INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

# *Project-Team Bang*

# *Biophysique, Analyse Numérique et Géophysique*

*Paris - Rocquencourt*

THEME NUM

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

# 1. Team

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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$^{th}$ 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 focusses 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 movments

This research activity aims at studying mathematical models related to tumors developments. Among the many biological aspects let us mention

- 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, population self-organization.

## 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

**Keywords:** *cancer treatments*, *individual medicine*, *pharmacokinetics-pharmacodynamics (PK-PD)*, *pharmacological control*, *physiologicall structured PDE*, *population dynamics*, *therapeutic optimization*.

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. It has in particular given rise to a CEA-EDF-INRIA school on cancer modelling, held in March 2008 in Rocquencourt (J. Clairambault and D. Drasdo organisers).

A new activity has recently emerged in this field, related to neurodegenerative disorders: modelling prion proliferation dynamics.

### *6.1.1. Cell division dynamics in structured cell populations*

**Participants:** Mostafa Adimy [Anubis project-team], Annabelle Ballesta, 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], Peter Kim [University of Utah, Salt Lake City], Thomas Lepoutre, Jean-Pierre Marie [INSERM Paris (Eq.18 de l'UMR 872) Hôtel-Dieu, Paris], Daniel Marin, 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 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 D. Marin's M2 internship in Spring, 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.* Starting from the *ARC INRIA ModLMC* (2006-2008), coordinated by M. Adimy (Anubis), 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). 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) has been studied with possible therapeutic implications (C. Bonnet, J. Clairambault, H. Özbay) in a conference paper that will be presented at the CDC conference in December 2008 in Cancun.

   This activity has also resulted in a workshop on haematopoiesis held in Paris in March 2008 (JC and J.-P. Marie organisers) and a review article on haematopoiesis modelling in the French journal *Hématologie*.
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 of the Mathematics Institute Beppo Levi (Rosario) and of

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 will be presented by V. Flores and E. Rofman at the 24th IFIP TC7 conference held in 2009 in Buenos Aires.

### *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], Herbert Gayrard, 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 pharlmacological) 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 and 2007, has been continued, resulting in an article published in the *IEEE-EMB Magazine* [11] and in another article accepted in *Mathematical Modelling of Natural Phenomena* [12], to which must be added another one submitted.
2. *Intracellular pharmacokinetic-pharmacodynamic (PK-PD) models for anticancer drugs* This activity takes place within the framework of the European projects BioSim and Tempo. New developments include a PK-PD model for 5FU+Leucovorin delivery (J. Clairambault, F. Lévi), 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, with S. Dulong in F. Lévi's laboratory), developed in collaboration with S. Soliman (Contraintes), both models having been presented in different conferences or workshops.
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 in the future drug delivery optimisation 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 has studied such a whole-body model, structured in compartmental ODEs, for Irinotecan, from infusion in the general circulation until its delivery in the intracellular medium.

### *6.1.3. Optimisation of cancer chemotherapy*

**Participants:** Annabelle Ballesta, Jean Clairambault, Jean-Charles Gilbert [ESTIME project-tean], Thomas Lepoutre, Francis Lévi [INSERM Villejuif (U 776)], Jean-Pierre Marie [INSERM Paris (Eq.18 de l'UMR 872) Hôtel-Dieu, Paris].

Optimising cancer chemotherapy, especially chronotherapy, is the final aim of the activities mentioned above. 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 big 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. Other resistance mechanisms, involving mutations of the drug target, are presently being considered, and will be developed by participants to the international workshop on *PK-PD of anticancer drugs: resistances and synergies*, held in December 2008 in Paris (co-organised by J. Clairambault and J.-P. Marie).

Using actual optimisation algorithms has been done in the past: articles of 2005 and 2007, plus a recent article in the *Phil .Trans. Roy. Soc. A* [19], but was at a standstill until recently. This activity is being revived by the submission of the *ARC INRIA Cantheroptim* proposal, coordinated by J.-C. Gilbert (Estime), involving members of the Bang project-team of other teams of applied mathematicians (V. Volpert, M. Adimy), and also of teams of oncologists (F. Lévi, J.-P. Marie).

