IN PARTNERSHIP WITH:
CNRS

Université Claude Bernard (Lyon 1)

Ecole normale supérieure de Lyon

Activity Report 2012

Project-Team NUMED

Numerical Medicine

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

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Observation, Modeling, and Control for Life Sciences

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Project-Team NUMED

Keywords: Mathematical Biology

Creation of the Project-Team: January 01, 2009 .

1. Members

Research Scientists

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]
Benjamin Ribba [Researcher (Inria)]
Marie-Aimée Dronne [Assistant Professor (Lyon I)]
Emeric Bouin [phD student (ENSL)]
Floriane Lignet [phD student (ENSL)]
Pauline Mazzocco [phD student (Grenoble)]

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, cell migration models, cell compressibility models, complex cancer models analysis.
- parametrization of complex systems using nonlinear mixed effect methods and populationnal pharmacokinetic pharmacodynamics models, with applications in oncology and virology.

Numed investigates two main applications

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

and a few other subjects (models of prion, motion of cells, vaccine,...).

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

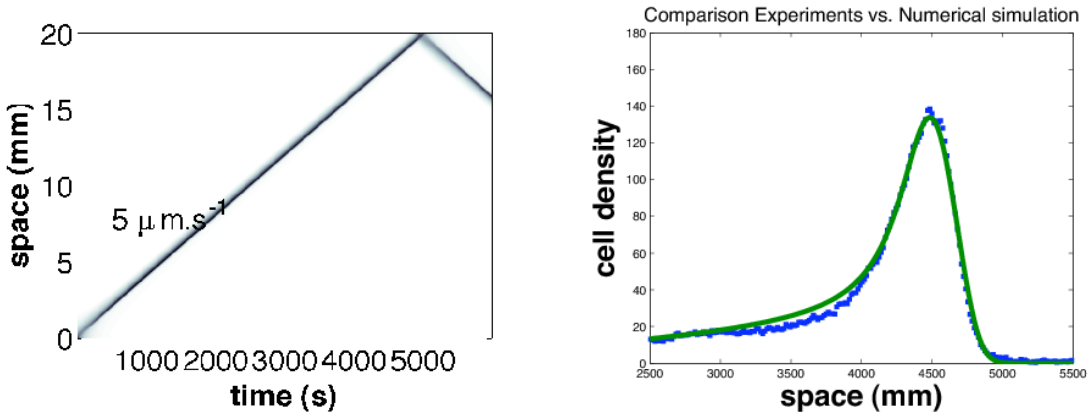

Figure 1. (left) Numerical simulation of a traveling pulse obtained with the kinetic model (right) Comparison between the bacteria density measured experimentally (blue dots) and the density computed from the kinetic model.

We have investigated kinetic models for bacterial chemotaxis following Alt and co-authors, Erban and Othmer, Dolak and Schmeiser.

We have developped a quantitative approach based on a couple of experiments performed by J. Saragosti in the team of A. Buguin and P. Silberzan (Institut Curie, Paris). These experiments describe with full statistical details solitary waves of bacteria E. coli in narrow channels. On the first set of experiments we have demonstrated that the drift-diffusion approximation of the kinetic model is valid and it fits the data very well (publication in PLoS Comput. Biol. 2010). On the second set of experiments we have simulated the kinetic model to obtain the best results as compared to the data (Fig. 1) (publication in PNAS 2011). Interestingly enough, the collaboration has led to the first experimental evidence of directional persistence of *E. coli* (the deviation angle after tumbling is smaller when the trajectory before tumbling goes in a favorable direction). We have demonstrated that this "microscopic effect" has a significant macroscopic influence on the solitary wave ($+30\%$ for the speed of the wave).

Based on these encouraging results, we have started a synthetic analysis of hyperbolic equations for chemotaxis and traveling waves.

In collaboration with Ch. Schmeiser (Univ. Vienna) we have investigated a simple (linear) kinetic equation for bacterial chemotaxis. We have obtained the existence of a stationary cluster (stable density distribution). We aim at applying the hypocoercivity results of Dolbeault-Mouhot-Schmeiser

to derive a quantitative speed of relaxation towards the stable configuration. This work is under finalization.

