IN PARTNERSHIP WITH:
CNRS

Université Claude Bernard (Lyon 1)

Ecole normale supérieure de Lyon

Activity Report 2014

Project-Team NUMED

Numerical Medicine

IN COLLABORATION WITH: Institut Camille Jordan, Unité de mathématiques pures et appliquées

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Modeling and Control for Life Sciences

Table of contents

Project-Team NUMED

Keywords: Mathematical Biology, Modeling, Medical Images, Cell Biology

Creation of the Project-Team: 2009 January 01.

1. Members

Research Scientists
Vincent Calvez [CNRS, Researcher]
Benjamin Ribba [Inria, Researcher, HdR]

Faculty Members
Emmanuel Grenier [Team leader, ENS Lyon, Professor, HdR]
Marie-Aimée Dronne [Univ. Lyon I, Associate Professor]
Paul Vigneaux [ENS Lyon, Associate Professor]

Engineers
Thierry Dumont [Univ. Lyon I]
Violaine Louvet [CNRS]

PhD Students
Emeric Bouin [ENS Lyon]
Alvaro Mateos Gonzalez [ENS Lyon]
Pauline Mazzocco [Inria]
Edouard Ollier [ENS Lyon]
Aziz Ouerdani [Inria]

Post-Doctoral Fellow
Laetitia Giraldi [ENS Lyon, until Sep 2014]

Administrative Assistant
Sylvie Boyer [Inria]

2. Overall Objectives

2.1. Overall Objectives

The purpose of Numed is to develop new numerical methods and tools to simulate and parametrize complex systems arising in biology and medicine. Numed focuses on two axes:

- Thema 1: Modeling using complex models: how to deal with multiple spatial or temporal scales (theoretical study, numerical simulations)?

  This covers several aims: design of models of propagation taking into account the microscopic phenomena and starting from small scale description, importance of mechanics in the growth of tissue, peculiarities of tumor tissues.

- Thema 2: Parametrization of complex models: how to find parameters for complex models, with particular emphasis on population approaches

  Parametrization is of course a central issue in modeling. The main issue is to parametrize complex models which are very computationally expensive.

and two main axes of applications

- Thema 3: Stroke

Stroke is one of the major disease in developed countries. Its modeling is very challenging and rich, involving imagery, cell death modeling, apoptosis, energy issues, inflammation, free radicals, anatomy, ...

- Thema 4: Cancer

  The aim is to develop models of cancer growth in close link with clinical data.

Thema 1 may be split in three objectives.

- Multiscale propagation phenomena in biology
- Growth of biological tissues
- Multiscale models in oncology

3. Research Program

3.1. Multiscale propagation phenomena in biology

3.1.1. Project team positioning

The originality of our work is the quantitative description of propagation phenomena for some models including several scales. We are able to compute the macroscopic speed of propagation and the distribution with respect to the microscopic variable at relevant locations (*e.g.* the edge and the back of the front) in a wide variety of models.

Multiscale modeling of propagation phenomena raises a lot of interest in several fields of application. This ranges from shock waves in kinetic equations (Boltzmann, BGK, etc...), bacterial chemotactic waves, selection-mutation models with spatial heterogeneities, age-structured models for epidemiology or subdiffusive processes.

Earlier works generally focused on numerical simulations, hydrodynamic limits to average over the microscopic variable, or specific models with only local features, not suitable for most of the relevant models. Our contribution enables to derive the relevant features of propagation analytically, and far from the hydrodynamic regime for a wide range of models including nonlocal interaction terms.

Our recent understanding is closely related to the analysis of large deviations in multiscale dispersion equations, for which we give important contributions too.

These advances are linked to the work of other Inria teams (BANG, DRACULA, BEAGLE), and collaborators in mathematics, physics and theoretical biology in France, Austria and UK.