### *6.1.4. Prion proliferation dynamics*

**Participants:** Vincent Calvez, Marie Domic-Jauffret, Pierre Gabriel, Tierry 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 lead to two articles (1 in press, 1 submitted). 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) and its inverse problem (see [17]).

### *6.1.5. Inverse problem in structured populations and fragmentation equations*

**Participants:** Marie Doumic-Jauffret, Pedro Maia [IMPA, Brazil], Benoît Perthame, J. Zubelli [IMPA, Brazil].

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. The comparison of various algorithms and their convergence analysis has been investigated, and has lead to an article currently under revision [17].

During his internship, P. Maia has applied these numerical methods to experimental data coming from a biological article (Kubitschek, 1969). All the analysed experimental data lead to an increasing convex birth rate ; these results will be published in the Edinburgh SMTB 08 proceedings and has yet to be discussed and interpreted by biologists.

Moreover, 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.

## 6.2. Tissue growth, regeneration and cell movment

### *6.2.1. Single-cell-based models of tumor growth and tissue regeneration and embryonic development*

**Keywords:** *biotechnological growth processes*, *cellular automaton models (CA)*, *early morphogenesis*, *growth dynamics*, *individual cell based models (IBM)*, *liver regeneration*, *multi-scale analysis*, *vaccine production*.

**Participants:** Margaret Buckingham [Institut Pasteur], Helen Byrne [Univ. of Nottingham, UK], Chadha Chattaoui, 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, Udo Reichl [Max-Planck-Institute, Magdeburg, Germany], Ignacio Ramis-Conde, Alain Roche [Institut Gustave Roussy], Shahragim Tajbakhsh [Institut Pasteur], Gerik Scheuermann [Univ. of Leipzig, Germany], Eckehard Schöll [Technical Univ. of Berlin, Germany], Luc Soler [ IRCAD, Coordinator EU-project PASSPORT], Alain Trubuil [INRA], Irene Vignon-Clementel [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.

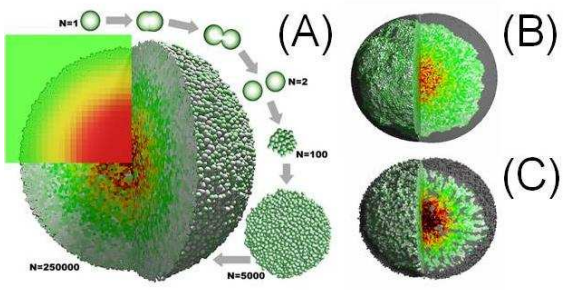


*Figure 1.* SIMULATED TUMOR GROWTH IN (A) LIQUID AND (B, C) GRANULAR MEDIUM. FOR SMALL MOBILITY OF THE GRANULAR PARTICLES, FINGER-LIKE STRUCTURES FORM (C). COMPUTER SIMULATION PREDICT THAT IF CO-CULTURES ARE CONSIDERED BY REPLACING THE GRANULAR MEDIUM IS BY A SECOND CELL LINE, THE RESULTS DO NOT CHANGE AS LONG AS THE CELLS DO NOT CHANGE THEIR BEHAVIOR AS A CONSEQUENCE OF REGULATION OR MULTATIONS.

In order to fill the existing gap have studied intracellular regulation networks [49], [43], multi-scale IBMs where intracellular regulation and differentiation was explicitly represented within each individual cell [23], [18], lattice-free IBMs [41] and continuum models that can capture their large scale behavior [9], and cellular automaton (CA) models [34] and their corresponding continuum equation [40].
Besides the methodical aspects we focus on a number of applications:

- unstructured cell populations growing in monolayer [41], [44].
- multicellular spheroids [41], [42] (Fig. 1)
- biotechnological applications such as the optimization of cell yield of MDCK-cells for vaccine production.
- complex tissue architectures in regenerative tissues such as the regeneration of liver lobules after toxic damage [46], [26] (Fig. 2; within the German BMBF-funded network ”Systems Biology of the Hepatocyte”).
- 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 [51], and developed an image processing chain to quanitatively analyze liver regeneration processes in liver lobules [26].

