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Activity Report 2013

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

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Project-Team NUMED

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

Creation of the Project-Team: 2009 January 01.

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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:

- 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 tumoral tissues.

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

  Parametrization is of course a central issue in modeling. The main issue is to try 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 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.

We emphasize that accurate modeling of bacterial chemotactic waves (described in Adler 1966) was still not achieved. Combination of massive tracking experiments together with a well-parametrized multiscale kinetic model enabled the first accurate description of such waves (Saragosti et al, PNAS 2011).

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

We began with the mathematical description of bacterial chemotactic waves (Saragosti et al 2010). We demonstrated that such waves are better described using a kinetic model for the run-tumble process in the phase space position/velocity (Saragosti et al, PNAS 2011). Taking into account local velocity heterogeneity of the bacterial population is now tractable both experimentally (massive tracking experiments) and mathematically (decorrelation of the asymptotic space decay and the distribution w.r.t. the microscopic variable at the edge of the front). This gave excellent matches in 1D (wave in a straight microchannel), see Figure 1 for the evolution of the spatial density profile.

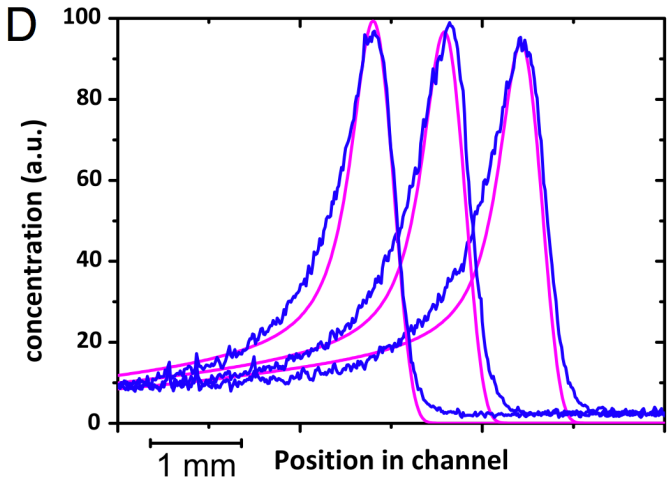

Figure 1. Comparison between experiments (blue) and numerical simulations (pink) for the 1D kinetic model describing chemotactic waves, far from the hydrodynamic regime (Saragosti et al, PNAS 2011).

We emphasize that Filbet and Yang (Univ. Lyon 1) have computed numerically very good predictions of bacterial waves in two-dimensional curved geometries using our model (results not shown).

Next we investigated the analytical computation of the relevant features of the wave (speed, velocity distribution), first in the hydrodynamic regime, then in the full kinetic model.

This work motivated the analysis of reaction-diffusion traveling waves, where diffusion is replaced by a transport-scattering operator. By analogy with the Fisher-KPP equation we proved existence and stability of traveling waves, and spreading properties of the model (Bouin-Calvez-Nadin 2013, Bouin-Calvez-Nadin 2013). A key assumption is the boundedness of the velocity set. Under this assumption we can perform the large deviation limit of the kinetic equation, leading to a new eikonal equation (Bouin-Calvez 2012). Spreading in the case of arbitrarily large speeds (even if they are arbitrarily rare) shows very unexpected properties. For this purpose we currently investigate the large deviation limit of the kinetic BGK model with a Gaussian redistribution of velocities, leading to a new kind of Hamilton-Jacobi equation with constraints (Bouin-Calvez-Grenier-Nadin, in progress). This yields accelerating waves in the corresponding transport-reaction model.

In parallel, we have investigated a selection-mutation model with spatial heterogeneities which combines ecological scales (propagation of invasive species) and evolutionary scales (selection of more motile individuals). This applies to the current invasion of cane toads in Northern Australia. [1]. Again we are able to compute the speed of the wave and the diversity of the population at the edge in the case of bounded phenotypical trait (Bénichou et al 2012, Bouin et al 2012). In the case where it is unbounded we observe accelerating waves, due to continual sorting of more motile individuals at the edge of the front (Bouin et al 2012), just as it is observed in Australia. We also derive formally the limit of adaptive dynamics of this multiscale model (only one trait is selected at each location)[2].

This work has already been cited in the context of tumor progression, taking into account heterogeneity and local competition (Orlando et al, Frontiers in Oncology 2013).

[1] We emphasize that, just as for kinetic models, the microscopic variable (trait = ability to move) acts on the spatial operator (here, diffusion).

[2] This leads to a Burgers equation with source term, due to sorting effects at the edge of the front.

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.

In parallel, we have built a realistic biomechanical models for the onset of instability in the growth of cranial sutures. The basic assumption is that mechanics influences the local orientation of fibers in the tissue. Then cells move preferentially in the direction of fibers, so that growth of the suture interface is coupled to the mechanics. On the other hand, the geometry of the interface has a strong impact on the distribution of mechanical stresses. We were able to perform the full linear stability analysis of this complex model, and derive analytical conditions for the instability of the planar interface. We also performed 2D numerical simulations using FreeFEM++.

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.
More classically, Séverine Enault and Emmanuel Grenier studied the coupling between transport equation and Darcy law in multi population models and obtained in some case existence of weak solutions for all time and in other case blow up in finite time. They in particular underline the link with Euler equations for incompressible fluids. It turns out that these equations are also used in petrology. As a by product they proved the well known Arp's law of exploitation of mature petroleum fields.