3.1.2. Recent results

Vincent Calvez has focused on the modelling and analysis of propagation phenomena in structured populations. This includes chemotactic concentration waves, transport-reaction equations, coupling between ecological processes (reaction-diffusion) and evolutionary processes (selection of the fittest trait, adaptation), evolution of age structured poulations, and anomalous diffusion.

He has also continued his work on the optimal control of monotone linear dynamical systems, using the Hamilton-Jacobi framework, and the weak KAM theory.

Emeric Bouin has defended his PhD on December 2nd, 2014. He has accomplished his work under the supervision of Vincent Calvez and Emmanuel Grenier. He has studied propagation phenomena in multiscale models. He has focused on some specific behaviours arising from the multiscale nature of the problem, which are not described by classical reaction-diffusion models. For example, he has discovered unexpected acceleration behaviour in kinetic reaction-transport equations (Bouin, Calvez and Nadin, Arch. Ration. Mech. Anal. 2014).

Laetitia Giraldi was a post-doctoral fellow funded by the ANR grant MODPOL under the supervision of Vincent Calvez. She studied thoroughly a biomechanical model for the growth of plant or yeats cells. This new model couples standard equations for the displacement of the cell wall under internal pressure, and a reaction-diffusion equation set on the membrane accounting for the growth pattern has a function of the cell geometry. A rigorous linear stability analysis of the growing spherical shape, together with the development of a stable numerical scheme opens the way to future research in the coupling between growth and geometry.

Alvaro Mateos Gonzalez has started a PhD on September 2014 under the supervision of Vincent Calvez, and Hugues Berry (BEAGLE). He has already collaborated fruitfully with Thomas Lepoutre (DRACULA) and Hughes Berry to investigate the long-time asymptotics of a degenerate renewal equation. This is a first step towards the mathematical analysis of anomalous diffusion processes.

3.1.3. Collaborations

- Mathematical description of bacterial chemotactic waves:
  - **N. Bournaveas** (Univ. Edinburgh), **V. Calvez** (ENS de Lyon, Inria NUMED) **B. Perthame** (Univ. Paris 6, Inria BANG), **Ch. Schmeiser** (Univ. Vienna), **N. Vauchelet**: design of the model, analysis of traveling waves, analysis of optimal strategies for bacterial foraging.
  - **J. Saragosti**, **V. Calvez** (ENS de Lyon, Inria NUMED), **A. Buguin**, **P. Silberzan** (Institut Curie, Paris): experiments, design of the model, identification of parameters.
  - **F. Filbet**, **C. Yang** (Univ. Lyon 1): numerical simulations in 2D in curved geometries.
- Transport-reaction waves and large deviations:
  - **E. Bouin**, **V. Calvez** (ENS de Lyon, Inria NUMED), **E. Grenier** (ENS de Lyon, Inria NUMED), **G. Nadin** (Univ. Paris 6)
- Selection-mutation models of invasive species:
  - **E. Bouin** (ENS de Lyon, Inria NUMED), **V. Calvez** (ENS de Lyon, Inria NUMED), **S. Mirrahimi** (Inst. Math. Toulouse): construction of traveling waves, asymptotic propagation of fronts,
  - **E. Bouin** (ENS de Lyon, Inria NUMED), **V. Calvez** (ENS de Lyon, Inria NUMED), **N. Meunier**, (Univ. Paris 5), **B. Perthame** (Univ. Paris 6, Inria Bang), **G. Raoul** (CEFE, Montpellier), **R. Voituriez** (Univ. Paris 6): formal analysis, derivation of various asymptotic regimes.
- Age-structured equations for subdiffusive processes (just starting)
  - **H. Berry** (Inria BEAGLE), **V. Calvez** (ENS de Lyon, Inria NUMED), **Th. Lepoutre** (Inria DRACULA), **P. Gabriel** (Univ. UVSQ)

This work is also supportet by a PEPS project (CNRS) "Physique Théorique et ses Interfaces", led by N. Vauchelet (Univ. Paris 6).