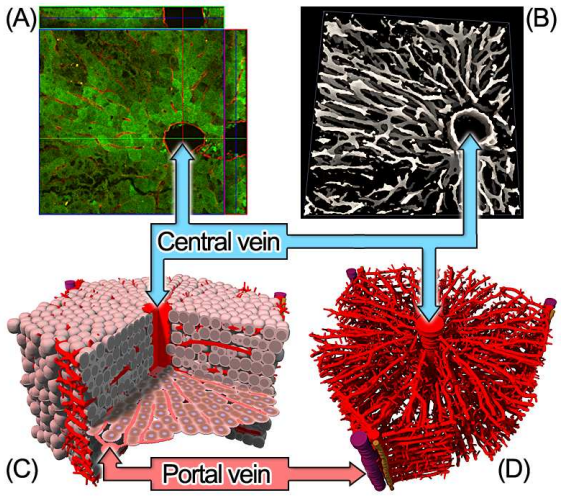


*Figure 2.* FROM TISSUE SECTION TO COMPUTER SIMULATION FOR LIVER LOBULES, THE REPETETIVE FUNCTIONAL SUBUNITS OF LIVER: (A) LIVER CELLS AROUND A CENTRAL VEIN UNDER A CONFOCAL MICROSCOPE. (B) VISUALISATION OF THE SINUSOIDS (MICRO-VESSELS). (C) SECTION OF A LIVER LOBULE IN THE COMPUTER SIMULATION WITH HEPATOCYTES (PINK) AND SINOSOIDAL STRUCTURE (RED). (D) SINUSOIDAL NETWORK.

Current and future directions include a stronger focus on models of in-vivo systems (within the German medical systems biology consortium "LungSys"; in collaboration which Institut Gustave Roussy, and within the EU-network "CancerSys") requires to take into account invasion, mutations and angiogenesis, three hallmarks of cancer and of linking the molecular to the multicellular scale. 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; starting collaboration with Institut Pasteur).

### 6.2.2. Chemotaxis and cell movement

**Keywords:** *biophysics*, *cancer modeling*, *chemotaxis*, *finite element*, *numerical algorithm*, *numerical software*, *reaction-diffusion models*.

**Participants:** Vincent Calvez, Thomas Lepoutre, Americo Marrocco, Benoît Perthame.

Movement of cells are important in various aspects of medical sciences and biology such as cancer development. We have developed some activity in the understanding of mathematical models of chemotaxis and in numerical simulation of bacterial colony growth (see [50] for a general presentation). Several results concerning blow-up and existence of solutions have been presented in [35] [36] [38] [33].

Models of cell movement were proposed by Keller-Segel several years ago, as coupled parabolic/elliptic systems. They describe the collective motion of bacteria taking into account the underlying biochemistry (chemotaxis). These models are defined by two partial differential equations, one for the bacterial density and one for the attractant concentration.

This system of equations is very similar to the drift-diffusion model for the (unipolar) semiconductor devices, so for the numerical simulation of bacteria aggregation, a new formulation has been derived by the introduction of an unknown variable which is called quasi-Fermi level in the semiconductor framework. This method allows us to adapt to the case of Keller-Segel system the discretization approach and the numerical schemes developped for the semiconductors.

Keller-Segel models taking also into account stimulant concentration have been studied numerically in the past years. More recently we have also investigated a mathematical model in which two types of bacteria are considered for the development of branching patterns. The Mimura model [48] appears to be specially well adapted for the colonial branching patterns developped by *Bacillus Subtilis* type of bacteria. In this model the unknown functions are the density of active bacteria, the density of inactive bacteria (or *"spores"*) and the concentration of nutrients. Various numerical experiences have been reported on [47]
Extended models taking into account active and inactive bacteria together with chemoattractant and chemorepellent have been developped and tested numerically during the ANR-project MACBAC (ended this year).
The theoretical analysis has been oriented to hyperbolic models [14], parabolic models [13], kinetic models [7], and existence of travelling waves [20]. Biomotors have also motivated theoretical papers [24] [25].