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 anti-cancer 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 series of breakthroughs and designed a new powerfull algorithm, leading to Monolix software.

However population parametrization is very costly. It requires several hundered 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 evalution 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 Monolix on such models, since it would be much too long. Moreover the underlying algorithm can not be parallelized.

We propose a new approach combining Monolix software together with a model precomputation on an adaptative grid. This strategy appears to be very efficient, since we were able to parametrize a PDE model as fast as a simple ODE model, after a precomputation step (which can be parallelized).

We develop all the necessary software (parallelized version of precomputation).

In collaboration with Popix project team.

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:

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

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. In the United States, this disease strikes once every 40s and causes death every 4 minutes, with an estimated 41.6% death rate in 2007. Most frequently (80%) strokes result from the occlusion of one or several brain vessels and are thus called ischemic strokes (in the other cases, strokes are hemorrhagic strokes). Ischemic stroke involves many pathophysiological mechanisms causing devastating neurological damage (see Figure 1). Understanding these mechanisms is of the most importance to develop new therapeutic strategies since no treatment are currently available for most stroke patients. Currently, the only FDA-approved treatment for stroke patients is a thrombolytic agent (tPA) which can only be given to less than 10% of patients because of its narrow time-window and its hemorrhagic risks. Many neuroprotective agents (aimed at blocking the ischemic cascade) have also been developed but, although they had given very promising results in preclinical studies in rodent models, they appeared ineffective or even noxious during the clinical trials in stroke patients. This discrepancy between the results in rodents and in humans is partly due to the anatomic and histological differences between rodent and human brains. In this case, results in rodents are thus difficult to extrapolate to stroke patients. As a consequence, a mathematical model and its numerical simulations can help both to test some biological hypotheses concerning the involved mechanisms and to give new insights concerning the effects of these neuroprotective agents.

Before 2009, we had mainly developped models based on the precocious mechanisms of stroke: ionic movements (Dronne et al., 2006; Dronne et al., 2007; Dronne et al., 2008) and propagation of spreading depressions (Grenier et al., 2008; Chapuisat et al., 2008; Descombes and Dumont, 2008). Since 2009, we have continued working on the propagation of spreading depressions in stroke (Dronne et al., 2009; Chapuisat et al., 2010, Grenier et al, 2010, Dumont et al, 2013) and we have developped other sub-models of some pathophysiological mechanisms of stroke such as several models of inflammation (Lelekov-Boissard et al., 2009; Di Russo et al., 2010, two papers in preparation), a model of free radical synthesis (one paper in preparation) and a model of brain energy metabolism in stroke (one paper in preparation). We have studied and qualitatively validated these models and have used them to carry out *in silico* experiments to study and to better understand these biological mechanisms and the relative treatments.

Note that this axe of Numed had to face several difficulties. The former advisor of Marie Aimée Dronne created a start up in this domain in 2009. As a result, we have lost some of our medical collaborators, creating an important gap between the physicians and the other scientists involved in this project. Another problem was the fact that the leader of the project, Marie-Aimée Dronne, had huge teaching tasks due to the series of reforms in pharmaceutical studies and was stopped for maternity leave.

3.6.2. Results

A - Model of cell death

We have built a model of cell death during stroke. This model is focused on the main features of necrosis and apoptosis and their consequences on the surrounding brain tissue. The main variables of the model are energy supply and released toxicity and the reactions are described with partial differential equations (PDE). The aims of this model are to study the role of apoptosis and to explore the effects of anti-apoptotic drugs in stroke patients.

Biological issue

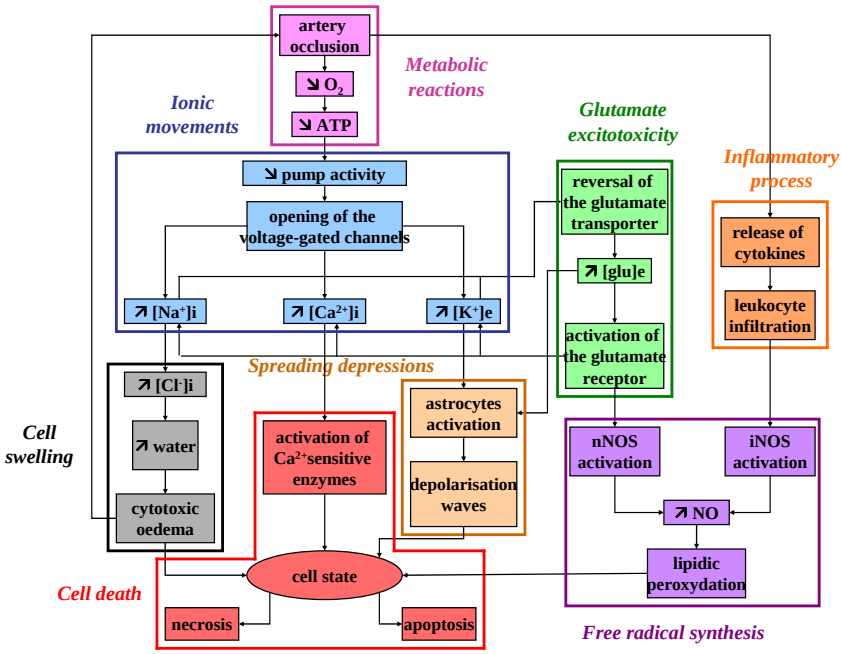

Figure 2. Discursive model representing the main pathophysiological mechanisms involved in an ischemic stroke