In collaboration with N. Bournaveas (Univ. Edinburgh), C. di Russo (Univ. Lyon 1) and M. Ribot (Univ. Nice Sophia-Antipolis) we are studying hyperbolic models for cell motion. We improve the results obtained by Natalini-di Russo. These models are preliminary models which are to be complexified in order to describe growth of biofilms. This work is under progress.

In collaboration with E. Bouin and G. Nadin, we are analysing traveling waves arising in kinetic-growth equations. Namely, we study the coupling between a simple kinetic BGK operator (relaxation towards a given Maxwellian) and a logistic growth term. We have improved earlier results by Gallay-Raugel and Fedotov concerning the one-dimensional case with only two velocities. This work has been submitted. We continue the analysis with the full BGK operator. Counter-intuitive results have to be investigated further.

3.1.2. Modeling of spontaneous cell polarization

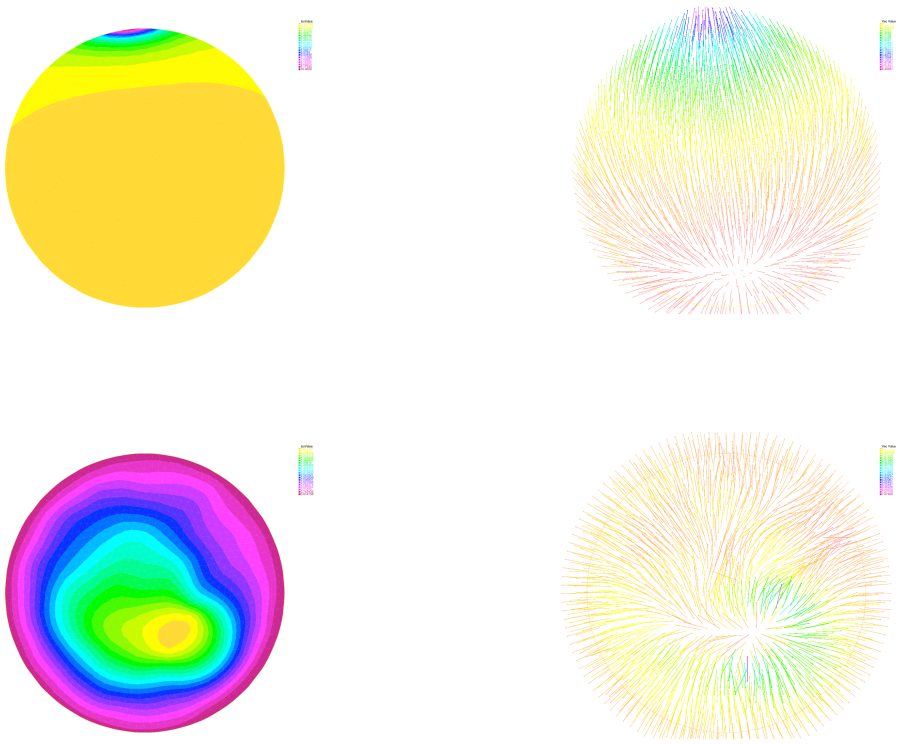

Figure 2. 2D numerical simulations of cell polarization on a round shaped cell. (Top) The actin network carries the attractive field: polarization occurs. (Bottom) The microtubules carry the attractive field: we observe no polarization. (Work in progress; simulations are done with FreeFEM++)

We have analysed recent models describing spontaneous polarization of cells (e.g. neuron growth cones or budding yeast). These models combine a diffusive term (in the cytoplasm) plus an advective field created at the membrane and diffusing in the cytoplasm (accounting for the actin network or the microtubules). This can be compared to the classical Keller-Segel model where diffusion competes with a non-local attractive field. Going beyond linear stability analysis we have used our know-how of the Keller-Segel system to derive

global existence (no polarization) and blow-up (possibly polarization) criteria. We have also performed some numerical experiments to determine the models which exhibit spontaneous polarization. We have confirmed the prediction made by the physicists claiming that the microtubules cannot drive the cell into spontaneous polarization whereas the actin network can (Fig. 2).

