IN PARTNERSHIP WITH:
CNRS

Ecole normale supérieure de Lyon

Université Claude Bernard (Lyon 1)

Activity Report 2017

Project-Team NUMED

Numerical Medicine

IN COLLABORATION WITH: Unité de Mathématiques Pures et Appliquées

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Modeling and Control for Life Sciences

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Project-Team NUMED

Creation of the Project-Team: 2009 January 01

Keywords:

Computer Science and Digital Science:

A6. - Modeling, simulation and control
A6.1. - Mathematical Modeling
A6.2. - Scientific Computing, Numerical Analysis & Optimization
A6.3. - Computation-data interaction

Other Research Topics and Application Domains:

B1. - Life sciences
B1.1. - Biology
B2. - Health
B2.2. - Physiology and diseases
B2.2.2. - Nervous system and endocrinology
B2.2.3. - Cancer
B2.2.4. - Infectious diseases, Virology
B2.4.1. - Pharmaco kinetics and dynamics
B2.4.2. - Drug resistance
B2.6.1. - Brain imaging

1. Personnel

Research Scientist

Vincent Calvez [CNRS, Researcher, until Oct 2017, HDR]

Faculty Members

Emmanuel Grenier [Team leader, Ecole Normale Supérieure Lyon, Professor, HDR]
Paul Vigneaux [Ecole Normale Supérieure Lyon, Associate Professor, HDR]

Post-Doctoral Fellow

Thibault Bourgeron [Ecole Normale Supérieure Lyon, until Aug 2017]

PhD Students

Mathilde Giacalone [Univ de Lyon, until Sep 2017]
Arthur Marly [Ecole Normale Supérieure Lyon]
Edouard Ollier [Hospices Civils de Lyon, until Sep 2017]

Technical staff

Monika Twarogowska [CNRS]

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 tissues, peculiarities of tumor tissues, nonlinear rheology, evolutionary perspectives.

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

and two main axes of applications

- Thema 3: Stroke
- Thema 4: Cancer

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

3. Research Program

3.1. Design of complex models

3.1.1. Project team positioning

The originality of our work is the quantitative description of propagation phenomena accounting for several time and spatial scales. Here, propagation has to be understood in a broad sense. This includes propagation of invasive species, chemotactic waves of bacteira, evoluation of age structures populations ... Our main objectives are the quantitative calculation of macroscopic quantities as the rate of propagation, and microscopic distributions at the edge and the back of the front. These are essential features of propagation which are intimately linked in the long time dynamics.

3.1.2. Recent results

- Mixed evolution - propagation models:

  Vincent Calvez is studying propagation phenomena at the mesoscale, including travelling waves, accelerating fronts, evolutionary adaptation of a population to a changing environment. The common feature between these projects is the strong heterogeneity inside the propagating front. It is a great mathematical challenge to be able to keep track of this heterogeneity throughout the mathematical analysis.

  This research is structured in several axes, which all belong to the ERC starting grant MESOPROBIO (2015-2020).

  – Modeling and data analysis of species' invasion:

    We are currently developing two directions of research on the case study of cane toads invasion in Northern Australia. The first direction is based on a dataset provided by Australian group of biologists. They recorded individual trajectories of individuals at a fixed location during ten consecutive years (2005-2015). We are using our expertise about waves of expansion in kinetic transport equations in order to calibrate some dedicated mesoscopic models on data. So far we experienced some difficulties because any approach severely underestimate the real speed of expansion. We are revisiting the problem based on this apparent counter-intuitive results. This was the purpose of Nils Caillerie's PhD thesis (defended July 2017).

    The second direction is more theoretical. Namely we are seeking the true rate of expansion of a minimal model for wave front acceleration inspired from the cane toad study. This mathematical question appeared to much more difficult than expected. We are attacking it using a mixture of theoretical and numerical computations (in collaboration with T. Dumont, C. Henderson, S. Mirrahimi and O. Turanova).