During a stroke, the ischemic cascade leads brain cells towards cell death, mainly towards necrosis and apoptosis. Necrosis is a fast and passive cell death involving cells with low ATP-level. Moreover, as necrosis is also responsible for the release of the cytoplasmic content in the extracellular space, it contributes to ischemic damage in the surrounding tissue. On the contrary, apoptosis is an active cell death involving cells with higher ATP supply. Contrary to necrotic cells, apoptotic bodies don't release intracellular constituents and are not accompanied by inflammatory response and surrounding tissue damage. Another feature of the apoptotic process is that two "stages" can be distinguished: the first one is a reversible stage during which the cell is still able to recover and the second one is the irreversible stage during which the cell will finally die. During a stroke, necrosis is observed mainly in the cells located in the infarcted core whereas apoptosis is observed mainly in the cells located in the surrounding area called penumbra. In order to salvage the penumbra, several anti-apoptotic approaches have been studied in rodent models. Some strategies were aimed at indirectly activate the anti-apoptotic activity of Bcl-2 and others were aimed at inhibiting the activities of some caspases. But these approaches encounter problems of use and bioavailability. Moreover, they appeared to be effective during a focal or a transient ischemia but not during global ischemia. Because of all these reasons, anti-apoptotic strategies haven't reach clinics yet. However, these strategies are interesting and would need more studies. Our model is thus aimed at studying the apoptosis process during ischemia depending on the size of the lesion with and without anti-apoptotic treatment.

Model and method

Our model is a qualitative model describing cell death at a global scale. The model takes into account three states of the cells: live cells, apoptotic cells (in the irreversible stage) and necrotic cells. The input variable is energy which represents the cerebral blood flow and the variable which describes the diffusion of the damage is toxicity (due to necrotic cells). The main variables are: Entropy, Apoptotic state and Toxicity. The corresponding equations are partial differential equations and more precisely reaction-diffusion equations.

Results

With this model, we have studied the influence of the value Sapop. This value is the entropy threshold over which the cell enters the irreversible stage of apoptosis. This value is all the more important as the anti-apoptotic strategies are supposed to increase this threshold. We have performed this study in two situations: the first situation describes damage extension in a stroke of small size as can be observed in rodent models and the second situation describes damage extension in a stroke of larger size as can be observed in stroke patients. The simulation results are given in Figures 2 and 3. Figure 2 shows that when Sapop increases in the case of stroke of small size, the number of cells which die from apoptosis decreases and thus, the volume of dead cells decreases. Figure 3 shows a more complex situation in the case of stroke of larger size. In this case, there is a value of Sapop which minimizes the volume of dead volume. Over this value, the volume of dead area increases with Sapop.

Conclusion

These simulation results suggest that, in the case of small stroke (as in rodent models), it would always be interesting to increase the "resistance" of the cells to apoptosis with anti-apoptotic strategies while, in the case of larger stroke (as in stroke patients), it could be interesting to increase the "resistance" of the cells to apoptosis with anti-apoptotic strategies but it would also be important to avoid blocking the apoptotic process since apoptosis has also a protecting role by "absorbing" the toxicity due to the necrotic cells.

B - Inflammation

We have developed several models of the inflammatory process in stroke. Two preliminary models have been built and two others are currently under study. These models takes into account the main molecules (cytokines, NO) and the main cells (microglial cells, neutrophiles and macrophages) involved in this process. They are based either on ODE or on PDE. They are all aimed at studying the complex role of the inflammatory process during a stroke and at studying the influence of some anti-inflammatory strategies in stroke patients.

Biological issue

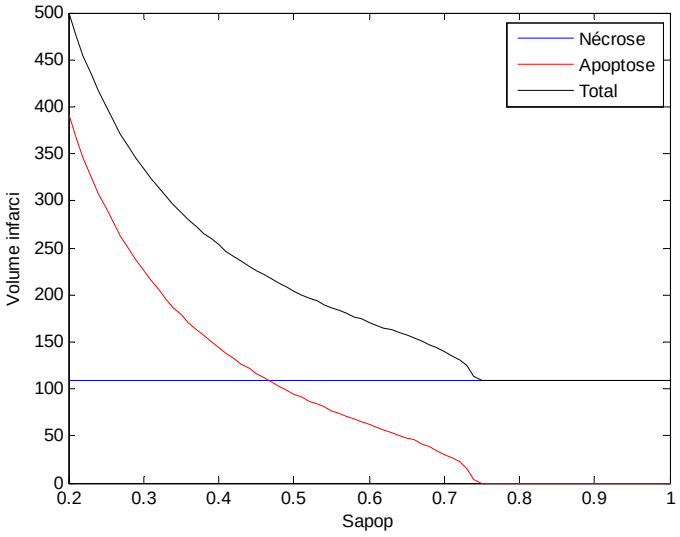

Figure 3. Ischaemic volume

During a stroke, the cerebral blood flow decreases, which results in the death of brain cells firstly through necrotic process. Necrotic cells release intracellular components, resulting in an inflammatory reaction. Microglial cells are activated and produce cytokines, chemokines and other molecules (such as PAF). As a consequence, neutrophiles and macrophages are attracted and begin to infiltrate brain tissue through adhesion molecules. These inflammatory cells produce NO and also cytokines and chemokines to attract other inflammatory cells. These cells have also phagocytic properties and are able to phagocytize damage cells. As a consequenec, the inflammatory process has a dual role: on one hand, it is responsible for the release of toxic molecules (such as NO and some cytokines) and, on the other hand, it decreases the number of necrotic bodies. These mechanisms are represented in Figure 4.

