INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team NUMED

Numerics for Medecine

Grenoble - Rhône-Alpes

Theme : Computational Medicine and Neurosciences

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Numed is a common project with Ecole Normale Supérieure of Lyon, Lyon I University and Cnrs. Numed has been created on january 2009.

1. Team

Research Scientist

Emmanuel Grenier [Team leader, Professor (ENSL), HdR]
Paul Vigneaux [Assistant Professor (ENSL)]
Vincent Calvez [Researcher (CNRS)]
Violaine Louvet [Research Ing. (CNRS)]
Thierry Dumont [Research Ing Lyon I]
Ribba Benjamin [Researcher (INRIA)]
Marie-Aimée Dronne [Assistant Professor (Lyon I)]
Branka Bernard [Post doc (Lyon I)]
Séverine Enault [phD student (ENSL)]
Floriane Lignet [phD student (ENSL)]

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 medecine. Numed focuses on two axes:

- numerical methods for complex systems with several time and spatial scales. In particular: numerical simulations in complex domains, stiff reaction diffusions equations, multifluids systems.
- parametrization of complex systems using nonlinear mixed effect methods and populationnal pharmacokinetic pharmacodynamics models.

Numed investigates two mains applications

- Stroke: models of brain stroke (ionic exchanges, inflammation, free radicals, ...)
- Cancer: local invasion, angiogenesis

and a few other subjects (prion models, FIV,...).

3. Scientific Foundations

3.1. Multiscale modeling and computations

3.1.1. Spatial complexity: collective motion of cells

The collective motion of cells (bacteries on a gel or endothelial cells during angiogenesis) is a fascinating subject, that involves a combinaison of random walk and chemotaxis. The modeling of these problems is still active, since the pioneering works of Keller and Segel, and the mathematical study of the arising equations is a very active area of research.

Vincent Calvez focuses its effort on the following questions:

- Mathematical analysis of the Keller-Segel model

  [In collaboration with J.A. Carrillo and J. Rosado (UAB, Barcelona)]

Following McCann 1997 and Otto 2001, we interpret the classical Keller-Segel system for chemotaxis as a gradient flow in the Wasserstein space. The free-energy functional turns out to be homogeneous. This viewpoint helps to understand better blow-up mechanisms, and to derive rates of convergence towards self-similar profiles. We investigate more precisely linear diffusion, porous medium diffusion and fast diffusion in competition with various interaction kernels.

[In collaboration with N. Meunier (Paris 5) and R. Voituriez (Paris 6)]

Another project consists in analyzing some variant of the Keller-Segel system when the chemoattractant is secreted at the boundary of the domain. This is motivated by modeling issues in cell polarization.

- Kinetic models for bacterial collective motion

  [In collaboration with N. Bournaveas (Univ. Edinburgh)]

  We shed a new light on the theoretical analysis of kinetic equations for chemotaxis: we exhibited a peculiar example subject to a critical mass phenomenon as for the two-dimensional Keller-Segel system. This shows a posteriori that previous attempts to show global existence were in fact borderline with respect to this critical example.

  [In collaboration with N. Bournaveas (Univ. Edinburgh), B. Perthame (Paris 6), A. Buguin, Jonathan Saragosti and P. Silberzan (Institut Curie, Paris)]

  We have developed a macroscopic model for bacterial traveling pulses based on a mesoscopic description of the run-and-tumble process. We are able to capture some key features observed in the experiments (asymmetric profile, speed of the pulse).

