IN PARTNERSHIP WITH:
CNRS

Ecole normale supérieure de Lyon

Université Claude Bernard (Lyon 1)

Activity Report 2018

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. - Methods in 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. Team, Visitors, External Collaborators

Research Scientist

Helene Leman [Inria, Researcher, from Oct 2018]

Faculty Members

Emmanuel Grenier [Team leader, Ecole Normale Supérieure Lyon, Professor, HDR]
Arthur Marly [Ecole Normale Supérieure Lyon, Associate Professor, from Sep 2018]
Paul Vigneaux [Ecole Normale Supérieure Lyon, Associate Professor, HDR]
Arthur Marly [Ecole Normale Supérieure Lyon, until Aug 2018]

Technical staff

David Coulette [CNRS, from Mar 2018]

Interns

Auriane Cadorin [Inria, from Jun 2018 until Aug 2018]
Florian Colrat [Inria, until Apr 2018]

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 on main axe of applications, namely 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 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

- Population models.

  H. Leman works at the interface between mathematics and biology, thanks to probabilist and determinist studies of models of populations. More precisely, she studies and develops probabilistic models, called agent models that described the population at an individual level. Each individual is characterized by one or more phenotypic traits and by its position, which may influence at the same time its ecological behavior and its motion. From a biological point of view these models are particularly interesting since they allow to include a large variety of interactions between individuals. These processes may also be studied in details to obtain theoretical results which may be simulated thanks to exact algorithms. To get quantitative results H. Leman uses changes of scales in space and time (large population, rare mutations, long time), following various biological assumptions.

  In a first study , H. Leman tries to understand the interactions between sexual preference mechanisms and evolutive forces inside spatially structured populations. Recently she got interesting in the description of necessary conditions to facilitate the emergence of such preferences by individuals.

  As a second example, H. Leman is also interested in the modeling and study of cooperative bacterias and tries to understand the impact of spatial structures in the eco - evolutions of these bacterias. Space seems to be an essential factor to facilitate the emergence of cooperation between bacteries.

- 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.

- 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

- Ecology: Orsay (C. Coron), Toulouse (IMT, M. Costa), MNHM Paris (V. Llaurens), LISC Paris (C. Smadi), ENS Paris (R. Ferrière, E. Abs), CIMAT (Mexique, J. C. P. Millan).
- Inviscid limit of Navier Stokes equations: Brown University (Y. Guo, B. Pausader), Penn State University (T. Nguyen), Orsay University (F. Rousset).
- 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

During 2018 we developed new collaborations with the Centre Léon Bérard (Lyon), in particular on the following topics

- Barcoding of cells: thanks to recent techniques, it is possible to mark each cell with an individual barcode, and to follow its division and descendance. The analysis of such data requires probabilistic models, in particular to model experimental bias.
- Apoptosis: the question is to investigate whether the fate of neighboring cells influence the evolution of a given cell towards apoptosis, starting from videos of in vitro drug induced apoptosis.
- Dormance: Study of the dynamics of cells under immunotherapy, starting from experimental in vitro data.
- Colorectal cancer: In vitro study of the role of stem cells in drug resistance, in colorectal cancer.

3.3.3. Collaborations

- Centre Léon Bérard (in particular: Pr Puisieux, G. Ichim, M. Plateroni, S. Ortiz).

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 2018

6. Bibliography

Publications of the year

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