  - Analysis of subdiffusive processes:

    H. Berry, V. Calvez and T. Lepoutre co-supervised the PhD of Alvaro Mateos Gonzalez. He studied large scale asymptotics of age-structured sub-diffusive models.

  - Concentration waves of chemotactic bacteria at the mesoscale:

    Vincent Calvez achieved a long standing goal in 2015, by proving the existence of traveling wave in a coupled kinetic/parabolic system of equations modeling bacteria chemotaxis. This project was grounded on biological experiments. There was several parallel sub-projects, including the PhD thesis of Emeric Bouin, and Nils Caillerie, as well as Hélène Hivert's post-doctoral project. VC is also collaborating with Laurent Gosse and Monika Twarogowska on well balanced schemes for kinetic traveling waves.

    This project led to new types of non-local Hamilton-Jacobi equations, including a collaboration with E. Bouin, G. Nadin and E. Grenier.

  - Adaptation of a population to a changing environment:

    Vincent Calvez moved recently to evolutionary biology, by some collaboration with biologists at Montpellier. The goal is to analyse quantitative genetics model using modern tools of PDE analysis, in particular WKB expansions, as initiated by Perthame and co-authors in 2005. We made two breakthroughs: firstly, we obtained quantitative results for age-structured population models, which add a level of complexity (the population is described by a phenotypic trait and age of individuals). Secondly, we realized that WKB expansions, which are well designed for linear equations (here, asexual mode of reproduction), could be extended to some non linear equations, including some sexual mode of reproduction. This paves the way for new mathematical challenges, as the asymptotic analysis requires new tools, and new quantitative results in evolutionary biology.

    Vincent Calvez is currently at UBC, Vancouver, over the period 08/2017-03/2018, to consolidate the last project and initiate new collaborations there.

- Inviscid limit of Navier Stokes equations.

  The question of the behavior of solutions of Navier Stokes equations in a bounded domain as the viscosity goes to 0 is a classical and highly difficult open question in Fluid Mechanics. A small boundary layer, called Prandtl layer, appears near the boundary, which turns out to be unstable if the viscosity is small enough. The stability analysis of this boundary layer is highly technical and remained open since the first formal analysis in the 1940's by physicists like Orr, Sommerfeld, Tollmien, Schlichting or Lin. E. Grenier recently made a complete mathematical analysis of this spectral problem, in collaboration with T. Nguyen and Y. Guo. We rigorously proved that any shear layer is spectrally and linearly unstable if the viscosity is small enough, which is the first mathematical result in that field. We also get some preliminary nonlinear results. A book on this subject is in preparation, already accepted by Springer.

- Qualitative properties.

  Sometimes a beautiful mathematical question arises from modeling. For instance the question to know whether the apparent size of a tumor on a MRI can decrease long after a radiotherapy is linked to the following mathematical question: if u is a solution of the classical KPP equation, does it satisfies $\partial_t u > 0$ everywhere provided t is large enough ? Despite its simplicity, this natural question appeared open and delicate. With the help of F. Hamel, E. Grenier managed to prove that this is true (to be published in JMPA) [13].

- Numerical analysis of complex fluids: the example of avalanches.

  This deals with the development of numerical schemes for viscoplastic materials (namely with Bingham or Herschell-Bulkley laws). Recently, with other colleagues, Paul Vigneaux finished the design of the first 2D well-balanced finite volume scheme for a shallow viscoplastic model. It is illustrated on the famous Taconnaz avalanche path in the Mont-Blanc, Chamonix, in the case of dense

snow avalanches. The scheme deals with general Digital Elevation Model (DEM) topographies, wet/dry fronts and is designed to compute precisely the stopping state of avalanches, a crucial point of viscoplastic flows which are able to rigidify [21].