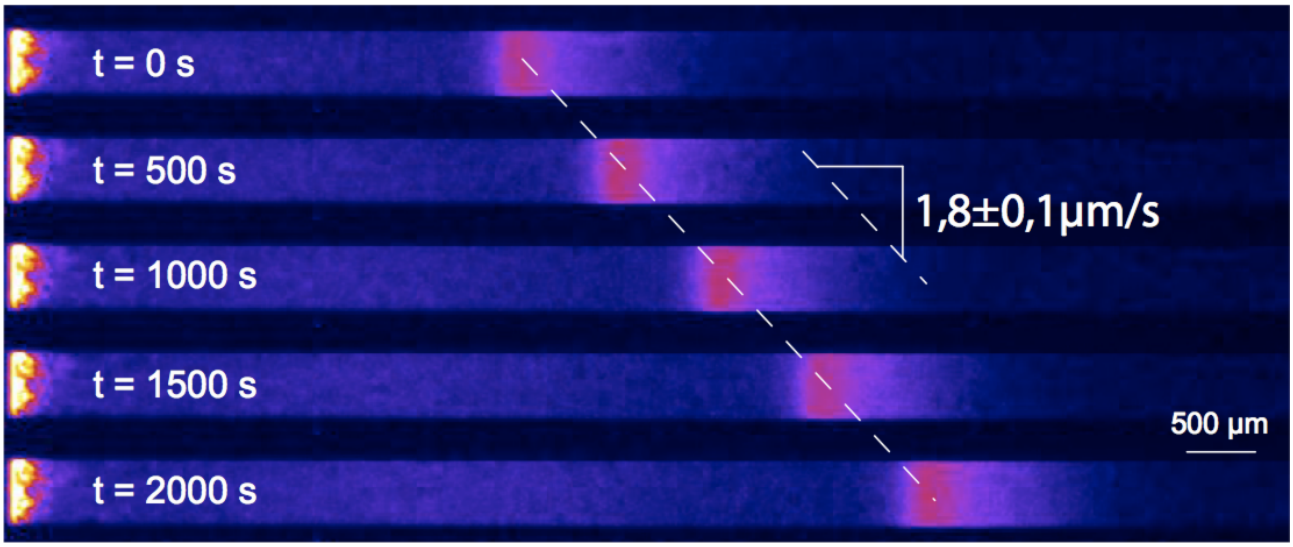

Figure 1. Collective motion of cells

3.1.2. Complex rheology

To investigate the growth of a tumor it is crucial to have a correct description of its mechanical aspects. Tumoral and normal cells may be seen as a complex fluid, with complex rheology.

Numerical investigations of complex flows is studied by P. Vigneaux who develops new numerical schemes fo Bingham type flows.

3.2. Parametrization of complex systems

The parametrization of complex systems in order to fit experimental results or to have a good qualitative behavior is a delicate issue since its require to simulate the complex systems for a large number of sets of parameters, which is very expensive.

Currently Numed team tries to develop strategies of "precomputation" of complex models to speed up the parametrization process.

4. Application Domains

4.1. Stroke

Stroke is a very complex pathology, involving many different time scales and phenomena. Numed is currently developping various models to describe some important aspects of stroke.

4.1.1. Inflammation modelling

MA Dronne has designed a first model of inflammation at cellular level, based on ordinary differential equations. To take into account spatial phenomena, a first partial differential equation based model is under study. Together with Taissia Lelekov Boissard (post doc of the ANR contrat "AVC in silico"), they tried to find biological data to parametrize these models, and to build a basis of qualitative facts that must be reproduced by the model.

MA Dronne has also developped a collaboration with the Mario Negri institute (Milano) through the team "inflammation and nervous system diseases" (MG de Simoni). This teams currently runs in vivo experiments in rodent that should provide new data to investigate the temporal evolution of various variables of the model.

The study and validation of these two models of inflammation will continue with the study of in silico experiments which will simulate the action of various anti inflammatory drugs, acting at various levels of the inflammatory reaction, work in common with biologists (INSERM 842, neurooncologie et neuro inflammation, Lyon), with clinicians (Creatis, Umr 5515, Inserm U 630 Lyon).

4.1.2. Free radicals

A first model of free radical synthesis has been initiated by V. Lemesle (post doc of ANR AVC in silico). This model is under developpment with P. Vigneaux. A collaboration begins with Michel Plotkine (EA 2510 pharmacology of cerebral blood flow, Paris 5 university) to get experimental data on the temporal evolution of the various variables of the model.

This model will be used to manage in silico experiments in order to study the effects of various drugs.

4.1.3. Ionic motions

A mechanistic model of ionic motions has already been developped, studied and validated to study in silico the dual role of astrocytes during ischemia, and to study the effect of various ionic chanels blockers in man and roden.