3.2. Growth of biological tissues

3.2.1. Project-team positioning

The originality of our work is the derivation, analysis and numerical simulations of mathematical model for growing cells and tissues. This includes mechanical effects (growth induces a modification of the mechanical stresses) and biological effects (growth is potentially influenced by the mechanical forces).

This leads to innovative models, adapted to specific biological problems (*e.g.* suture formation, cell polarisation), but which share similar features. We perform linear stability analysis, and look for pattern formation issues (at least instability of the homogeneous state).

The biophysical literature of such models is large. We refer to the groups of Ben Amar (ENS Paris), Boudaoud (ENS de Lyon), Mahadevan (Harvard), etc.

Our team combines strong expertise in reaction-diffusion equations (V. Calvez) and mechanical models (P. Vigneaux). We develop linear stability analysis on evolving domains (due to growth) for coupled biomechanical systems.

Another direction of work is the mathematical analysis of classical tumor growth models. These continuous mechanics models are very close to classical equations like Euler or Navier Stokes equations in fluid mechanics. However they bring there own difficulties: Darcy law, multispecies equations, non newtonian dynamics (Bingham flows). Part of our work consist in deriving existence results and designing acute numerical schemes for these equations.

3.2.2. Recent results

We have worked on several biological issues. Cell polarisation is the main one. We first analyzed a nonlinear model proposed by theoretical physicists and biologists to describe spontaneous polarisation of the budding yeast *S. cerevisae*. The model assumes a dynamical transport of molecules in the cytoplasm. It is analogous to the Keller-Segel model for cell chemotaxis, except for the source of the transport flux. We developped nonlinear analysis and entropy methods to investigate pattern formation (Calvez et al 2012). We are currently validating the model on experimental data. The analysis of polarization of a single cell is a preliminary step before the study of mating in a population of yeast cells. In the mating phase, secretion of pheromones induces a dialogue between cells of opposite types.

We also derive realistic models for the growth of the fission yeast *S. pombe*. We proposed two models which couple growth and geometry of the cell. We aim to tackle the issue of pattern formation, and more specifically the instability of the spherical shape, leading to a rod shape. The mechanical coupling involves the distribution of microtubules in the cytoplasm, which bring material to the cell wall.

Over the evaluation period, Paul Vigneaux developped expertise in modelling and design of new numerical schemes for complex fluid models of the viscoplastic type. Associated materials are involved in a broad range of applications ranging from chemical industry to geophysical and biological materials. In the context of NUMED, this expertise is linked to the development of complex constitutive laws for cancer cell tissue. During the period, NUMED used mixed compressible/incompressible fluid model for tumor growth and viscoelastic fluid model. Viscoplastic is one of the other types of complex fluid model which is usable in the field. Mathematically, it involves variational inequalities and the need for specific numerical methods.

3.2.3. Collaborations

- **V. Calvez** (ENS de Lyon, Inria NUMED), **Th. Lepoutre** (Inria DRACULA), **N. Meunier**, (Univ. Paris 5), **N. Muller** (Univ. Paris 5), **P. Vigneaux** (ENS de Lyon, Inria NUMED): mathematical analysis of cell polarisation, numerical simulations
- **V. Calvez** (ENS de Lyon, Inria NUMED), **N. Meunier**, (Univ. Paris 5), **M. Piel**, (Institut Curie, Paris), **R. Voituriez** (Univ. Paris 6): biomechanical modeling of the growth of *S. pombe*
- **D. Bresch** (Univ. Chambéry), **V. Calvez** (ENS de Lyon, Inria NUMED), **R.H. Khonsari** (King's College London, CHU Nantes), **J. Olivier** (Univ. Aix-Marseille), **P. Vigneaux** (ENS de Lyon, Inria NUMED): modeling, analysis and simulations of suture formation.
- **Didier Bresch** (Univ Chambéry), **Benoit Desjardins**(Moma group): petrology.

