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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1. Team

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

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2. Overall Objectives

2.1. Introduction

BANG (Biophysique, Analyse Numérique et Géophysique) is a continuation of the former project M3N. It aims at developing models and numerical methods for two kinds of problems involving Partial Differential Equations. Firstly problems from life sciences (cell movement, tissue growth, 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.

2.2. Highlights of the year

- Bang is preparing a CEA-EDF-INRIA school on cancer modeling.
- B. Perthame has been hired as a senior member of IUF.

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 XIXth 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: GAMMA, REO.

4.2. Tissue growth and cell movment

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

- cell movments (chemotaxis, vasculogenesis, angiogenesis),
- cell cycle, immune reaction and adaptive dynamics (structured population dynamics),
- modelling and optimization of chemotherapy through differential systems,
- tissue growth and regeneration, and biomechanical aspects of cell interaction, migration and growth control.

4.3. Free surface flows

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

4.4. Semiconductors

Mathematical models based on drift-diffusion systems or energy transport systems are solved using mixed finite elements methods. BANG has developed a highly sophisticated code which is able to simulate very stiff semiconductor devices.

5. Software

5.1. Introduction

Softwares initiated and developped within former projects (Menusin, M3N) and currently in use in the present project.

5.2. OPTMTR

Generation of metric maps for use with *adapted meshes* generator (with Gamma project)

5.3. EMC2

Interactive 2D mesh generator (with Gamma project)

5.4. HET_2D

Participants: Americo Marrocco [correspondant], Philippe Montarnal [Former PhD student M3N], Abderrazzak El Boukili [Former PhD student M3N], Frédéric Hecht [LAN, Université Paris 6.], Jean-Christophe Rioual [Former PhD student, CERFACS].

Research software for the numerical simulation of semiconductor devices. Drift-Diffusion and Energy-Transport models are implemented. The mathematical formulation is described using as unknowns the electrostatic potential, the quasi Fermi levels and additionaly the electron temperature. The approximation is carried out via mixed finite elements (Raviart-Thomas element RT_0). Parallel computation via domain decomposition is available for some modules and an interface with the **Bamg** software (Gamma project) has been developped for automatic mesh adaption.

5.5. 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. Tissue growth and cell movment

Keywords: *cancer chronotherapy*, *cancer modeling*, *cell population*, *differential equations*, *liver regeneration*, *numerical algorithm*, *optimal control*.

6.1.1. Dynamics of age-and-cyclin structured cell populations; applications to cell cycle modelling:

Participants: Annabelle Ballesta, Jean Clairambault, Luna Dimitrio, Marie Doumic-Jauffret, François Fages [Contraintes project-team], Stéphane Gaubert [MaxPlus project-team], Sriram Krishnamachari [Contraintes project-team], Thomas Lepoutre, Philippe Michel [Ecole Centrale Lyon], Benoit Perthame, Sylvain Soliman [Contraintes project-team].

- **Circadian rhythm and tumour growth in a 1- to 4-phase cell cycle model.**

  The work initiated in 2003 by the design of a model of the cell cycle and its circadian control [40] has been continued by another Note to the Academy of Sciences (Paris) in close collaboration with Stéphane Gaubert (Maxplus project-team)[17]. In this Note it is shown that the main result, comparing Perron and Floquet eigenvalues, published in a previous Note of 2006, can be generalized by using a particular (both arithmetic and geometric) mean for the constant coefficients of the system of PDEs in the Perron case.

  Emilio Seijo Solis has concluded his INRIA internship in February on a fast algorithmic estimation of the Perron and Floquet eigenvalues in a model of the cell cycle with 1 to 3 phases and periodic control of phase transitions and transmitted it to Thomas Lepoutre, who has studied it especially in the 1-phase case during his M2 (Paris VI) internship in Bang (February-June) and the beginning of his PhD thesis (from September on). A “devil’s staircase” phenomenon relating the Floquet eigenvalue to the duration of the cell cycle time has been disclosed and is under study (joint work with Stéphane Gaubert, Maxplus).

- **Quiescent and proliferative phase cell cycle models for healthy and tumoral tissues**

  The work initiated during Fadia Bekkal Brikci’s postdoc stay at INRIA [35] has been continued and has led to 2 articles (one published, one submitted) with Fadia Bekkal Brikci as first author, and another one by Marie Doumic-Jauffret , accepted [18]. In these articles are in particular studied the asymptotic properties of the age- and cyclin-structured PDE model used, together with existence and uniqueness theorems on the Perron eigenvalue.