This model is now used to study in silico the effect of the combination of several neuroprotectors acting on ionic channels, transporters or receptors. This work should help to understand antagonist or synergic effects of blockers.

4.1.4. Spreading depression

Spreading depressions are propagative waves which travel in brain during ischemia and which may have a major role in the extension of the ischemic core. Currently 3D computations in real geometry are run to study their speed and the role of brain anatomy in their propagation.

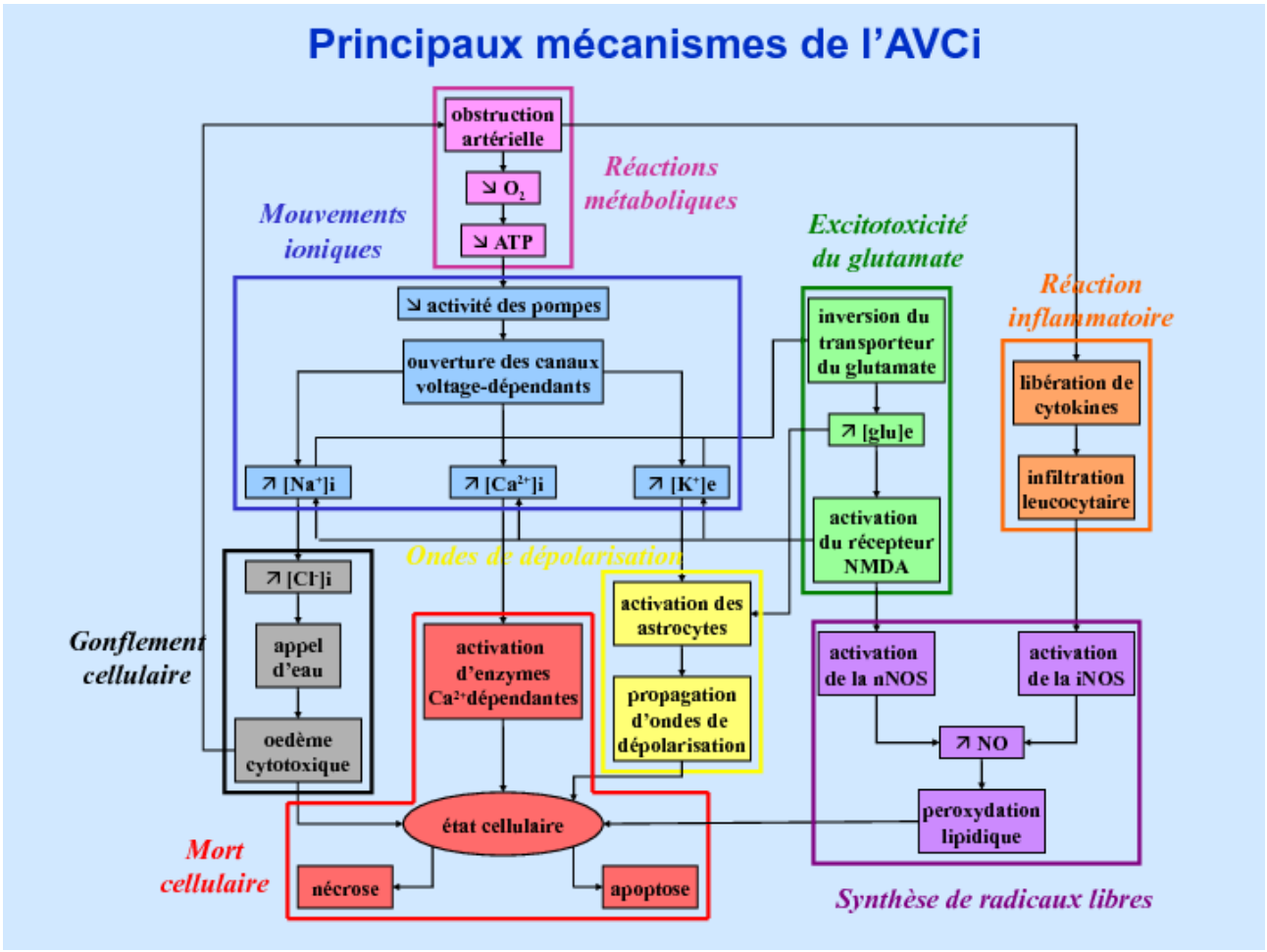

Figure 2. An example of a pdf map reconstructed by using geometrical methods in detecting landmarks

4.1.5. Apoptosis during stroke

A collaboration has begun with Christiane Charriaut Marlangue (INSERM U676, Hopital Robert Debré) to study the apoptotic cascade during stroke.