ANR JCJC project "MODPOL", *Mathematical models for cell polarization*, led by Vincent Calvez (ENS de Lyon, CNRS, Inria NUMED).

3.3. Multiscale models in oncology

3.3.1. Project-team positioning

Since 15 years, the development of mathematical models in oncology has become a significant field of research throughout the world. Several groups of researchers in biomathematics have developed complex and multiscale continuous and discrete models to describe the pathological processes as well as the action of anticancer anticancer drugs. Many groups in US (e.g. Alexander Anderson's lab, Kristin Swansson's lab) and in Canada

(e.g. Thomas Hillen, Gerda de Vries), quickly developed and published interesting modeling frameworks. The setup of European networks such as the Marie Curie research and training networks managed by Nicolas Bellomo and Luigi Preziosi constituted a solid and fertile ground for the development of new oncology models by teams of biomathematicians and in particular Zvia Agur (Israel), Philip Maini (UK), Helen Byrne (UK), Andreas Deutsch (Germany), or Miguel Herrero (Spain).

3.3.2. Results

We have worked on the development of a multiscale system for modeling the complexity of the cancer disease and generate new hypothesis on the use of anti-cancer drugs. This model relies on a multiscale formalism integrating a subcellular level integrating molecular interactions, a cell level (integrating the regulation of the cell cycle at the levels of individual cells) and a macroscopic level for describing the spatio-temporal dynamics of different types of tumor tissues (proliferating, hypoxic and necrotic). The model is thus composed by a set of partial differential equations (PDEs) integrating molecular network up to tissue dynamics using lax from fluid dynamic. This formalism is useful to investigate theoretically different cancer processes such as the angiogenesis and invasion. We have published several examples and case studies of the use of this model in particular, the action of phase-specific chemotherapies (Ribba, You et al. 2009), the use of anti-angiogenic drugs (Billy, Ribba et al. 2009) and their use in combination with chemotherapies (Lignet, Benzekry et al. 2013). This last work also integrates a model of the VEGF molecular pathway for proliferation and migration of endothelial cells in the context of cancer angiogenesis (Lignet, Calvez et al. 2013).

If these types of models present interesting framework to theoretically investigate biological hypothesis, they however present limitation due to their large number of parameters. In consequence, we decided to stop the development of the multiscale platform until exploration of alternative modeling strategies to deal with real data. We focus our interest on the use of mixed-effect modeling techniques as classically used in the field of pharmacokinetic and pharmacodynamics modeling. The general principal of this approach lies in the integration of several levels of variability in the model thus allowing for the simultaneous analysis of data in several individuals. Nowadays, complex algorithms allow for dealing with this problem when the model is composed by few ordinary differential equations (ODEs). However, no similar parameter estimation method is available for models defined as PDEs. In consequence, we decided: 1. To develop more simple models, based on systems of ODEs, assuming simplistic hypothesis of tumor growth and response to treatment but with a real focus on model ability to predict real data. 2. To work alone the development of parameter estimation methods for PDE models in oncology.

3.4. Parametrization of complex systems

3.4.1. Project-team positioning

We focus on a specific problem: the "population" parametrization of a complex system. More precisely, instead of trying to look for parameters in order to fit the available data for one patient, in many cases it is more pertinent to look for the distribution of the parameters (assuming that it is gaussian or log gaussian) in a population of patients, and to maximize the likelihood of the observations of all patients. It is a very useful strategy when few data per patients are available, but when we have a lot of patients. The number of parameters to find is multiplied by two (average and standard deviation for each parameter) but the number of data is greatly increased.

This strategy, that we will call "population" parametrization has been initiated in the eighties by software like Nonmem. Recently Marc Lavielle (Popix team) made a series of breakthroughs and designed a new powerfull algorithm, leading to Monolix software.

However population parametrization is very costly. It requires several hundred of thousands of model evaluations, which may be very long.