6.1.2. Pharmacokinetic-pharmacodynamic (PK-PD) modelling for anticancer therapy

Participants: Jean Clairambault, Luna Dimitrio, Francis Levi [INSERM U776, Hospital Paul-Brousse, Villejuif].

PK-PD modelling at the molecular level of anticancer therapy by Oxaliplatin (presented in various workshops and seminars) has been extended to the representation of the action of the cytotoxic drug Irinotecan within the Tempo (FP6) European project, and 5FluoroUracil is planned to be added (work also led within WP13 of the BioSim European project).

Luna Dimitrio's M2 (Paris VI) internship has led to the production of a model of intracellular action of Irinotecan for the Tempo project [30].

These PK-PD systems of ODEs are meant to represent averaged (the mean molecular concentrations being taken over all cells) but dynamic control by anticancer drugs at the cell population level of progression in the cell division cycle. The targets of these drugs are phase transition rates (cyclin-CDK dimers), death rates inside phases, and progression speeds in the phases, dependent on the structure variables age and cyclin content, w. r. to time, in the age- and cyclin-structured PDE models that are studied independently.

6.1.3. Inverse problem in structured populations

Participants: Marie Doumic-Jauffret, Benoit 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 is under investigation.

6.1.4. Single-cell-based models of tumor growth and tissue regeneration

Participants: Helen Byrne [Univ. of Nottingham, UK], Mark Chaplain [Univ. of Dundee, UK], Dirk Drasdo, Rolf Gebhardt [Univ. of Leipzig, Germany], Jan G. Hengstler [Leibniz Research Center, Dortmund, Germany], Stefan Höhme, Nick Jagiella, Axel Krinner, Benoit Perthame, Udo Reichl [Max-Planck-Institute, Magdeburg, Germany], Gerik Scheuermann [Univ. of Leipzig, Germany], Eckehard Schöll [Technical Univ. of Berlin, Germany].

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. In order to bridge the existing gap have studied different approaches: intracellular regulation networks [49], [45], lattice-free IBMs [19], cellular automaton (CA) models [11], continuum models [43].

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

- unstructured cell populations growing in monolayer [19], [46] (Fig. 1).
- multicellular spheroids [19], [44] (Fig. 2)
- 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 [20] (within the German BMBF-funded network "Systems Biology of the Hepatocyte".

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 this later to predict and optimize therapy or biotechnological growth processes.

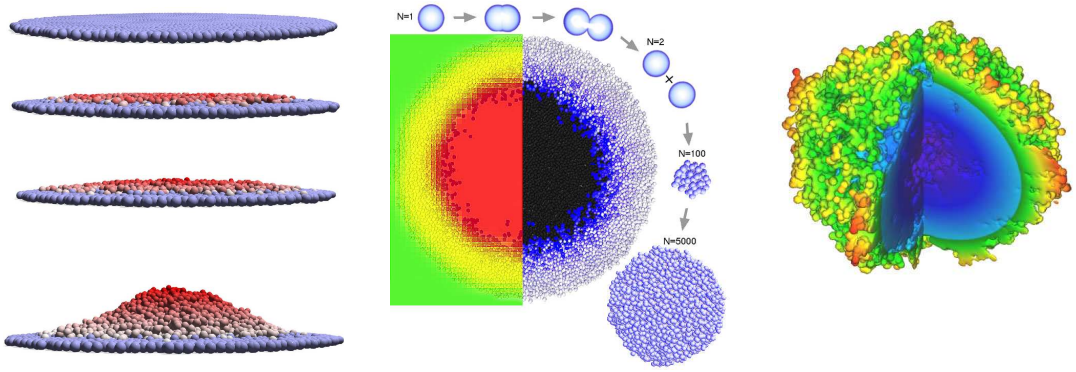

Figure 1.