4.2. Oncology

4.2.1. Tumor growth in mice

Through a collaboration with University of Lyon and Lyon-Sud Hospital, we setup several mechanistic models to predict the evolution of tumor growth in mice including the complex biological process of angiogenesis. This work was presented at the eighteen PAGE (population approach group in Europe) meeting in Saint-Petersburg in June.

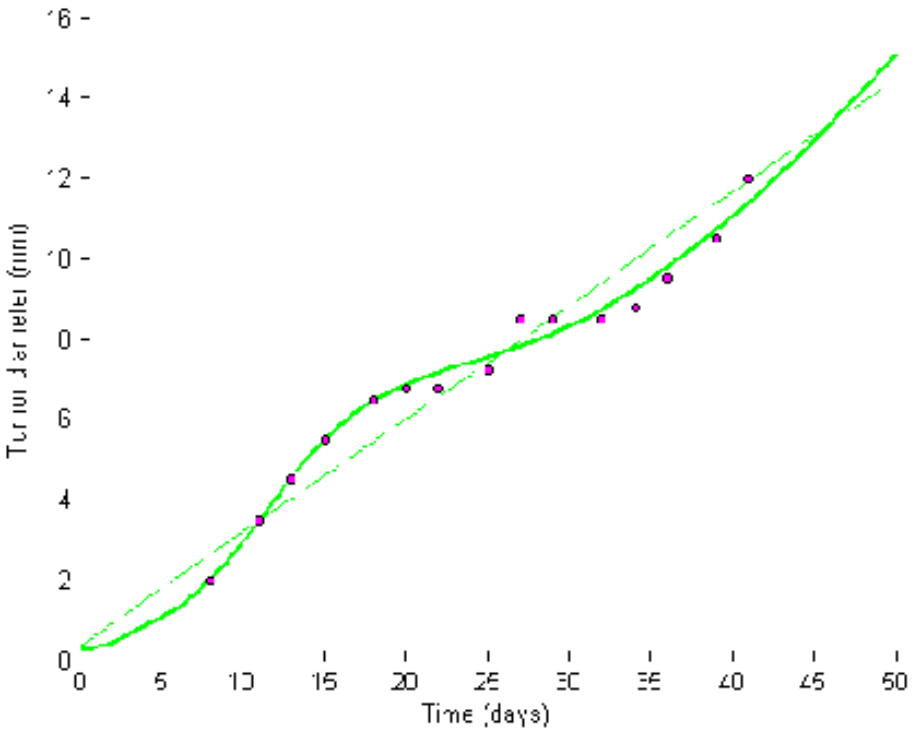

Figure 3. Modeling tumor growth in mice

4.2.2. Radioresistance

Within the framework of the project ETOILE, B. Bernard is part of the team that is building a predictive model of tumor responses to the conventional treatment and irradiation with carbon ions. During 2009, Branka has been working under supervision of Jean-Pierre Boissel and Benjamin Ribba. In collaboration with the group of Claire Rodriguez-Lafrasse (Radiobiology group, Hospital Lyon Sud), her research activities included the analysis of microarray data from different head and neck cancer cell lines, irradiated with X-ray and carbon ions. They detected differences in the irradiation response of different cancer cell lines that underlie their different radiosensitivities. Within GRAAL project, a lot of radiobiological information will be acquired on a several glioma cell lines and cell lines representing healthy brain tissue. Therefore, our interest is to model the dynamics of the glioma tumor growth and its response to radiation therapy. At the moment, we are working on the estimation of parameters describing tumor growth and diffusion from the MRI images of glioblastoma patients (collaboration with Francois Ducray).