Model 1:
This model is focused on the cells involved in the inflammatory process. It takes into account the inflammatory cells (microglial cells, macrophages and neutrophiles) and the "target" cells (neurons, astrocytes) which can die through necrosis or apoptosis. The relationships between these cells are represented in Figure 5. This model is based on a set of 6 ODE. Its aims were to qualitatively study the dual role of inflammation and to differentiate the role of the precocious inflammation (through microglial activation) and the role of the late inflammation (through neutrophile and macrophage infiltration) by simulating the effect of different anti-inflammatory drugs. The simulation results show that when neutrophile infiltration is blocked, the number of dead cells decrease. The results are the same when the production of cytokines and NO is inhibited. These simulation results suggest the deleterious role of neutrophile infiltration and of the production of cytokines and NO. The role of microglial cells appears to be more complex. The simulation results show that the inhibition of microglial activity as well as the increase of phagocytic activity of microglial cells decrease the number of dead cells. All these results are described in a publication (Lelekov-Boissard et al., 2009). As a consequence, this model gave some preliminary interesting results but need improvements in order to take into account more quantitative aspects and diffusion aspects.

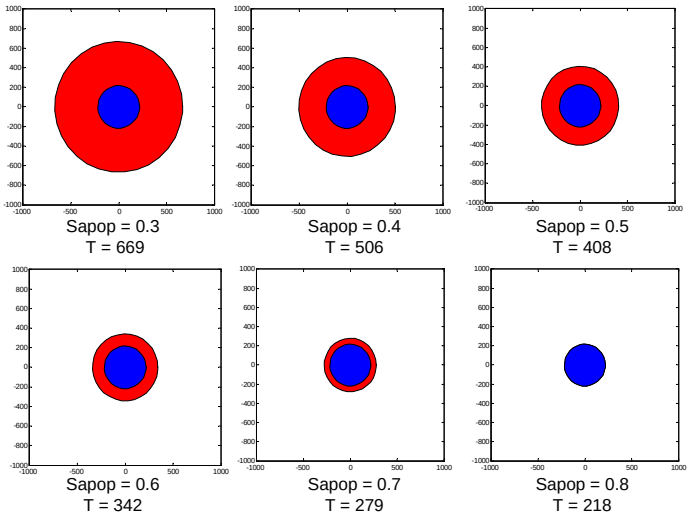

Figure 4.

Section of the ischaemic area
(T = dead volume)

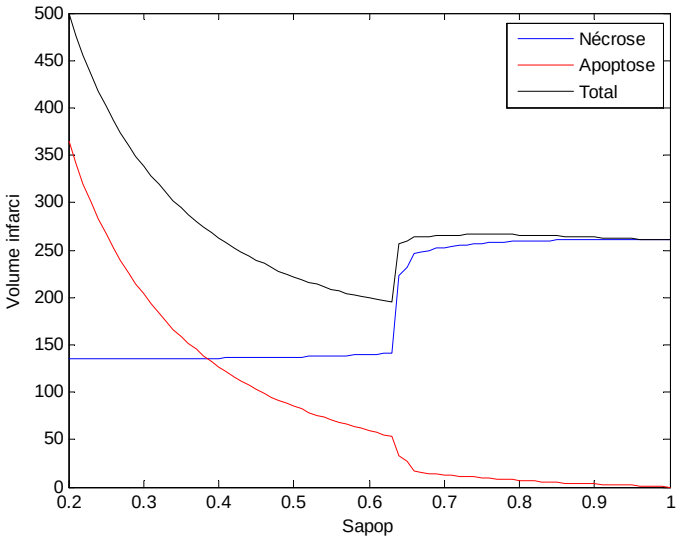

Figure 5. Ischaemic volume

Model 2:
This model is also a cellular model focused on the cells involved in the inflammatory process (Figure 6) but it also take into account the spatial reactions through diffusion and attraction of cells. This model is based on a set of 13 equations (including 7 ODE and 4 PDE) . Two equations are equations of chemotaxis and 2 equations are reaction-diffusion equations. This model was aimed at qualitatively studying the spatial and temporal evolutions of the density of the inflammatory cells and of the concentrations of the inflammatory molecules during a stroke. And it was aimed at studying the influence of the size of the ischemic area on cell death due to the inflammatory process. This model gives rise to a mathematical study and to studies of sensibility and robustness. The simulation results show that when the initial ischemic area is small, the number of cells dead by inflammation is much less important than when the initial ischemic area is larger. These results suggest that the size of the initial stroke has an influence on the extension and the severity of the inflammatory process. All these results are discussed in a publication (Di Russo et al, 2010). As a consequence, this model gives complementary results as the first model presented above but it is always a qualitative model which needs other quantitative data to be improved and to be better validated.