3.4.2. Results

We address the problem of computation time when the complex model is long to evaluate. In simple cases like reaction diffusion equations in one space dimension, the evaluation of the model may take a few seconds of even a few minutes. In more realistic geometries, the computation time would be even larger and can reach the hour or day. It is therefore impossible to run a SAEM algorith on such models, since it would be much too long. Moreover the underlying algorithm can not be parallelized.

We propose a new iterative approach combining a SAEM algorithm together with a kriging. This strategy appears to be very efficient, since we were able to parametrize a PDE model as fast as a simple ODE model.

We are currently developing the corresponding software.

3.5. Models for the analysis of efficacy data in oncology

3.5.1. Project-team positioning

The development of new drugs for oncology patients faces significant issues with a global attrition rate of 95 percents and only 40 percents of drug approval in phase III after successful phase II. As for meteorology, the analysis through modeling and simulation (MS), of time-course data related to anticancer drugs efficacy and/or toxicity constitutes a rational method for predicting drugs efficacy in patients. This approach, now supported by regulatory agencies such as the FDA, is expected to improve the drug development process and in consequence the treatment of cancer patients. A private company, Pharsight, has nowadays the leader team in the development of such modeling frameworks. In 2009, this team published a model describing tumor size time-course in more than one thousand colorectal cancer patients. This model was used in an MS framework to predict the outcome of a phase III clinical trials based on the analysis of phase II data. From 2009 to 2013, 12 published articles address similar analysis of different therapeutic indications such as lung, prostate, thyroid and renal cancer. A similar modeling activity is also proposed for the analysis of data in preclinical experiments, and in particular, experiments in mice. Animal experiments represent critical stages to decide if a drug molecule should be tested in humans. MS methods are considered as tools to better investigate the mechanisms of drug action and to potentially facilitate the transition towards the clinical phases of the drug development process. Our team has worked in the development of two modeling frameworks with application in both preclinical and clinical oncology. For the preclinical context, we have worked on the development of models focusing on the process of tumor angiogenesis, i.e. the formation of intra-tumoral blood vessels. At the clinical level, we have developed a model to predict tumor size dynamics in patients with low-grade glioma.

At Inria, several project-teams have developed similar efforts. The project-team BANG has a solid experience in the development of age-structured models of the cell cycle and tissue regulation of tumors with clinical applications for chronotherapy. BANG is also currently applying these types of partial differential equation (PDE) models to the study of leukemia through collaboration with the project-team DRACULA. Project-team MC2 has recently shown that the analysis, through a simplified PDE model of tumor growth and treatment response, of 3D imaging, could lead to correct prediction of tumor volume evolution in patients with pulmonary metastasis from thyroid cancer. Regarding specifically the modeling of brain tumors, project-team ASCLEPIOS has brought an important contribution towards personalized medicine in analyzing 3D data information from MRI with a multiscale model that describes the evolution of high grade gliomas in the brain. Their framework relies on the cancer physiopathological model that was mainly developed by Kristin Swanson and her group at the university of Washington.

Outside from Inria, we wish to mention here the work of the group of Florence Hubert in Marseille in the development of models with an interesting compromise between mathematical complexity and data availability. A national ANR project led by the team is expected to support the development of an MS methodology for the analysis of tumor size data in patients with metastases.

3.5.2. Results

Regarding our contribution in preclinical modeling, we have developed a model to analyze the dynamics of tumor progression in nude mice xenografted with HT29 or HCT116 colorectal cancer cells. This model, based

on a system of ordinary differential equations (ODEs), integrated the different types of tumor tissues, and in particular, the proliferating, hypoxic and necrotic tissues. Practically, in our experiment, tumor size was periodically measured, and percentages of hypoxic and necrotic tissue were assessed using immunohistochemistry techniques on tumor samples after euthanasia. In the proposed model, the peripheral non-hypoxic tissue proliferates according to a generalized-logistic equation where the maximal tumor size is represented by a variable called "carrying capacity". The ratio of the whole tumor size to the carrying capacity was used to define the hypoxic stress. As this stress increases, non-hypoxic tissue turns hypoxic. Hypoxic tissue does not stop proliferating, but hypoxia constitutes a transient stage before the tissue becomes necrotic. As the tumor grows, the carrying capacity increases owing to the process of angiogenesis (Ribba, Watkin et al. 2011). The model is shown to correctly predict tumor growth dynamics as well as percentages of necrotic and hypoxic tissues within the tumor.