Preliminaries results have been published in CRAS 2010 and SIAM J. Appl. Math (in press). We continue this project towards comparison with experimental data obtained in Matthieu Piel's lab at Institut Curie. A secondary goal consists in deriving a mechanistic model for the growth of the fission yeast Pombe. This is an ongoing work with A. Boudaoud (ENS de Lyon), N. Meunier (Univ. Paris 5), M. Piel (Institut Curie), P. Vigneaux (ENS de Lyon) and R. Voituriez (Univ. Paris 6). This is part of an ANR project JCJC, named "MODPOL" (Jan. 2012 – Dec. 2014). The project is coordinated by V. Calvez. It involves Th. Lepoutre (Inria Dracula), N. Meunier (Univ. Paris 5), M. Piel (Institut Curie), P. Vigneaux (ENS de Lyon) and R. Voituriez (Univ. Paris 6).

3.1.3. Polymerization-fragmentation processes

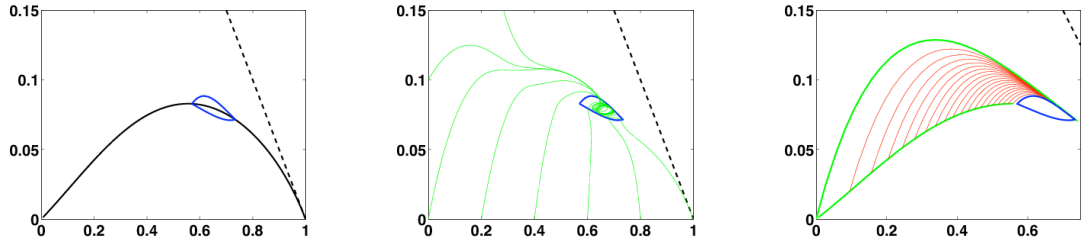

Figure 3. Dynamics of trajectories of the control system projected on the simplex. (left) Remarkable sets in the simplex: the line of eigenvectors parametrized by the control parameter, and the small "ergodic" set. (middle) All trajectories eventually enter the ergodic set. (right) We prove a tunelling effect: all trajectories are confined in a neighbourhood of the ergodic set, and moves towards it.

In collaboration with M. Doumic (Inria Bang) and P. Gabriel (Inria Beagle) we have studied the behaviour of the eigenvalue problem for genuine growth-fragmentation equations. We have focused on the dependence of the couple eigenvalue-eigenvector with respect to the growth and fragmentation coefficients. We have mainly used blowing-techniques and asymptotic estimates. We have shown counter-intuitive (non-monotonic) dependence. We have also discussed the possible consequences on applications.

Together with P. Gabriel (Inria Beagle) we are investigating the optimal control problem for a baby polymerization-fragmentation process mimicking the controlled growth of PrPres (prion) polymers. It consists in a three compartments system (small, intermediate and large polymers) with linear transitions between the compartments. We have a single control parameter acting on the fragmentation process.

We first assume that the control parameter has to be chosen constant. Under certain conditions, there is a best possible choice with infinite-time horizon. It maximizes the exponential growth by optimizing the eigenvalue of the polymerization-fragmentation matrix.

When we relax the condition of constant control, we have to deal with an optimal control problem. It can be translated into a Hamilton-Jacobi-Bellman equation. Although it is a very degenerated case, we can prove existence and uniqueness of an infinite-horizon eigenvalue, as in the constant case. We use the notion of ergodic set introduced by Arisawa-Lions (1998). The success of the proof relies on refined analysis of the dynamics of close-to-optimal trajectories projected on the simplex (Fig. 3). This work is under finalization.

3.1.4. 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.