Model 3:
This model is under study. It takes into account 4 variables: two variables for the state of the target cells (alive or dead), another for the inflammatory cells (microglial cells, macrophages and neutrophiles) and the last one for the inflammatory molecules (pro-inflammatory cytokines, chemokines, NO). The model is based on a set of 4 ODE in which the two stages of inflammation are distinguished and in which the cells can be alive, dead or phagocytized. The aim of this study is to use the quantitative data obtained by Maria Grazia de Simoni (Neurosciences, Mario Negri Institute, Milan, Italy) and funded by the ANR "AVC-in silico" project (2006-2009) for the parametrisation and the validation of the model. The model is then aimed at studying the time evolution of the inflammatory process in different situations: in moderate or severe ischemia and with various anti-inflammatory molecules. The simulation results show that the infiltration of neutrophiles and macrophages is all the more important as the ischemic lesion is severe. It also shows other more surprising results: The

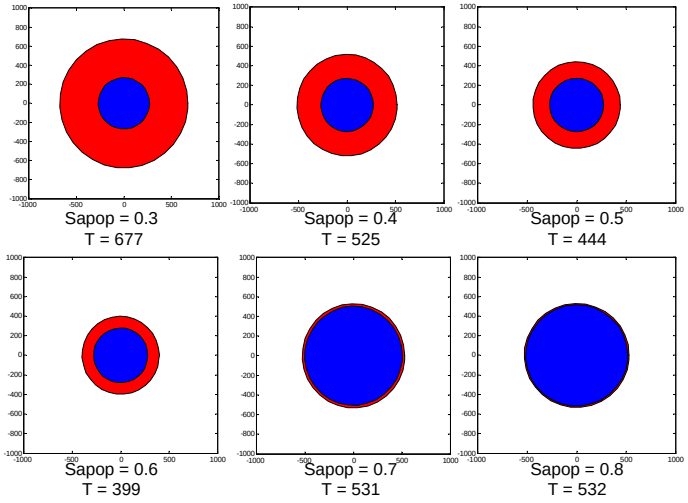

Figure 6.

Section of the ischaemic area
(T = dead volume)

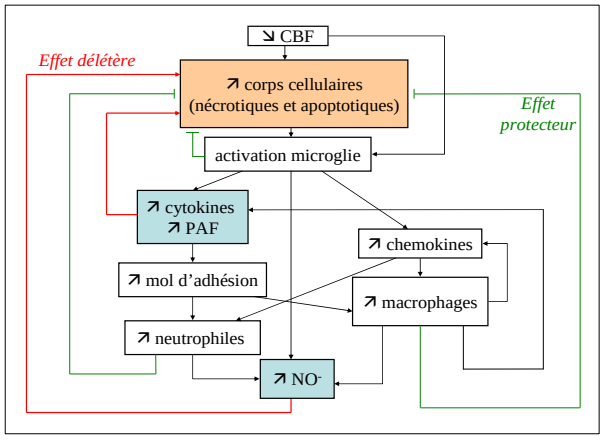

Figure 7. Discursive model representing the main cells and molecules involved in the inflammatory process during an ischemic stroke

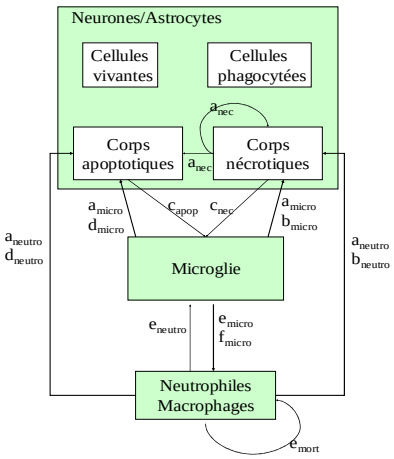

Figure 8. Discursive model representing the cells taken into account in the first model of inflammation

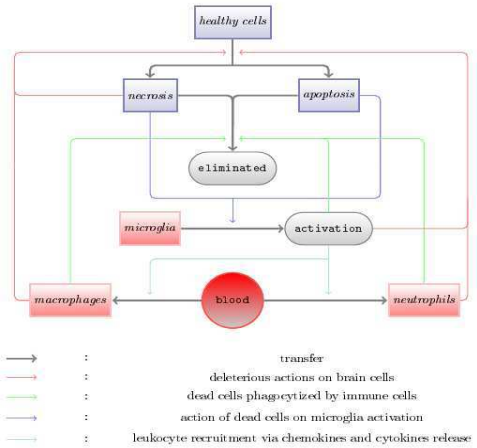

Figure 9. Discursive model representing the cells and the mechanisms taken into account in the second model of inflammation

blockade of the infiltration of neutrophiles and macrophages appears to be more beneficial during moderate than during severe ischemia whereas inhibiting the cytokines is always beneficial whatever the severity of ischemia. These results are qualitative results and the quantitative study of the model needs to be continued. Even if the model has been built with the advise of the scientists who carried out the experiments, the data obtained with these experiments are difficult to exploit because the measured entities don't match the variables of the model. This work is thus under progress.