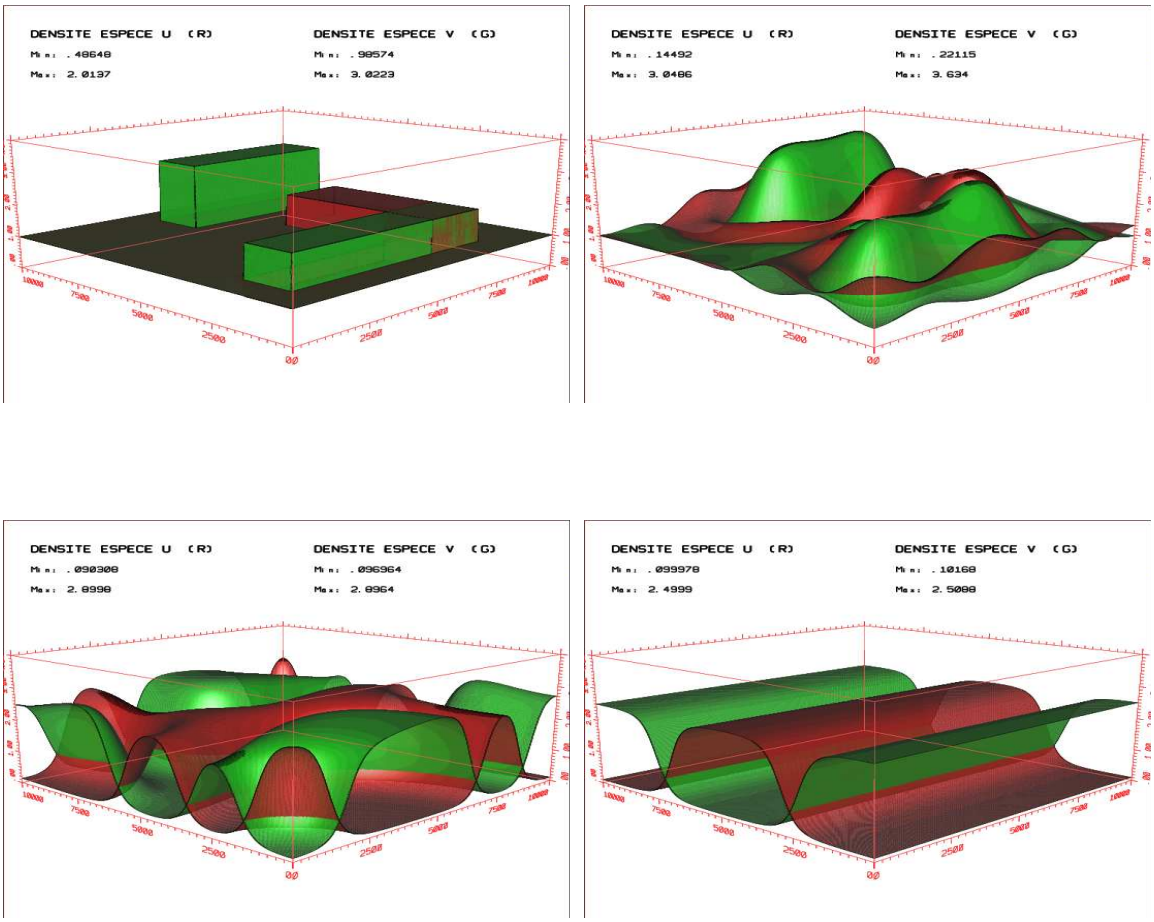


*Figure 3.*

3D VIEW OF THE DISTRIBUTIONS U AND V, ( $\delta$ 2 =0.001)
UPPER LEFT: VERY CLOSE TO THE INITIAL STATE, UPPER RIGHT: DISTRIBUTION AT T=0.0035
LOWER LEFT: DISTRIBUTION AT T= 0.084 LOWER RIGHT: STATIONNARY STATE .