Regarding our contribution in clinical oncology, we developed an ODE model based on the analysis of mean tumor diameter (MTD) time-course in low-grade glioma patients (Ribba, Kaloshi et al. 2012).

In this model, the tumor is composed of proliferative (P) and non-proliferative quiescent tissue (Q) expressed in millimeters. The proportion of proliferative tissue transitioning into quiescence is constant. The treatment directly eliminates proliferative cells by inducing lethal DNA damage while these cells progress through the cell cycle. The quiescent cells are also affected by the treatment and become damaged quiescent cells (k_{PQ}). Damaged quiescent cells, when re-entering the cell cycle, can repair their DNA and become proliferative once again (transition from Q_P to P) or can die due to unrepaired damages. We modeled the pharmacokinetics of the PCV chemotherapy using a kinetic-pharmacodynamic (K-PD) approach, in which drug concentration is assumed to decay according to an exponential function. In this model, we did not consider the three drugs separately. Rather, we assumed the treatment to be represented as a whole by a unique variable (C), which represents the concentration of a virtual drug encompassing the three chemotherapeutic components of the PCV regimen. We modeled the exact number of treatment cycles administered by setting the value of C to 1 (arbitrary unit) at the initiation of each cycle(T_{Treat}): $C(T = T_{Treat}) = 1$.

The resulting model is as follows:

$$\begin{aligned}
\frac{dC}{dt} &= -KDE \times C \\
\frac{dP}{dt} &= \lambda_P P \left(1 - \frac{P^{\bigstar}}{K}\right) + k_{Q_p P} Q_p - k_{PQ} P - \gamma \times C \times KDE \times P \\
\frac{dQ}{dt} &= k_{PQ} P - \gamma \times C \times KDE \times Q \\
\frac{dQ_p}{dt} &= \gamma \times C \times KDE \times Q - k_{Q_p P} Q_p - \delta_{Q_p} Q_p
\end{aligned} \tag{1}$$

We challenged this model with additional patient data. In particular, MTD time-course information from 24 patients treated with TMZ (subset of the 120 patients from SH) and 25 patients treated with radiotherapy (SH). Note that exactly the same K-PD approach was used to model treatment pharmacokinetic (including for radiotherapy). This choice, though not really realistic was adopted for simplicity reasons: the same model can be indifferently applied to the three different treatment modalities of LGG patients.

3.5.3. Collaborations

François Ducray and Jérôme Honnorat (Pierre Wertheimer Hospital in Lyon)

External support: grant INSERM PhysiCancer 2012 and Inria IPL MONICA

3.6. Stroke

3.6.1. Project team positioning

Stroke is a major public health problem since it represents the second leading cause of death worldwide and the first cause of acquired disability in adults.

Numed is currently starting completely new issues with D. Rousseau (INSA) and his team. We have now at hand a large data base of clinical images. Our aim is to develop model which are able to predict the final size of the dead brain area as a function of the first two clinical data.

4. New Software and Platforms

4.1. SimPHyT

SimPHyt has been developed by Morgan Martinet (junior engineer). SimPHyt is an implementation in Python of the low grad glioma model developped by Benjamin Ribba. The aim is to predict the evolution of the glioma size of patients. It is used by Dr François Ducray in Pierre Wertheimer Hospital in Lyon.