3.1.3. Collaborations

- Mixed evolution: N. Bournaveas (Edinburgh), B. Perthame (Paris 6), C. Schmeiser (Vienna), P.Silberzan (Institut Curie), S. Mirrahimi (Toulouse).
- Inviscid limit of Navier Stokes equations: Brown University (Y. Guo, B. Pausader), Penn State University (T. Nguyen), Orsay University (F. Rousset).
- Qualitative properties: F. Hamel (Marseille University).
- Numerical analysis of complex fluids: Enrique D. Fernandez - Nieto (Univ. de Sevilla, Spain), Jose Maria Gallardo (Univ. de Malaga, Spain).

3.2. Parametrization of complex systems

3.2.1. Project-team positioning

Clinical data are often sparse: we have few data per patient. The number of data is of the order of the number of parameters. In this context, a natural way to parametrize complex models with real world clinical data is to use a Bayesian approach, namely to try to find the distribution of the model parameters in the population, rather than to try to identify the parameters of every single patient. This approach has been pioneered in the 90's by the Nonmem software, and has been much improved thanks to Marc Lavielle in the 2000's. Refined statistical methods, called SAEM, have been tuned and implemented in commercial softwares like Monolix.

3.2.2. Recent results

The main problem when we try to parametrize clinical data using complex systems is the computational time. One single evaluation of the model can be costly, in particular if this model involves partial differential equations, and SAEM algorithm requires hundreds of thousands of single evaluations. The time cost is then too large, in particular because SAEM may not be parallelized.

To speed up the evaluation of the complex model, we replace it by an approximate one, or so called metamodel, constructed by interpolation of a small number of its values. We therefore combine the classical SAEM algorithm with an interpolation step, leading to a strong acceleration. Interpolation can be done through a precomputation step on a fixed grid, or through a more efficient kriging step. The interpolation grid or the kriging step may be improved during SAEM algorithm in an iterative way in order to get accurate evaluations of the complex system only in the domain of interest, namely near the clinical values [14],[15].

We applied these new algorithms to synthetic data and are currently using them on glioma data. We are also currently trying to prove the convergence of the corresponding algorithms. We will develop glioma applications in the next section.

Moreover E. Ollier in his phD developed new strategies to distinguish various populations within a SAEM algorithm [23].

We have two long standing collaborations with Sanofi and Servier on parametrization issues:

- Servier: during a four years contract, we modelled the pkpd of new drugs and also study the combination and optimization of chimiotherapies.
- Sanofi: during a eight years contract, Emmanuel Grenier wrote a complete software devoted to the study of the degradation of vaccine. This software is used worldwide by Sanofi R&D teams in order to investigate the degradation of existing or new vaccines and to study their behavior when they are heated. This software has been used on flu, dengue and various other diseases.

3.2.3. Collaborations

- Academic collaborations: A. Leclerc Samson (Grenoble University)
- Medical collaborations: Dr Ducray (Centre Léon Bérard, Lyon) and Dr Sujobert (Lyon Sud Hospital)
- Industrial contracts: we used parametrization and treatment improvement techniques for Servier (four years contract, on cancer drug modeling and optimization) and Sanofi (long standing collaboration)

3.3. Multiscale models in oncology

3.3.1. Project-team positioning

Cancer modeling is the major topic of several teams in France and Europe, including Mamba, Monc and Asclepios to quote only a few Inria teams. These teams try to model metastasis, tumoral growth, vascularisation through angiogenesis, or to improve medical images quality. Their approaches are based on dynamical systems, partial differential equations, or on special imagery techniques.

Numed focuses on the link between very simple partial differential equations models, like reaction diffusion models, and clinical data.

3.3.2. Results

We managed to build a clinical database, which gathers clinical data from about twenty different patients which were treated in Lyon Hospital. For each patient, we have five to twenty different MRIs. Each MRI has been segmented manually by A. Peters, and checked by Dr Ducray. There are about two hundred different MRIs.

With this database, we can try to parametrize various models of glioma, thanks to the population parametrization techniques developed under axis 2. We are currently trying to parametrize a simple reaction diffusion model for the decay of glioma after chemotherapy [7].