4.3. Virology

In collaboration with MERIAL SA and Edouard Heriot Hospital in Lyon, B. Ribba develops mathematical models to describe the dynamic of Feline immunodeficiency virus (FIV) in infected cats. A translational approach is developed in the context of parameter estimation for complex biologically-based model. He intensively uses mixed-effect modeling approaches and its SAEM algorithm implementation in MONOLIX (INRIA Saclay).

4.4. Prion.

[In collaboration with M. Doumic (INRIA Rocq.), P. Gabriel and B. Perthame (Paris 6) – ANR TOPPAZ]

We study mathematically and numerically the polymerization/fragmentation equation involved in prion aggregation. We have investigated first the case of a size-dependent polymerization rate motivated by recent experiments. We now focus on some issue in optimization of protocol. This is closely related to recent challenges in fitness optimization, and optimal control.

4.5. Atheroma

[In collaboration with N. Meunier (Paris 5)]

Following El Khatib et al. (2007) we have proposed a mathematical model for the inflammatory processes driving the growth of early atherosclerotic plaques. This model is coupled with blood flow, with particular emphasis on the influence of shear stress.

5. Software

5.1. Zebre

Participant: Thierry Dumont [correspondant].

Thierry Dumont is currently developping a toolbox to solve stiff reaction diffusion equations using splitting methods, together with refined numerical schemes for ODEs (RADO 5).

6. Contracts and Grants with Industry

6.1. Merial

Participant: Benjamin Ribba.

Modeling of feline immunodeficiency virus (FIV) and parametrization of related models using populationnal data.