Left: DIFFERENT GROWTH PHENOTYPES OF MONOLAYERS DEPENDING ON THE PRESENCE OF GROWTH CONTROL MECHANISMS. FROM THE UPPER TO THE LOWER PICTURE, CONTACT INHIBITION OF GROWTH, ANCHORAGE-DEPENDENT CONTROL OF CELL PROLIFERATION, AND ANCHORAGE-DEPENDENT CONTROL OF CELL DEATH ARE SUCCESSIVELY KNOCKED OUT.
Middle: GROWTH SCENARIO OF A MULTI-CELLULAR SPHEROID IN LIQUID SUSPENSION (COLORS: GREEN: HIGH, YELLOW: MEDIUM, AND BLACK: LOW NUTRIENT CONCENTRATION; WHITE: HIGH CELL DIVISION FREQUENCY, BLUE: MEDIUM CELL DIVISION FREQUENCY, BLACK: NO CELL DIVISION).
Right: MULTI-CELLULAR SPHEROID GROWN IN AN ENVIRONMENT OF OTHER CELLS. THE SURFACE IS MUCH ROUGHER. THE COLOR DENOTES THE DISTANCE FROM THE CENTER OF THE SPHEROID.

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 [28].

Current and future directions include a stronger focus on models of in-vivo systems which requires to take into account invasion, mutations and angiogenesis, three hallmarks of cancer and of linking the molecular to the multicellular scale.

6.1.5. Chemotaxis and cell movement

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

Participants: Vincent Calvez, Americo Marrocco, Neijla Nouaili, Benoit Perthame, Hatem Zaag.

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 [5] for a general presentation). Several results concerning blow-up and existence of solutions have been presented in [38] [39] [41] [36].

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.

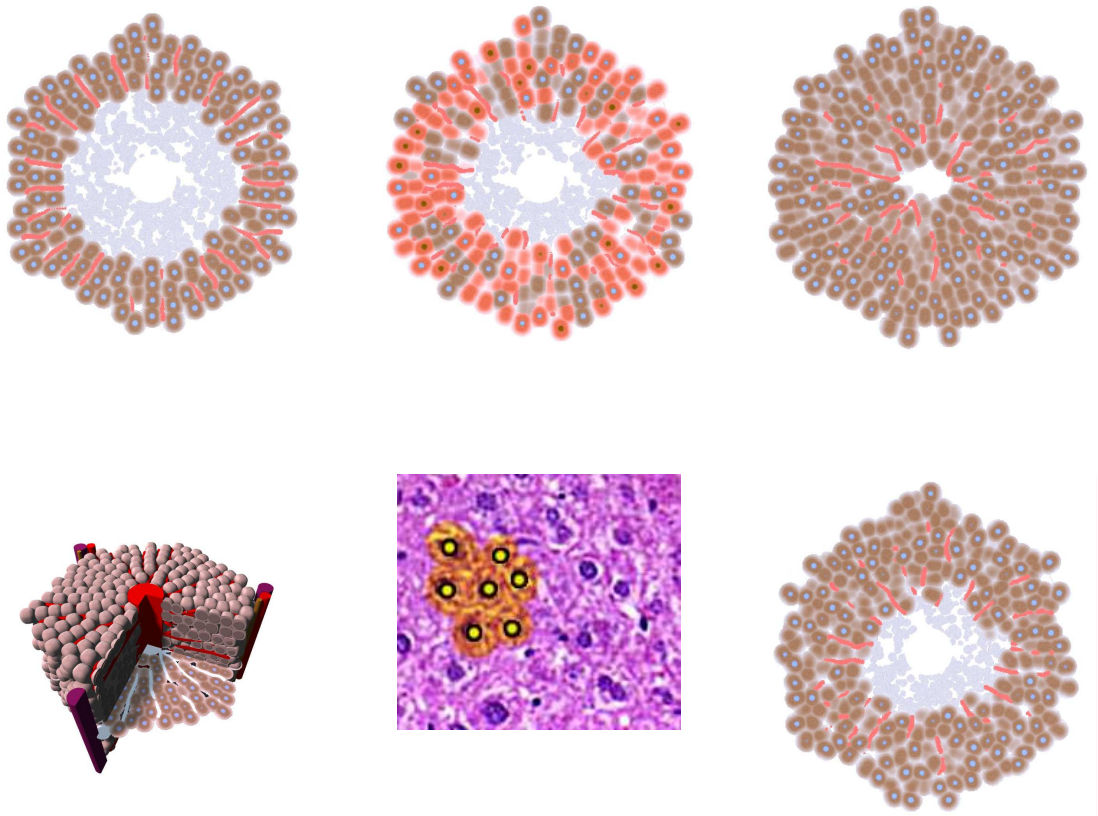

Figure 2.

LIVER LOBULE REGENERATION AFTER INTOXICATION BY CCl_4 . LIVER LOBULES ARE THE REPETETIVE UNITS THAT MAKE UP THE LIVER.