Model 4:
This model is based on the equations and the parameters used in model 3 but it also takes into account some spatial aspects in order to describe the diffusion of cytokines and the attraction of neutrophiles and macrophages by chemokines. This model thus contains one equation of chemotaxis and one reaction-diffusion equation. As the previous model, it is aimed at studying the effect of the severity of ischemia on cell death through inflammation and at studying the effect of various anti-inflammatory molecules. Meanwhile, numerical methods have been developed in order to use this model on a realistic brain geometry. The aim is to validate this model with medical images (RM images). Some collaborations have been initiated and will be developed with different scientists working in CREATIS (Marlr`ene Wiart, David Rousseau).

C - Model of free radicals

We have built a model focused on the free radical synthesis. This model takes into account the main free radicals involved during a stroke: NO, O2-., ONOO-, H2O2 and OH. and it also takes into account some protecting mechanisms such as glutathion and some enzymes. The chemical reactions are described with non linear ordinary differential equations (ODE). The aims of this model are to study this process and its influence on cell damage during a stroke and to carry out *in silico* experiments with various free radical scavengers.

Biological issue
During a stroke, some free radicals are produced and they will contribute to the degradation of cell state. First of all, some NO is produced in the endothelial cells (through the eNOS) in order to vasodilate the vessel. This production is precocious and rather beneficial. But, after several minutes, much more NO is produced by nNOS in the neurons and by iNOS in neutrophils which have been infiltrating the lesion area. This large production of NO will be all the more deleterious as it will combine with O2-. to produce some ONOO- which are known to degrade membranes, DNA and proteins of the cells and to lead the cells towards cell death. The high production of O2-. is mainly due to the dysfunction of the respiratory chain and is amplified during a transient stroke. It will combine with NO to produce ONOO- but it will also produce H2O2 and OH. with is highly deleterious for cells. Some protecting mechanisms try to limit the production of some free radicals such as glutathion (GSH) and some enzymes (SOD and catalase) but, during a stroke and especially during a transient stroke, these mechanisms are overwhelmed. Figure 7 represents these mechanisms.

Model and first results
The variables of the model are the free radicals and the protecting mechanisms described above. The model inputs are the production of NO and the entry of oxygen. The model outputs are ONOO- and OH. which are the most noxious free radicals. The chemical reactions are described with a set of ten non linear ordinary differential equations. Most of the chemical constants can been obtained in the literature from experimental studies. However, the input variables of the model and the initial conditions are difficult to quantify. As a consequence, the study of the model has first been a qualitative study. First of all, we studied the time evolution of the production of ONOO- and of OH. in two cases: a permanent stroke and a transient stroke. The results show that, during a permanent stroke, ONOO- decreases and OH. increases while, during a transient stroke, ONOO- increases as well as OH. We also carried out *in silico* experiments by simulating the effect of Edaravone which is a free-radical scavenger which has been used in clinical trials in stroke patients.

Conclusion

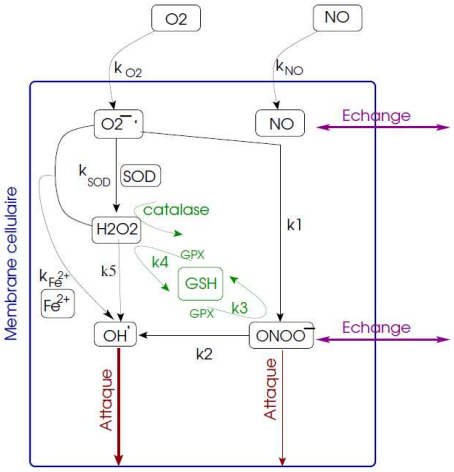

Figure 10. Discursive model representing the main free radicals involved in an ischaemic stroke

These simulation results suggest that, during a permanent stroke, some noxious free radicals are produced but, in the meantime, the protecting mechanisms are stimulated and block the production of some other free radicals. On the contrary, during a transient stroke, the simulation results suggest that the production of all free radicals is increased. These first qualitative results have to be further explored and quantitative data have to be used to validate the model.

D - Spreading depressions

Biological issue

During a stroke, waves of spreading depressions are triggered from the infarcted core. They are supposed to contribute to the extension of ishemic damage. They can be observed in the grey matter of stroke patients with medical imaging. Before 2009, we have already worked on models focused on these spreading depressions (Grenier et al., 2008; Chapuisat et al., 2008; Descombes and Dumont, 2008). Since 2009, we have continued working on models of these depolarisation waves in stroke (Dronne et al., 2009; Chapuisat et al., 2010, Grenier et al, 2010, Dumont et al, 2013). These models are all based on reaction-diffusion equations and are mainly phenomenological models aimed at studying the extension of the damage due to these spreading depressions on realistic geometries of human brain.

Phenomenological models

These models gave rise to mathematical and numerical studies. Two of these models explored the influence of the geometry on the propagation of these waves (Dronne et al, 2009; Grenier et al, 2010). Another model was used to study the influence of intensity and duration of blood flow reduction on cell death during the propagation of these waves (Chapuisat et al, 2010). Another model was a mathematical study on the extension of the necrotic area due to these spreading depressions (Grenier et al, 2010).