In many medical contexts, the available data for one particular patient are rather poor (a few MRI for instance). However many patients are studied (20 to 100 or even more in frequent pathologies). Therefore it is difficult or even impossible to parametrize a model for a given patient (too many parameters with respect to the number of available clinical data). However, it is possible to infer the distribution of the parameters in the global population by using all the data of all the patients at the same time. This is the principle of populational parametrization: to look for the distribution of the parameters (Gaussian or log Gaussian) and not to try to study each patient individually.

Many algorithms have been developed for populational parametrization, in particular so called SAEM (Stochastic Approximation Expectation Maximization) algorithms, based on MCMC (Monte Carlo Markov Chain) algorithms. These algorithms are very expensive, and require hundreds of thousands of evaluations of the model. For ordinary differential equation based models, SAEM converge quickly (it takes ten to twenty minutes on a laptop for the Monolix implementation of SAEM. Monolix is developped by M. Lavielle at Inria).

However for PDE based models, the evaluation of one single model may be long (a few minutes, up to ten minutes), hence the evaluation of hundreds of thousands models is completely out of range. Moreover, SAEM can not be parallelized in an efficient way.

Numed has set a general strategy to allow populational approaches on complex systems or on PDE based models. It relies on a precomputation strategy, combined iteratively with SAEM algorithms.

With such a strategy, populational parametrization of a PDE like reaction diffusion equation (KPP) may be done on a few hours on a small cluster of cores (32 cores).