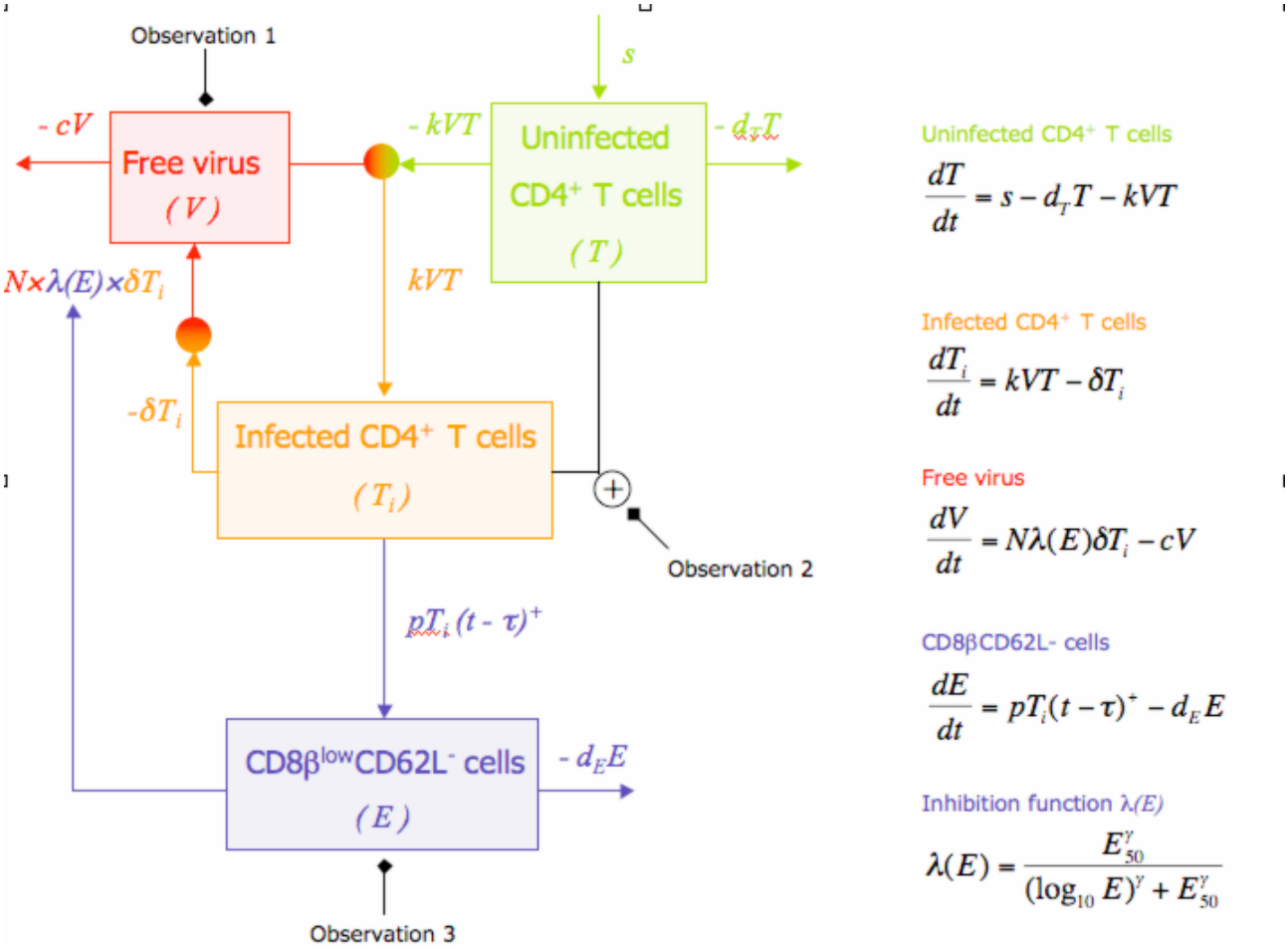

Figure 4. Model of FIV

6.2. Etoile Projet

Participants: Benjamin Ribba, Branka Bernard.

Etoile is a research consortium on hadrontherapy. B. Ribba is responsible for the modeling part and focuses on the study tumor growth models.

6.3. ANR Avc In Silico

Participants: Marie-Aimée Dronne, Thierry Dumont, Emmanuel Grenier.

2009 is the last year of the ANR Biosys projet "AVC in silico" which gathers biologists, clinicians and mathematicians to study various aspects of stroke (inflammation, free radicals, ionic motions, ...).

6.4. ANR "Bimbo"

Participants: Marie-Aimée Dronne, Thierry Dumont, Emmanuel Grenier.

The "Bimbo" ANR project (head: F. Gueyffier, Lyon I) is devoted to the study or atheroma. Numed members has the task to help to parametrize the various models which will emerge from this project.

6.5. Weizmann Institute

Participants: Benjamin Ribba, Floriane Lignet.

B. Ribba is involved in the PhD direction of Floriane Lignet (MSc) on the modeling of in vivo tumor growth data from the Weizmann Institute of Science (on-going collaboration with Prof. Yossi Yarden, dept Biological Regulation).

6.6. Teaching

E. Grenier regularly teaches complex system modeling and parametrization at ENSL and Lyon I University (L3, M1, M2 lectures).

7. Bibliography

Year Publications

Doctoral Dissertations and Habilitation Theses

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Articles in International Peer-Reviewed Journal

[2] F. BILLY, B. RIBBA, O. SAUT, H. MORRE-TROUILHET, T. COLIN, D. BRESCH, J.-P. BOISSEL, E. GRENIER, J. FLANDROIS. *A pharmacologically based multiscale mathematical model of angiogenesis and its use in investigating the efficacy of a new cancer treatment strategy.*, in "J Theor Biol", vol. 4, 2009, 17.

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[9] M.-A. DRONNE, E. GRENIER, T. DUMONT, M. HOMMEL, J.-P. BOISSEL. *A mathematical approach to model stroke pathophysiology*, in "International Heart Forum, Beijing, China", 2009 CN .

Scientific Books (or Scientific Book chapters)

[10] D. BRESCH, E. D. FERNANDEZ-NIETO, I. IONESCU, P. VIGNEAUX. *Augmented Lagrangian Method and Compressible Visco-Plastic Flows : Applications to Shallow Dense Avalanches, Advances in Mathematical Fluid Mechanics*, in "New directions in Mathematical Fluid Mechanics", 2010, 33.

Other Publications

[11] F. LIGNET. *Pkpd modeling*, Lyon I, 2010, Masters thesis.