This year we have also investigated a mathematical model of cross-diffusion in which two species are in competition. For the numerical applications we have considered a relaxation model of cross-diffusion given by the following equations

$$\frac{\partial u}{\partial t} - \Delta[u(1+\widetilde{v}^2)] = 0, \qquad \frac{\partial v}{\partial t} - \Delta[v(1+\widetilde{u}^2)] = 0$$

$$-\delta^2\Delta\widetilde{u} + \widetilde{u} = u, \qquad -\delta^2\Delta\widetilde{v} + \widetilde{v} = v$$

with homogeneous Neumann boundary conditions on $u, v, \widetilde{u}, \widetilde{v}$ and initial conditions $u^0$ and $v^0$. It is rather intuitive that for "large $\delta$" diffusion is dominant, this is also the case for small initial data. Therefore the appearence of patterns depends upon a relation between the average densities of population $u$ and $v$ and the parameter $\delta$. If $\delta$ is sufficiently large, $u$ and $v$ tend to the stationnary solution $u \equiv < u^0 >$, $v \equiv < v^0 >$ (mean values of the initial states). For smaller $\delta$, patterns appear, as we can see on fig.(3)

## 6.3. Free surface geophysical flows

**Keywords:** *Boussinesq system*, *Geophysical flows*, *Saint-Venant equations*, *free surface flows*, *multilayer system*, *overland flows*.

**Participants:** Emmanuel Audusse [Université Paris 13, Institut Galilée], Marie-Odile Bristeau, 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...

The basic model for these problems is the 3D free surface Navier-Stokes system leading to a 3D solver [39] with a moving mesh. However for efficiency reasons, vertically averaged models such as the Saint-Venant system [45] are often used.

We have developped some extensions of the Saint-Venant system where the basic Saint-Venant solver [32] 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 by omitting one of the assumptions of the Saint-Venant model:
- With the multilayer systems, we recover a vertical profile of the velocities.
- A non-hydrostatic pressure gives Boussinesq type models.

### *6.3.1. Multilayer Saint-Venant system*

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 [4] 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.

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 (see Fig.4).

We have studied the derivation of this model, its main properties (hyperbolicity, energy equality, kinetic interpretation,...) and proved its validity through numerical simulations. The basic tool remains the Saint-Venant solver [32], [31] with a kinetic scheme and an hydrostatic reconstruction to take into account the bottom topography.

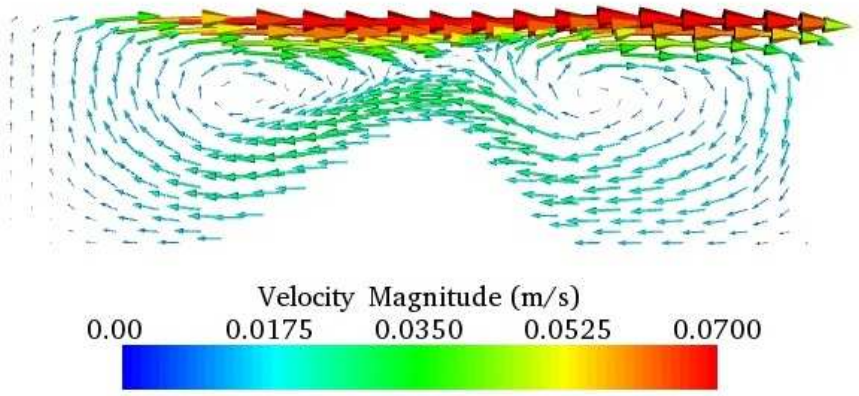


*Figure 4. Wind effect on a lake with varying bottom.*

We are now working on the introduction of a variable density (related to salinity or temperature) in order to simulate stratifications and upwelling phenomena with this type of models.

### *6.3.2. Derivation of a non-hydrostatic shallow water model*

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, we derive a non-hydrostatic Saint-Venant system (pressure depends of the vertical acceleration) including friction and viscosity. The derivation leads to two formulations of growing complexity depending on the level of approximation chosen for the fluid pressure [8]. The obtained models are compared with the Boussinesq models.

