allamagne), juin 2009. Présentation d'un poster
- Ramis-Conde Ignacio: Workshop on multi-scale models of cell processes, -Invited Speaker-, Politecnico di Torino, Turin (Italie), mars 2009
- Ramis-Conde Ignacio: Multi-scale modelling of cell adhesion systems, -Invited speaker-, Dundee University (Ecosse), octobre 2009
- Pelanti Marica: SIAM Conference on Mathematical and Computational Issues in the Geosciences (Minisymposium on Well-balanced, stable, high order simulations of multi-layer, multi-phase shallow flows), Leipzig (Allemagne), 15-18 juin 2009
  Paper: "A Roe-type scheme for two-phase shallow granular flows over variable topography" (with F. Bouchut and A. Mangeney)
- Pelanti Marica: NumHyp2009, Conference on Numerical Approximations of Hyperbolic Systems with Source Terms and Applications, Castro-Urdiales (Espagne), 7-11 septembre 2009
  Paper: "A Multilayer Saint-Venant System with Varying Density" (with J. Sainte-Marie)
- Ballesta Annabelle: Séminaire de la Société Francophone de Chronobiologie, Aussois (France), mars 2009
- Ballesta Annabelle: Spring workshop on Mathematical Modelling in Biology and Medicine, Dubrovnik (Croatie), avril 2009
- Ballesta Annabelle: XXIXème séminaire de la SFBT. Démarches quantitatives, qualitatives et philosophiques en sciences du vivant, Saint-Flour (France), juin 2009
  Obtention du prix Delattre (meilleure présentation d'un doctorant)
- Ballesta Annabelle: 1^{e} journée de l'Institut des Technologies de la Santé, Paris, septembre 2009.
- Ballesta Annabelle: Séminaire Bio-maths de l'Université Lyon I, décembre 2009
- Chettaoui Chadha: GDR 3070 -Physique de la cellule au tissu, Sète (France)
  Présentation orale et poster

- Chettaoui Chadha: Séminaire au Max Planck Institute of Molecular Cell Biology and Genetics, Dresde (Allemagne)
  Présentation orale
- Chettaoui Chadha: Conference on Morphogenesis in Living Systems, Paris
- Audusse, E., *A Multilayer Saint-Venant System: Derivation and Numerical Validation*, 2009 SIAM Conference on Mathematical and Computational Issues in the Geosciences, Leipzig, june 2009.
- Audusse, E., Bristeau, M.O., Sainte-Marie, J. *A Multilayer Saint-Venant System with Mass Exchanges*, Conference "Numerical approximations of hyperbolic systems with source terms and applications", Castro-Urdiales, Spain, september 2009.
- Sainte-Marie Jacques: *From Saint-Venant to Navier-Stokes with variable density. Modeling, kinetic interpretation, simulations*, Séminaire Roberval, Université de Compiègne, january 2009.
- Sainte-Marie Jacques: Séminaire du Collège de France, march 2009.
- Sainte-Marie Jacques: Séminaire de calcul scientifique, INRIA, may 2009.
- Sainte-Marie Jacques: Séminaire UME, ENSTA, june 2009.
- Sainte-Marie Jacques: Séminaire MAPMO, Université d'Orléans, october 2009.
- Sainte-Marie Jacques: Séminaire de mathématiques, Université Paris-Sud, october 2009.
- Sainte-Marie Jacques: Séminaire ASCIOM, Université de Montpellier, november 2009.
- Sainte-Marie Jacques: *Le système de Saint-Venant, les équations de Navier-Stokes et le couplage hydrodynamique-biologie,* Séminaire du groupe de travail Maths-Bio, Université P. et M. Curie, Paris, november 2009.

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[3] S. TUMULURI. *Age-structured nonlinear renewal equation*, Université Pierre et Marie Curie, july 2009, Ph. D. Thesis.

Articles in International Peer-Reviewed Journal

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