Mechanistic model on realistic 3D geometry

The last model (Dumont et al, 2013) is a mechanistic model involving the ionic movements, glutamate excitotoxicity, cytotoxic oedema and spreading depressions and is based on a previous model (Dronne et al., 2006; Dronne et al., 2007). It thus focuses on the first hour of a stroke, when the ionic exchanges are the main mechanisms leading to cell death. In this model, brain tissue is composed of two cell types, namely neurons and glial cells, and of extracellular space. Two domains are considered: the white and the grey matter

which differ in their glial cell composition (astrocytes in grey matter and oligodendrocytes in white matter) and in their "neuronal area" composition (neuronal somas in grey matter and neuronal axons in white matter). Human brain cortex is exclusively composed of grey matter whereas human brain medium is mainly composed of white matter (except the grey kernels). For simplicity reasons, we consider in the model that brain cortex only contains grey matter and brain medium only contains white matter. The ionic species considered in this model are K^+, Na^+, Cl^-, Ca^{2+} and the Glutamate (glu). They pass through neuronal and glial membranes via ionic channels and via ionic pumps and transporters. Altogether, the mean field model has 19 unknowns and is of reaction-diffusion type, except that there is no diffusion for 4 unknowns. There is also a difference in the number of reaction-diffusion equations in grey matter and in white matter. Since grey matter contains astrocytes (which are linked into an astrocytic synticium thanks to gap-junctions), ions are able to diffuse in the astrocytic space as well as in the extracellular space in grey matter. On the contrary, as the main glial cells in white matter are oligodendrocytes, ions are considered to be only able to diffuse in extracellular space in white matter. As a consequence, the model contains 10 reaction-diffusion equations in grey matter (for the concentrations of K+, Na+, Ca2+, Cl- and Glu in astrocytes and in the extracellular space) and 5 reaction-diffusion equations in white matter (for the concentrations of K+, Na+, Ca2+, Cl- and glu in the extracellular space). The domain corresponds to a human brain and is divided in grey and white matter. These two matters differ in several coefficients in the reaction term (corresponding to the cell composition) and in their diffusion coefficients. To run this model on such a complex geometry, we had to develop new numerical methods. A first description of the algorithms used for the numerical solution of this stroke model on 1D and 2D geometries was presented in a previous article (Descombes and Dumont, 2008). However, since we need to take into account the anatomic and histological specificities of human brain, this model needs to run on a 3D realistic geometry, which implies to develop powerful numerical methods able to deal with a broad spectrum of spatial and temporal scales. The numerical method is based on operator splitting and explicit/implicit Runge-Kutta methods. We then show, for the first time, numerical simulations in 3D obtained thanks to a particular implementation of parallelism, in the framework of shared memory machines. The simulation results show spreading depressions which propagate exclusively in grey matter, which was expected. We then studied the evolution of the extracellular concentration of potassium and of the rADCw (which reflect the severity of ischemia) in the domain. The quantitative values obtained for these two biomarkers in the infarcted core and in the surroundings are consistent with the values measured during biological experiments or with medical imaging.

Model of cell death

Studying the relationships between necrosis and apoptosis in stroke with simulations is of the most importance since they are difficult to study with *in vitro* or *in vivo* experiments. Moreover, this question is currently important since new anti-apoptotic strategies are currently under study in stroke patients (such as the CsA). This model is currently a qualitative model and can't be validated with quantitative data yet. But we plan to use perfusion images and diffusion images to have some "input" situations and some "output" situations of the damage extension. We are currently discussing these questions with physicians in the neurologic unit in Lyon hospital.

Inflammation

These models are important to continue and to develop since the role of the inflammatory process in stroke needs to be better understood. We need to use and to obtain new quantitative data from *in vivo* experiments (biological dosages or medical imaging) to improve the parametrisation of the models (the ODE and the PDE models) and their validation. That's why we need to continue working with biologists and scientists working on medical images (such as in CREATIS in Lyon).

Free radicals

The model gives first interesting results but it needs to be developed. We will continue working on this model with data coming from Michel Plotkine and Isabelle Margaill (EA 2510, pharmacie, Paris 5). An M2 master student will be supervised in 2013-2014 on this subject. These data should help to complete the parametrisation of the model and to validate the model.

Spreading depressions

The study of spreading depressions in stroke has been an important subject of the "AVC-in silico" team but our current models are not focused on this mechanism. However, the numerical methods developed during these studies are currently used in other models such as in models of inflammation (which contain reaction-diffusion equations and also equations of chemotaxis).

3.6.3. Collaborations

- Chapuisat Guillemette (LATP, UMR CNRS 6632, Université Aix-Marseille 3)
- Di Russo Cristiana (MAPMO, UMR CNRS 7349, Université d'Orléans)
- De Simoni Maria Grazia (Neurosciences, Mario Negri Institute, Milan, Italy)
- Berthezène Yves, Wiart Marlene, Rousseau David (neurologic unit, Lyon hospital and CREATIS, CNRS UMR 5220 - INSERM U1044 - Université Lyon 1 - INSA Lyon)
- Plotkine Michel and Margaill Isabelle (EA 2510, pharmacie, Paris 5)
- Lemesle Valèrie (Montpelliers)
- Descombes Stṕhane (Laboratoire J.A Dieudonné, UMR CNRS 7351)

4. 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.

4.3. 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).