The interest of the model is proved by comparaison of numerical results with experiments.

It is also possible to couple this approximation with the multilayer discretization.

### *6.3.3. 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.

We have justified how to introduce the rain in the Saint-Venant model. As a mean rain on a sloping plane induces a very small water depth ( $10^{-4}$m), an accurate Saint-Venant solver (2nd order in space and time) is strictly necessary. As a first step, we have compared numerical simulations with different friction terms (Darcy-Weisbach, Manning) to laboratory measurements. This example which has been developped at Inra (Orléans) concerns the overland flow due to some rain on a sloping channel with different roughnesses.

This work is a participation to the ANR project “METHODE” (url http://methode.netcipia.net).

# 7. Other Grants and Activities

## 7.1. Actions at region level

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

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

Participation to the ANR project “METHODE”(Modélisation de l’Ecoulement sur une Topographie avec des Hétérogénéités Orientées et des Différences d’Echelles) in collaboration with Orléans University, INRA, BRGM, CERMICS. (url http://methode.netcipia.net)

The main part of the work concerning the free surface flows is done in collaboration with EDF/LNHE and Saint-Venant Laboratory. A grant with EDF/LNHE is to be signed at the beginning of 2009 for the support of a post-doctoral position.

ENS-DMA and Bang project-team take part to the ANR project *MACBAC* (Analyse multidisciplinaire du processus de colonisation de surface par les bactéries: surfactine, migration, formation des profils) managed by S. Seror at the *Institut de génétique et microbiologie* -Université de Paris Sud.

The collaboration with Stéphane Gaubert (Maxplus INRIA project-team) initiated with Emilio Seijo Solis’s INRIA internship (common between Bang and Maxplus) has been continued by a M2 (Paris VI) internship followed by a PhD thesis supervised between Bang and Maxplus, and to a joint article, published in the Comptes Rendus (Mathématique) de l’Académie des Sciences (Paris) [37]. Other projects on the theme of control of the PDE system under study are under consideration.

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. This apparatus will allow for measurements of parameters of the models under study, the variables of which are concentrations of proteins: determinants of cell cycle control, of molecular circadian clocks and of cell processing enzymes for cytotoxic drugs.

A Collaboration is beginning with the Département d’hémato-oncologie de l’Hôtel-Dieu (Jean-Pierre Marie, Paris), on the themes of the ARC INRIA ModLMC. A 2-day workshop has been organised in Paris in March 2008 on mathematical methods for the modelling of haematopoiesis and its disorders, jointly with the yearly conference of the Société Française d’Hématologie.

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. ARC INRIA ModLMC*

(url http://www.math.u-bordeaux1.fr/~adimy/modlmc/) Two plenary meetings have been organised (Bordeaux, February, Paris, May) by Mostafa Adimy (Bordeaux) with the participation of mathematicians (in particular of the Bang project-team) and haematologists from Lyon and Bordeaux, and will be continued. Among other achievements, this action has led to the organisation of a workshop on haematopoiesis modelling.

## 7.2. European actions

### *7.2.1. RTN network M3CS-TuTh*

Participation to the european network M3CS-TuTh (Modelling, Mathematical Methods and Computer Simulation of Tumour Growth and Therapy). (url http://calvino.polito.it/~mcrtn). Ended in may 2008.

### *7.2.2. 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.

### *7.2.3. 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 two SMEs, Helios Biosciences (Créteil) and Physiomics PLC (Oxford). Participation of J. Clairambault at the first plenary meeting in Rome.
The Contraintes team (S. Soliman) has taken an active part in helping Luna Dimitrio build a PK-PD model of Irinotecan intracellular action. The model development, continued in Annabelle Ballesta's PhD thesis, is now extended from Scilab programming to modelling in Biocham thanks to this collaboration. Other collaboration projects are being considered, and the Contraintes project (S. Krishnamachari) has been in particular associated to the CEA-EDF-INRIA Cancer Modelling School (url http://www.inria.fr/actualites/colloques/cea-edf-inria/2008/models-cancer/info.en.html) organised in March 2008 in Rocquencourt.