3.4. Stroke

3.4.1. Project-team positioning

Many teams work on medical imagery, in order to improve diffusion images or MRIs, or to improve their mathematical analysis. But there are few academic teams working on ischemic stroke modeling in Europe, mainly because there are few available clinical data for a given patient. Except routine imagery, often with low definition because it is taken very quickly, in an emergency context, there are no biochemical data. The follow up is also very sparse.

However the domain is very rich. Ischemic stroke involves blood flow, ionic exchanges, cell swelling, cell death (including necrosis and apoptosis), reperfusion, free radicals ... It is possible to build very detailed descriptive models of stroke, however it is not possible to parametrize these models using clinical data. Only a crude parametrization using bibliographical data or ad hoc parameters is possible. We followed this path at the beginning of Numed. Now we are focused on clinical data, namely diffusion and perfusion maps.

The scientific challenge is to try to predict the outcome of the patient, starting from the initial clinical images, obtained when the patient enters the hospital. By *outcome*, we mean the final size of the dead area, or patient abilities (speech, walk, standing). It is particularly important to try to know whether clinicians have to give some particular drug to try to reopen blood flow, or whether this reopening would be harmful for the patient.

3.4.2. Results

Through the PhD thesis of Mathilde Giacalone, we built a strong collaboration with an imagery team of the Creatis lab (Lyon I). This team is very strong in the analysis of clinical images of stroke and in particular on perfusion. It closely works with clinicians (Pr Nighoghossian at Lyon Bron hospitals). We have therefore built a strong connection with clinicians and image specialists.

Thanks to the work of Mathilde Giacalone, we have now at hand a large database of clinical data (more than 50 patients). For each of these patients we have at hand their perfusion and diffusion maps at their entry, together with diffusion one week and one month later. All these images have been checked and segmented. All the data have been supervised by a clinician. The database is therefore very reliable. Its setup took almost two years. This database will grow with time, according to the patients treated in Lyon.

Mathilde Giacalone worked on new algorithms to improve perfusion images. A perfusion image describes the blood flow in the brain. We also fulfilled a preliminary analysis to know what kind of image (there are several protocols to get perfusion images) is the best to predict the outcome of the patient, using information theory.

4. New Software and Platforms

4.1. Bingham flows

FUNCTIONAL DESCRIPTION: 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.

- Contact: Emmanuel Grenier

4.2. OptimChemo

FUNCTIONAL DESCRIPTION: 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.

- Participants: Ehouarn Maguet, Emmanuel Grenier, Paul Vigneaux and Violaine Louvet
- Contact: Emmanuel Grenier

4.3. SETIS

KEYWORDS: Health - DICOM - Medical imaging - Drug development
FUNCTIONAL DESCRIPTION: SETIS software 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 colleagues in Lyon Hospital).

- Participants: Ehouarn Maguet and Paul Vigneaux
- Partner: ENS Lyon
- Contact: Paul Vigneaux

4.4. SIMPHYT

KEYWORDS: Bioinformatics - Cancer - Drug development
FUNCTIONAL DESCRIPTION: SimPHyt is an implementation in Python of the low grad glioma model. The aim is to predict the evolution of the glioma size of patients.

- Participant: Benjamin Ribba
- Contact: Benjamin Ribba

4.5. SITLOG

- Participants: Benjamin Ribba and Morgan Martinet
- Contact: Emmanuel Grenier

4.6. VAXSIMSTAB

KEYWORDS: Bioinformatics - Health - Drug development
FUNCTIONAL DESCRIPTION: VAXSIMSTAB is a modeler stability prediction of vaccine software.

- Participants: Benjamin Ribba, Emmanuel Grenier and Vincent Calvez
- Contact: Benjamin Ribba

5. Partnerships and Cooperations

5.1. National Initiatives

5.1.1. ANR

CNRS InFIniti, 2017-2018 (P. Vigneaux): 12ke in 2017 (pending for 2018)

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Invited Conferences

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