4.2. SETIS

We are currently developing the SETIS software which is a GUI allowing to treat DICOM medical images to extract pathological data. These data can then be exported and used in a SAEM software (including Monolix (Inria & Lixoft)) for the parameters' estimation of models in the context of population approaches. As an example SETIS can be used to segment and compute the tumor size of a patients from MRI scans taken at different times. The software is sufficiently general to be used in various situations by clinicians (already done by our colleagues in Lyon Hospital). It will be freely distributed and is based on open source technology, so that it can easily be adapted to specific needs by other users.

SETIS is filed under APP number IDDN.FR.001.150013.000.S.A.2014.000.21000.

4.3. OptimChemo

Participants: Violaine Louvet [correspondant], Emmanuel Grenier, Paul Vigneaux, Ehouarn Maguet.

OptimChemo is a userfriendly software designed to study numerically the effect of multiple chemotherapies on simple models of tumour growth and to optimize chemotherapy schedules.

4.4. Simstab

Stability prediction of vaccine, property of Sanofi, developper by E. Grenier

4.5. Bingham flows

A 1D and 2D code with a new method for the computation of viscoplatic flows with free-surface. It essentially couples Optimization methods and Well-Balanced Finite-Volumes schemes for viscous shallow-water equations (induced by the viscoplastic nature of the fluid). Currently applied to avalanches of dense snow, it is a private code currently actively developed (in C++). One of the key feature is that its well-balanced property allows to obtained the stationary states which are linked to the stopping of the snow avalanche for this highly non-linear type of fluid.

5. New Results

5.1. Highlights of the Year

Vincent Calvez has been awareded an ERC Grant and the prestigious Bronze medal CNRS.

6. Bilateral Contracts and Grants with Industry

6.1. Bilateral Contracts with Industry

- Annual contract with Sanofi Pasteur on vaccine fiability (third annual contract, including a 6 months temporary position.
- Four years framework contrat with Servier.

7. Partnerships and Cooperations

7.1. Regional Initiatives

Two regional grants for mobility to develop collaborations with A. Samson (Grenoble) and Didier Bresch (Chambéry) respectively.

7.2. European Initiatives

7.2.1. FP7 & H2020 Projects

7.2.1.1. DDMoRE

Type: FP7

Duration: February 2011 - January 2016

Inria contact: Marc Lavielle

URL : http://www.ddmore.eu/

7.2.2. Collaborations with Major European Organizations

ERC Grant for Vincent Calvez.

7.3. International Research Visitors

7.3.1. Explorer programme

Emeric Bouin will spent three months as a post doc at Stanford university.

7.3.2. Research stays abroad

E. Bouin and V. Calvez worked two weeks in Austarlia. E. Grenier spent one week in Princeton. P. Vigneaux goes for two months in Sevilla.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific events organisation

P. Vigneaux: ANR's ARP workshop Simulation of avalanches : modelling and numerics, in Seville (March 11-14) 2014. http://arpavalanche14.sciencesconf.org/

P. Vigneaux: 12th French-Romanian Conference on Applied Mathematics (August 25-30, 2014. Lyon) CFR2014: invited to organize the Special Session on Numerical Analysis.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

E. Grenier is professor at ENSL and teaches in L3 and agregation (PDE, Topology, Modeling).

P. Vigneaux is assistant professor at ENSL and teaches in M2 and agregation (Modeling, PDE).

V. Calvez teachs in M2 (modeling and PDE).

8.2.2. Supervision

- E. Bouin defended its thesis in novembre 2014 under the supervision of V. Calvez.