Upper line: REGENERATION PROCESS IF CELLS AFTER DIVISION RE-ORIENT TOWARDS THE CENTRAL VEIN (WHITE SPACE IN THE MIDDLE). SHOWN ARE CROSS-SECTIONS (COMPARE LEFT PICTURE OF LOWER LINE). BROWN: NON-PROLIFERATING, RED: PROLIFERATING CELLS, LONG RED "SNAKES": SINUSOIDS (SMALL CAPILLARIES).

Lower line: LEFT: FULL 3D GEOMETRY OF A LIVER LOBULE, MIDDLE: HEXAGONAL NODULES CHARACTERISTIC FOR LIVER ADENOMA, RIGHT: SIMULATION RESULT IF CELLS DO NOT RE-ORIENT TOWARDS THE CENTRAL VEIN. IN THE LATTER CASE HEXAGONAL NODULES AND AN INCOMPLETE REGENERATION PROCESS IS OBSERVED.

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 [32]. 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.
The initial condition for usual experimentations (practical and numerical) are a uniform distribution of nutrient and an inoculum of bacteria (small region of the domain where the density of bacteria is relatively high). During the evolution process, the (active) bacteria expands into the domain and "eat" the nutrient. At the end of the process, the concentration of nutrient is very low for the numerical simulation. In fact, for the biologists, in the various experimentations for building the branching patterns with Bacillus Subtilis, the concentration of nutrients remains at a very high level and the formation of branching patterns cannot be explained by a lack of nutrient.
A new model has been elaborated in which the nutrient does not determine the dynamics. In this model, active and inactive bacteria, as in Mimura model, are considered together with two chemicals which act on the active bacteria as chemoattractant and chemorepellent. This model is under numerical investigation. Some branching patterns are obtained (see Fig. 3) but the global shape of the colony, until now differs from the experimental ones for Bacillus Subtilis.

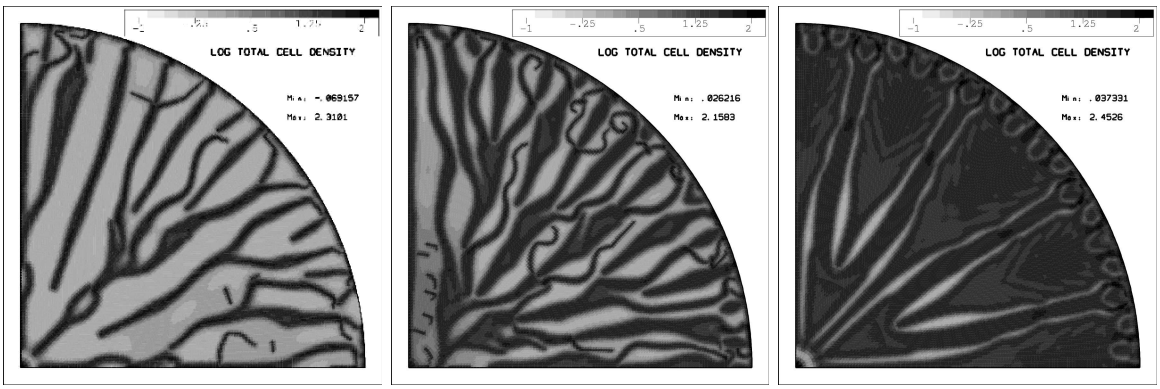

Figure 3. PATTERNS OBTAINED WITH A REACTION-DIFFUSION MODEL INCLUDING CHEMOATTRACTANT AND CHEMOREPELLENT .

The theoretical study of this extended Keller-Segel system has also been initiated. The main technical difficulty is that the extended system does not have an energy structure. Several scales of initial data can be treated using modified energy fnctional.

This is a long term program because several levels of modelling lead to different energy structures.

6.2. Free surface geophysical flows

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

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

The basic model for these problems is the 3D free surface Navier-Stokes system leading to a 3D solver [42] with a moving mesh. If the shallow water assumption is satisfied and if, in addition, the bottom slope is small, these phenomena can be simulated by the Saint-Venant equations [47] which give horizontal velocities constant along the vertical.

We have developped some extensions of the Saint-Venant system where the basic Saint-Venant solver [34] 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 different 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.
- Small slope variations in front of small bottom slope hypothesis leads to a Savage-Hutter model tested for overland flows.