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

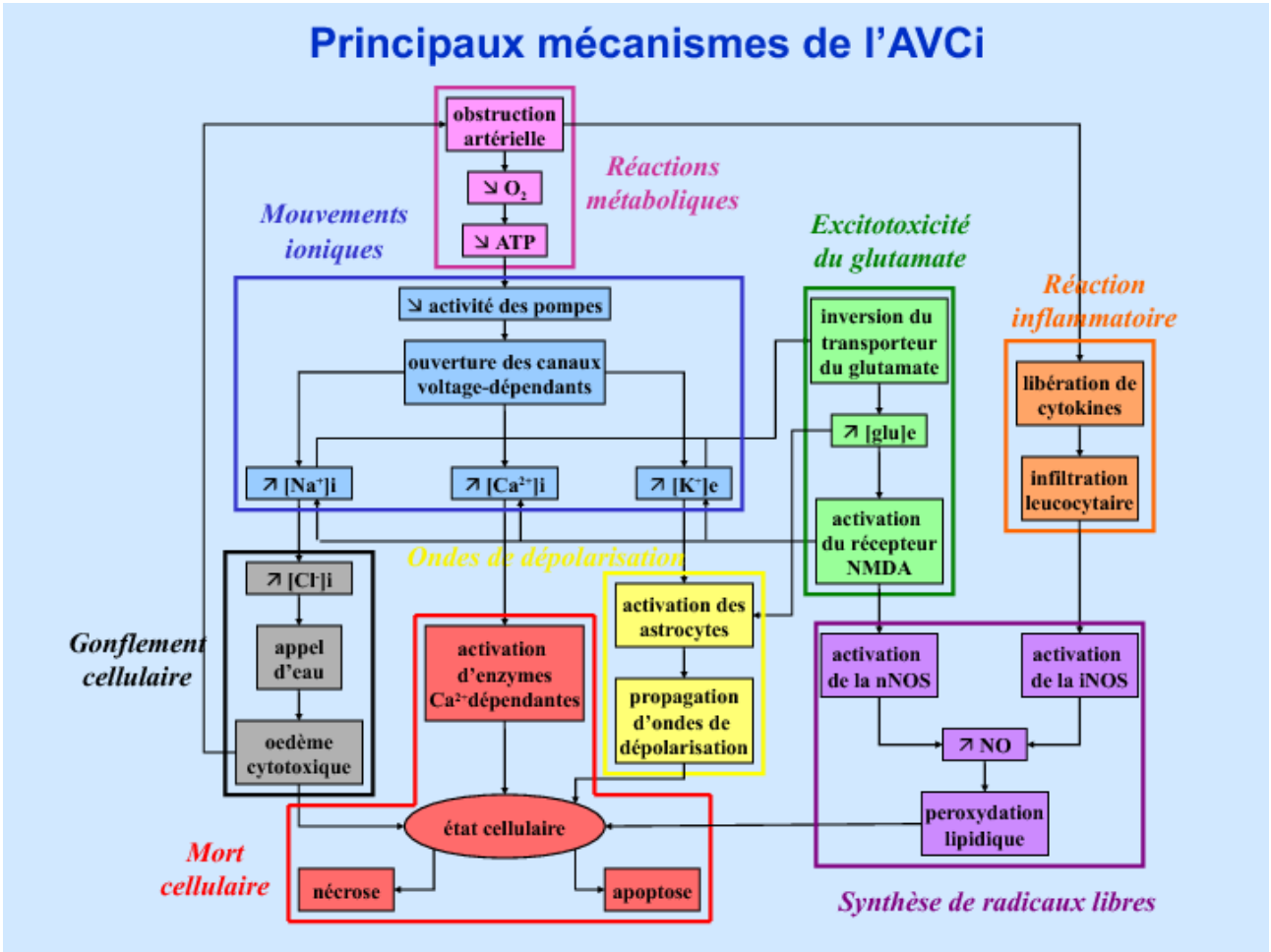

Figure 4. An example of a pdf map reconstructed by using geometrical methods in detecting landmarks

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.

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.

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.