8.3. Popularization

V. Calvez is responsible of "Math à Lyon", a serie of conferences in high school.

E. Grenier gave a public conference in Nancy in november 2014 on "mathematics and drugs".

P. Vigneaux took part of a general book "Brèves de Maths - Mathématiques pour la planète Terre. Nouveau Monde" éditions. ISBN 9782365838962. Octobre 2014. 255p. Patronage de l'INSMI-CNRS, Inria, SMAI, SMF, SFdS

P. Vigneaux is a member of the board of "Images des Maths", a pedagogic website.

9. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

[1] E. D. FERNANDEZ-NIETO, J. GALLARDO, P. VIGNEAUX. *Efficient numerical schemes for viscoplastic avalanches. Part 1: the 1D case*, in "Journal of Computational Physics", January 2014, vol. 264, pp. 55-90 [*DOI :* 10.1016/J.JCP.2014.01.026], https://hal.archives-ouvertes.fr/hal-01011373

[2] E. GRENIER, V. LOUVET, P. VIGNEAUX. *Parameter estimation in non-linear mixed effects models with SAEM algorithm: extension from ODE to PDE*, in "ESAIM: Mathematical Modelling and Numerical Analysis", July 2014, vol. 48, n^{o} 5, pp. 1303-1329 [*DOI :* 10.1051/M2AN/2013140], https://hal.archives-ouvertes.fr/hal-00936373

[3] B. RIBBA, N. HOLFORD, F. MENTRÉ. *The Use of Model-Based Tumor-Size Metrics to Predict Survival*, in "Clinical Pharmacology and Therapeutics", August 2014, vol. 96, n^{o} 2, pp. 133 - 135 [*DOI :* 10.1038/CLPT.2014.111], http://www.hal.inserm.fr/inserm-01084276

[4] O. WOLKENHAUER, C. AUFFRAY, O. BRASS, J. CLAIRAMBAULT, A. DEUTSCH, D. DRASDO, F. GERVASIO, L. PREZIOSI, P. MAINI, A. MARCINIAK-CZOCHRA, C. KOSSOW, L. KUEPFER, K. RATEITSCHAK, I. RAMIS-CONDE, B. RIBBA, A. SCHUPPERT, R. SMALLWOOD, G. STAMATAKOS, F. WINTER, H. BYRNE. *Enabling multiscale modeling in systems medicine: From reactions in cells to organ physiology*, in "Genome Medicine", May 2014, vol. 6, n^{o} 21, 3 p. , https://hal.inria.fr/hal-01109002

Invited Conferences

[5] P. VIGNEAUX. *Numerical schemes for viscoplastic avalanches*, in "2me Ecole du GdR CNRS EGRIN", Domaine de Chalès, France, June 2014, https://hal.archives-ouvertes.fr/hal-01019923

Scientific Books (or Scientific Book chapters)

[6] J.-S. DHERSIN (editor). *Statistical inference for partial differential equations*, ESAIM: Proceedings and Surveys, SMAISeignosse le Penon, France, September 2014, vol. 45, https://hal.inria.fr/hal-00920853

[7] E. D. FERNANDEZ-NIETO, P. VIGNEAUX. *Some Remarks on Avalanches Modelling: An Introduction to Shallow Flows Models*, in "Advances in Numerical Simulation in Physics and Engineering - Lecture Notes of the XV 'Jacques-Louis Lions' Spanish-French School", C. PARÉS, C. VAZQUEZ CENDON, F. COQUEL (editors), SEMA SIMAI Springer Series, Springer, June 2014, pp. 51-106 [*DOI :* 10.1007/978-3-319-02839-2_2], https://hal.archives-ouvertes.fr/hal-01066445

Other Publications

[8] V. CALVEZ, P. GABRIEL, S. GAUBERT. *Non-linear eigenvalue problems arising from growth maximization of positive linear dynamical systems*, March 2014, 8 pages, https://hal.archives-ouvertes.fr/hal-00974749

[9] V. CALVEZ, T. GALLOUËT. *Particle approximation of the one dimensional Keller-Segel equation, stability and rigidity of the blow-up*, March 2014, https://hal.inria.fr/hal-00968347

[10] V. CALVEZ, G. RAOUL, C. SCHMEISER. *Confinement by biased velocity jumps: aggregation of Escherichia coli*, April 2014, 15 pages, https://hal.archives-ouvertes.fr/hal-00971302