### *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 Conception (Chili) a research axis on cross-diffusions has been launched.

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 (Jean Clairambault and Dirk Drasdo) of a CEA-EDF-INRIA School on cancer modelling, ' "Models of cancer and its therapeutic control: from molecules to the organism" (INRIA-Rocquencourt, March 2008).

"PK-PD of anticancer drugs: resistances and synergies", international workshop, Paris, december 18-19, 2008, (organisers: Jean-Pierre Marie (Paris) and Jean Clairambault).

Haematopoiesis and its disorders. Modelling, experimental and clinical approaches. ModLMC international workshop, Paris, march 20-21, 2008, (organisers: Mostafa Adimy (Bordeaux), Fabien Crauste (Lyon), Jean-Pierre Marie (Paris), Jean Clairambault)

Organization of a weekly informal, interactive seminar by Marie Doumic-Jauffret, Dirk Drasdo and Irene Vignon-Clementel (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.

Supervision of Herbert Gayrard's M2 internship (March-July 2008) by Jean Clairambault. Supervision of Daniel Marin's M2 internship (February-June 2008) by Jean Clairambault and Stéphane Gaubert (Maxplus prject-team). Supervision of Annabelle Ballesta's PhD thesis (since June 2007) by Jean Clairambault. Supervision of Chadah 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 (since September 2007) by Jean Clairambault, Benoît Perthame and Stéphane Gaubert (Maxplus). Supervision of William Weens's PhD thesis (since September 2008) by Dirk Drasdo and Irene Vignon-Clementel (REO project-team).

## 8.2. 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 Pharmacoly & Cancerology (Paris XI): 2 h; (Jean Clairambault)
3. École Doctorale "Innovation thérapeutique" (Paris XI): 2 h; (Jean Clairambault)
4. M2, Mathematics ("Growth, reaction movement and diffusion from biology") (Paris VI): 8 h; (Dirk Drasdo)

## 8.3. Participation to congresses, workshops,...

- Clairambault, J. Towards optimisation of cancer chronotherapeutics by taking into account patient-specific constraints: mathematical models for individualised medicine. Invited speaker at *Conférence du réseau européen (STREP) PROUST "Genes at work on time"*, Turin, october 2008.
- Clairambault, J. Modelling combined chronotherapeutic delivery of 5-fluorouracil and Leucovorin. Communication at *4th BioSim conference*, Budapest, september 2008.
- Bekkal Brikci, F. , Clairambault, J., Doumic-Jauffret, M., Gaubert, S., Lepoutre, T., Michel, P., Mischler, S., Perthame, B. The continuing story of circadian rhythm and tumour growth. Communication at $7^e$ *conférence internationale de l'European Society for Mathematical and Theoretical Biology (ESMTB)*, Edimbourg, july 2008.
- Clairambault, J., Modelling to optimise cancer chemotherapy, in particular circadian chronotherapy. Communication at $7^e$ *conférence internationale de l'European Society for Mathematical and Theoretical Biology (ESMTB)*, Edimbourg, july 2008.