6.2.1. Multilayer Saint-Venant system

Participants: Emmanuel Audusse [Université Paris 13], Marie-Odile Bristeau, Tomas Morales, Benoit Perthame, Jacques Sainte-Marie [LNHE/CETMEF and MACS project-team].

For some applications, we need to know the vertical profile of the velocity and by definition, we cannot get relevant information from Saint-Venant equations. In this case, and in order to avoid the 3D Navier-Stokes system when large scale problems are considered, a first multilayer Saint-Venant system [7] has been introduced where the interfaces are advected by the flow and so there is no mass exchange between the layers. This approximation of the hydrostatic Navier-Stokes equations consists in a set of coupled Saint-Venant systems. The fluid is divided in a given number of layers, each layer satisfies the Saint-Venant equations and is linked to the others by pressure terms (water height coupling) and viscosity (velocity coupling).

A new multilayer approximation has been proposed by J. Sainte-Marie where the total water height is divided at each time step in a given distribution (for instance layers of equal height), this allows mass exchange between layers. Then there is only one continuity equation for the total height and a momentum equation for each layer.

These multilayer models extend the range of validity and give a precise description of the vertical profile of the horizontal velocity while preserving the computational efficiency of the classical Saint-Venant system. These approaches are a transition step towards 3D simulations with the Navier-Stokes system with two main advantages: we have not to deal with a moving mesh and the vertical velocity is only an output variable, it is deduced of the incompressibity condition. The interest of the second approach is that it allows to simulate recirculating area (for instance, effect of the wind on a lake).

The basic tool remains the Saint-Venant solver [34], [33] with a kinetic scheme and an hydrostatic reconstruction.

6.2.2. Derivation of a non-hydrostatic shallow water model

Participants: Marie-Odile Bristeau, Jacques Sainte-Marie [LNHE/CETMEF and MACS project-team].

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 [25]. The obtained models are compared with the Boussinesq models.

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

6.2.3. Overland flows

Participants: Emmanuel Audusse [Université Paris 13], Marie-Odile Bristeau, Benoit Perthame, Jacques Sainte-Marie [LNHE/CETMEF and MACS project-team].

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.

A first difficulty, independent of the furrows, is related to the fact that a mean rain on a sloping plane induces a water depth which is small (10^{-4}) versus the slope (10^{-2}), so besides the first results obtained with a Saint-Venant solver, we are developping a Savage-Hutter [37] solver for comparisons. Actually the Saint-Venant model assumes that the bottom slope is small (same order of magnitude as the water depth) while the Savage-Hutter model assumes only small slope variations, which is more appropriate for overland flows. Then the variables are the water thickness in the direction normal to the topography and the tangential velocity.

This work is a participation to the ANR project “METHODE”.

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 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)

ENS-DMA and Bang project 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, accepted, to be published in the Comptes Rendus (Mathématique) de l’Académie des Sciences (Paris). 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 will be 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.

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 HYKE

Participation to the european network HYKE (Hyperbolic and Kinetic equations). (url http://www.hyke.org).

7.2.2. 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). Participation of all PhD students in the Bang project-team (with oral presentation of their works) in the last Summer school in Dundee)

7.2.3. 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.

7.2.4. 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.

7.3. International actions

Collaboration with the 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.

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 Nottingham, UK, on matching single-cell-based an continuum models, 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, and the Computer Science department of the University of Leipzig on quantification of tumor shapes. Starting collaboration with University of Warwick, UK, on modelling the role of c-myc in growth control. This activity would include co-supervision of a PhD-thesis of Yi-Fang Wang (Univ. of Warwick, UK). Papers are published, submitted and in preparation.

8. Dissemination

8.1. Scientific community

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

Organisation (Jean Clairambault and Dirk Drasdo) of a CEA-EDF-INRIA School on cancer modelling (INRIA-Rocquencourt, March 2008).

Organization of a weekly informal, interactive seminar by Marie Doumic-Jauffret and Dirk Drasdo. 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 Luna Dimitrio's M2 internship (March-June 2007) by Jean Clairambault. Supervision of Thomas Lepoutre's M2 internship (March-June 2007) by Jean Clairambault, Benoît Perthame and Stéphane Gaubert (Maxplus). Supervision of Annabelle Ballesta's PhD thesis (from June 2007) by Jean Clairambault. Supervision of Nick Jagiella's PhD thesis (from July 2007) by Dirk Drasdo and Benoît Perthame. Supervision of Thomas Lepoutre's PhD thesis (from September 2007) by Jean Clairambault, Benoît Perthame and Stéphane Gaubert (Maxplus).