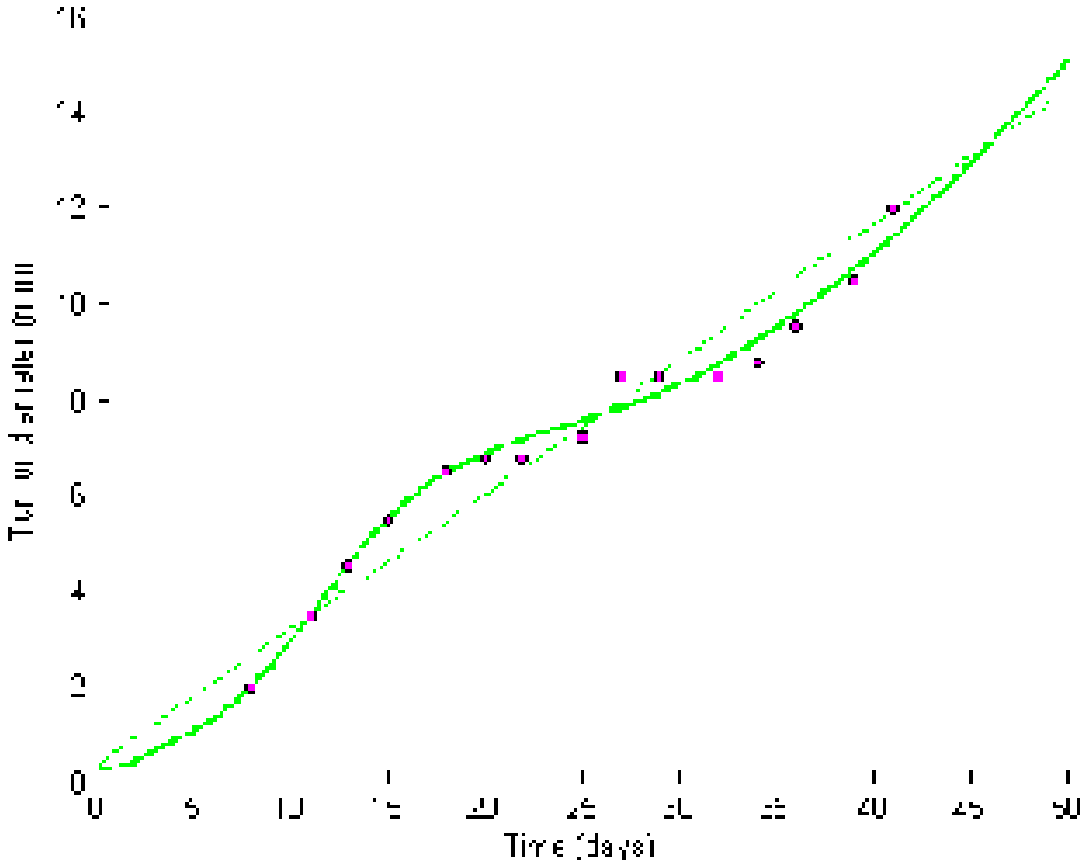

Figure 5. Modeling tumor growth in mice

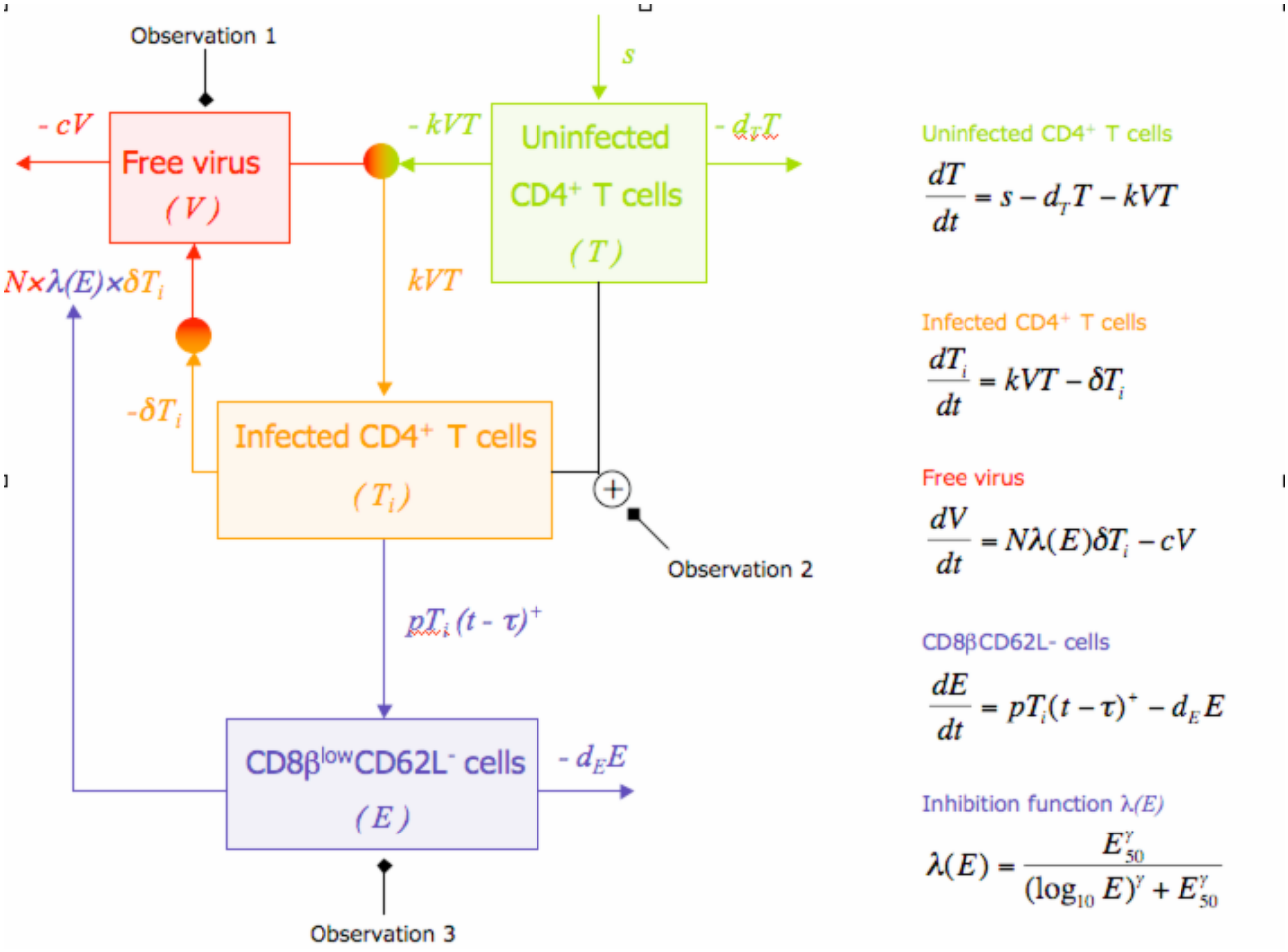

Figure 6. Model of FIV

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).