- Clairambault, J. Modélisation mathématique de la prolifération cellulaire et de son contrôle : signification médicale / Giving medical sense to mathematical modelling of cell proliferation and its control. Communication at premières rencontres CRM-INRIA-MITACS, Montréal, may 2008.
- Clairambault, J. Optimisation thérapeutique en cancérologie : position des problèmes et quelques réalisations. Communication at Séminaire du GT Commande Optimale, CMAP, Palaiseau, february 2008.
- Clairambault, J. Modélisation de la prolifération cellulaire et de son contrôle physiologique et pharmacologique. Communication at Séminaire *Monolix*, Orsay, january 2008.
- Clairambault, J. Giving medical sense to mathematical modelling of cell proliferation and its control. Communication at Séminaire IRMAR, Rennes, novembre 2007 et à l'*International Conference and Workshop on Mathematical Biology*, Marrakech, january 2008.
- Drasdo, D. Multiscale approaches in cell mechanics, (Invited lecture), Autrans/Grenoble, France, january 2008.
- Drasdo, D. CMBBE 2008, Porto, Portugal, february-march 2008.
- Drasdo, D. Workshop on systems biology, (Invited lecture), Barcelona, Spain, april 2008.
- Drasdo, D. CRM INRIA MITTACS-MEETING, School, (invited lecture), Montreal, Canada, may 2008.
- Drasdo, D. Workshop on "Cancer Angiogénèse et Outils mathématiques",(Invited lecture), Paris june 2008.
- Drasdo, D. Meeting on the GRASB (Grand Action Plan for Systems Biology: Implementation of the recommendations of the Forward Look on Systems Biology),(Invited lecture) Amsterdam
- Drasdo, D. (World conference on Computational Mechanics, ECCOMAS08 Venice, Italy, -june-july 2008.
- Drasdo, D. Organization of a minisymposium "Cells based models in biology and medicine" Edinburgh, UK (ECMTB 2008), july 2008.
- Drasdo, D. Euro EvoDevo, (Invited lecture), Ghent, Belgium july-august 2008.
- Drasdo, D. (9th International Conference on Systems Biology, (Invited lecture),Gothenburg, august 2008.
- Drasdo, D. Galderma meeting,(Invited lecture), Nice, France, october 2008.
- Drasdo, D. ICT-Bio 2008, (Invited lecture), Brussels, Belgium, october 2008
- Drasdo, D. (workshop on Hepatocyte regeneration, Freiburg, Germany, october 2008.
- Drasdo, D. MPG/CNRS Workshop on Systems Biology (Invited lecture), Grenoble, november 2008.
- Doumic-Jauffret, M. "Multiscale approaches in cell mechanics" Conference, Autrans, january 2008.
- Doumic-Jauffret, M. Workshop of numerical analysis of T. Colin in Bordeaux, march 2008.
- Doumic-Jauffret, M. Journées de Metz 2008, april 2008.
- Doumic-Jauffret, M. CancerSim2008, Torino, Italy, may 2008.
- Doumic-Jauffret, M. ECMTB08: organization with J. Zubelli of a mini-symposium on "Inverse problems for growth models", Edinburg, july 2008.
- Jagiella, N. ECMTB 2008, july 2008.
- Perthame, B. Seminar Northwestern univ. (February 2008).
- Perthame, B. Conf. on Nonlinear PDEs , Haifa (march 2008, speaker).
- Perthame, B. BIRS workshop on nonlocal PDEs (April 2008, BANFF, Canada).
- Perthame, B. Carnegie-Mellon University (may 2008, short course).
- Perthame, B. Hyp2008 (june 2008, plenary speaker).

- Perthame, B. Conf. Hyperbolic PDEs Oslo (august 2008, speaker).
- Perthame, B. Escuola J.-L. Lions, Valladolid (short course, sept. 2008).
- Perthame, B. Zurich Math Colloquirium (october 2008).
- Perthame, B. Tokyo-France LIA meeting (nov. 2008, speaker).
- Perthame, B. ICCPDE08 Bombay (dec. 2008, plenary speaker).
- Ramis-Conde, I. ECMTB 2008, july 2008.

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## Major publications by the team in recent years

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[2] B. PERTHAME. *Transport equations in biology*, Frontiers in Mathematics, Birkhäuser Verlag, 2007.

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## Year Publications

### Articles in International Peer-Reviewed Journal

[4] E. AUDUSSE, M.-O. BRISTEAU, A. DECOENE. *Numerical simulations of 3D free surface flows by a multilayer Saint-Venant model*, in "International Journal for Numerical Methods in Fluids", doi:10.1002/fld.1534, vol. 56, 2008, p. 331-350.

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[6] F. BEKKAL-BRIKCI, J. CLAIRAMBAULT, B. RIBBA, B. PERTHAME. *An age-and-cyclin-structured cell population model for healthy and tumoral tissues.*, in "Journal of Mathematical Biology", vol. 57, n$^{o}$ 1, 2008, p. 91-110.

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