8.2. Teaching

1. 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. Diplôme Universitaire de chronobiologie (Paris VI): 2h (Jean Clairambault)
5. M2, Mathematics ("Growth, reaction movement and diffusion from biology") (Paris VI): 7 h; (Dirk Drasdo)

8.3. Participation to congresses, workshops,...

- Clairambault, J. Modélisation moléculaire et macroscopique de la pharmacologie des cytotoxiques pour optimiser le traitement des cancers. Oral communication to the first meeting of the ARC INRIA "Modélisation de la leucémie myéloïde chronique" (ModLMC), Bordeaux, February 2007.
- Clairambault, J. Modelling healthy and tumoral tissue growth to optimise anticancer therapeutics. Oral communication to the Journées de modélisation mathématique en biologie et en médecine, Université d'Evry, February 2007.
- Clairambault, J. Modelling normal and tumoral tissue to optimise cancer treatment. Oral communication to the NIH-INRIA workshop, theme "Systems Biology", Bethesda (MD), April 2007.
- Clairambault, J. *I.* Cancer growth and therapy and the use of mathematical models ; *II.* Modelling circadian and pharmacological controls on the cell cycle and tumour growth. Oral communications to the Journées de l'équipe d'analyse appliquée de l'Université de Provence, Porquerolles, June 2007.
- Clairambault, J. WP2: Integration and modelling. Oral communication to the first plenary meeting of the Tempo (FP6) project, Rome, June 2007.
- Clairambault, J. Modelling circadian and pharmacological controls on the cell cycle and tumour growth. Oral communication to the workshop "Mathematical Methods and Modeling of Biophysical Phenomena", Buzios (Brazil), August 2007.

- Clairambault, J. Physiological (circadian) and pharmacological control of the cell division cycle. Consequences for the optimisation of cancer treatment, including chronotherapy. Oral communication to the COST B25 Expert meeting (Physiologically Based Pharmacotoxicokinetics and Dynamics, WG2: Modern developments in the modelling of origin and treatment of cancer), Prague, September 2007.
- Clairambault, J. "Giving medical sense to mathematical modelling of cell proliferation and its control", IRMAR seminar, Rennes nov. 2007
- Doumic-Jauffret, M. DEASE workshop, Vienna 12-15th july 2007
- Doumic-Jauffret, M. Euro-mediterranean Conference on Biomathematics, Cairo (Egypt) 26-28th june 2007
- Doumic-Jauffret, M. IMPA workshop "Mathematical Methods and Modeling of Biophysical Phenomena", Buzios, Rio de Janeiro, 27-31th august 2007
- Drasdo, D. School on mathematical biology (3 lectures), Shanghai (China), 9-17th february 2007
- Drasdo, D. Workshop on systems biology, Ile de Berder, 25-31th march 2007
- Drasdo, D. Workshop INRIA/NIH, Bethesda (USA) 14-18th april 2007
- Drasdo, D. Workshop on Modelling in Biotechnology, (invited talk), Nottingham University, 5-7th july 2007
- Drasdo, D. Workshop on Biophysical modelling (invited talk), University of Saarbrüken, 11-12th September 2007
- Drasdo, D. Workshop on regeneration in hepatic systems, Freiburg (Germany), 16-17th september 2007
- Drasdo, D. Workshop on hepatocyte systems , Heidelberg (Germany), 14-15th october 2007
- Drasdo, D. Workshop on systems biology of cancer, (invited talk), organized by EU-project, november 2007
- Perthame, B. Course CIM/UC Summer school "Adaptive evolution", Coimbra (Portugal) 22-26th July 2007
- Perthame, B. First French-Spanish Congress of Mathematics, plenary conference, Zaragoza 9-13th July 2007
- Perthame, B. PIMS 25th birthday, Edmonton (Canada) (3 conferences) may 2007
- Perthame, B. Workshop on biomechanics and chemotaxis, Wien (Austria) 10-14th december 2007

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Major publications by the team in recent years

[1] A. MARROCCO, P. MONTARNAL. *Simulation des modèles energy-transport à l'aide des éléments finis mixtes*, in "C.R. Acad. Sci. Paris", vol. 323, n^{o} Série I, 1996, p. 535-541.

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