5.2. OptimChemo

Participants: Violaine Louvet [correspondant], Emmanuel Grenier.

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.

6. New Results

6.1. New result 1

Numed has developped a general strategy and generic softwares (to be released soon) to allow populational parametrization on complex models like PDEs.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

SANOFI Pasteur: second contrat on vaccine degradation study.

7.2. Bilateral Contracts with Industry

SERVIER: four years frame contract.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

Vincent Calvez is head of on ingoing ANR contract on cell mobility.

8.1.2. Competitivity Clusters

Vincent Calvez organizes a special semester on mathematical biology within Lyon mathematical and computer science LABEX Milion.

8.2. European Initiatives

8.2.1. FP7 Projects

8.2.1.1. DDMoRE

Title: DDMoRE

Duration: February 2011 - January 2016

Coordinator: Pfizer (United Kingdom)

8.3. International Initiatives

8.3.1. Participation In International Programs

8.4. International Research Visitors

8.4.1. Visits of International Scientists

8.4.1.1. Internships

Nuria BUIL-BRUNA (from Oct 2012 until Dec 2012)

Subject: Prediction of long-term clinical outcome in cancer patients based on the modeling of tumor size dynamic

Institution: University of Malaga (Spain)

8.4.2. Visits to International Teams

B. Ribba has visited UCSB in autumn.

9. Dissemination

9.1. Scientific Animation

Vincent Calvez organizes mathematical researches visit and talks to high schools students.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence : Enseignant, titre du cours, nombre d'heures en équivalent TD, niveau (L1, L2, L3), université, pays

Master : Enseignant, titre du cours, nombre d'heures en équivalent TD, niveau (M1, M2), université, pays

Doctorat : Enseignant, titre du cours, nombre d'heures en équivalent TD, université, pays

9.2.2. Supervision

PhD & HdR :

PhD : Floriane Lignet, Etude de modèles mathématiques de l'angiogenèse, Université de Lyon, novembre 2012, E. Grenier and B. Ribba.

PhD in progress : Pauline Mazzocco, Modèles mathématiques de survie, 2012, B. Ribba

9.2.3. Juries

E. Grenier has taken part to different phD juries.

9.3. Popularization

Paul Vigneaux is in the editorial board of the vulgarization website "Image des Maths".

10. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

[1] B. RIBBA, H. EL GARCH, S. BRUNET, E. GRENIER, F. CASTIGLIONE, H. POULET, P. VANHEMS. *Time-course analysis of main markers of primary infection in cats with the feline immunodeficiency virus.*, in "Computational and Mathematical Methods in Medicine", 2012, vol. 2012, 342602 [*DOI :* 10.1155/2012/342602], http://hal.inria.fr/hal-00756348.

[2] B. RIBBA, G. KALOSHI, M. PEYRE, D. RICARD, V. CALVEZ, M. TOD, B. CAJAVEC-BERNARD, A. IDBAIH, D. PSIMARAS, L. DAINESE, J. PALLUD, S. CARTALAT-CAREL, J.-Y. DELATTRE, J. HONNORAT, E. GRENIER, F. DUCRAY. *A Tumor Growth Inhibition Model for Low-Grade Glioma Treated with Chemotherapy or Radiotherapy.*, in "Clinical Cancer Research", September 2012, vol. 18, n^{o} 18, p. 5071-5080 [*DOI :* 10.1158/1078-0432.CCR-12-0084], http://hal.inria.fr/hal-00744626.

Other Publications

[3] N. ANDRE, D. BARBOLOSI, F. BILLY, G. CHAPUISAT, F. HUBERT, E. GRENIER, A. ROVINI. *Mathematical model of cancer growth controled by metronomic chemotherapies*, 2012, 18 pages, http://hal.inria.fr/hal-00751645.