This code was first designed to serve as demonstrator of the theoretical results of Descombes and Massot on the solution of stiff reaction-diffusion systems by alternate directions methods, and as a first step towards complex chemistry simulations. Later it was used and improved to solve the ionic model of strokes, and incorporated stabilized explicit Runge Kutta methods for diffusion steps. Coded in C++, it solves stiff systems with various schemes in dimension 1, 2 and 3, in complex geometries. The code is multithreaded.

4.4. 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.

4.5. Simstab

Stability prediction of vaccine, intellectual property of Sanofi, covered by a US patent demand (Sanofi, Benjamin Ribba, Emmanuel Grenier).

4.6. 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. Bilateral Contracts and Grants with Industry

5.1. Bilateral Contracts with Industry

- Sanofi Pasteur: design and implementation of a software to study drug stability. Currently used in a dozen of Sanofi projects, with large possibilities of expansion.
- Servier: four years framework agreement. PK PD modeling of new drug in oncology.

6. Partnerships and Cooperations

6.1. National Initiatives

6.1.1. ANR

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

6.1.2. Competitivity Clusters

Vincent Calvez organized a special semester on mathematical biology within Lyon mathematical in spring 2013. and computer science LABEX Milion.

6.2. European Initiatives

6.2.1. FP7 Projects

6.2.1.1. DDMoRE

Member: Benjamin Ribba.

7. Dissemination

7.1. Scientific Animation

- Vincent Calvez: Organization of a thematic trimester in Lyon "Mathematical Biology 2013" (ENS and Univ. Lyon 1): 3 months, 4 conferences, 1 workshop and 1 summer school, more than 400 participants, focus on interdisciplinary conferences with biologists and theoretical physicists (evolutionary biology, cell biology, drug development, system biology).
- Paul Vigneaux and Vincent Calvez are editors of the **CEMRACS 2009 - Mathematical Modelling in Medicine** Proceedings. ESAIM. Vol. 30, August 2010, 165 pages.
- **Organization of Conferences :**
  In 2008/2009, Vincent Calvez and Paul Vigneaux co-organize the **CEMRACS 2009 - Mathematical Modelling in Medicine**, 14^{th} edition of this 6-week international summer school (at the CIRM, Marseille, France, July 20 to August 28, 2009). CEMRACS is supported by the SMAI (French Industrial and Applied Mathematics Society).
  In 2010, Paul Vigneaux co-organizes the **8^{th} JERAA**, 25-26 Nov., a two days conference on Partial Differential Equations gathering the community from Rhône-Alpes-Auvergne (France).
- **Seminars :**
  Since September 2008, Paul Vigneaux and Vincent Calvez co-organize the "Modelling and Partial Differential Equations" seminar, joint with ENS de Lyon and Institut Camille Jordan (4 talks by month, from September to June).
- **Commissions and Boards :**
  - Paul Vigneaux is member of the Board of **MILYON**, the Laboratory of Excellence (Labex) in Mathematics of Lyon. This Labex aims at federating international research, higher education and society activities.
  - Paul Vigneaux is member of the Hiring Commissions (“Comités de Sélection”) at the University of **Clermont-Ferrand 2**, **Lyon 1**, **Montpellier 2**, **Centrale Nantes**, **INSA Lyon** and **ENS de Lyon** : it consists in the selection of candidates for permanent positions in the Mathematics department.
  - Paul Vigneaux is member of the Boards of the Numerical Modelling Center (**PSMN**) of Lyon, of **UMPA**, the mathematics research lab at ENS de Lyon, of the Board of the Department of Mathematics (teaching) at ENS de Lyon.
  - Emmanuel Grenier created, together with Didier Bresch, the first national network gathering most of the french academic teams working on mathematical models for life sciences (GDR Mabem $2008-2011$). He is in the scientific board of the GDR Metice, successor of GDR Mabem.

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

- Marie Aimée Dronne teaches 192h per yer, in Lyon 1 University and in INSA de Lyon (Licence and Master, "master of neurosciences", "master of cancerology", "master of drug development"), teaching in mathematics and statistics for medical students and modeling for INSA students (electrophysiological models, epidemiological models, pharmacocinetic models)
- Vincent Calvez teaches 64h per year, L3, M2 (mathematics, complex systems) at ENS de Lyon

- Paul Vigneaux has his Associate Professor's teaching service (192 hours each year in 2010, 2011, 2012) at ENS de LYON. A few hours are done at L3 level and the majority of the service is done at 'Agregation' Training (M2 level): Numerical/Analysis, Partial Differential, Scientific Computing and Modelling. Excellent results are obtained by his students at the National Competition "Agregation de Mathematiques" (Several 20/20 and one first total rank (over 300 competitors) in 2012).
- In 2013, Paul Vigneaux only teaches 64 hours thanks to an Inria "delegation". The same year, he was an invited lecturer at the well established CNRS thematic school on "Computational Fluid Mechanics" (13th edition, each 2 years). This school is intended for Tenure-Track Researchers' as well as PhD students' training. He was also invited to give a 12 hours Doctoral lecture in the framework of the PhD program of the Institute of Mathematics of Seville, Spain (with Excellence Label from the Ministry of Education). He is also teaching at the M2-Recherche level at ENS de Lyon, a core lecture of the Mathematical Doctoral Program training of Lyon.
- Emmanuel Grenier is professor. He teaches 192h per year, at L3, M1, M2, Agrégation level (modeling, pde, analysis, ...). He was responsible of third year students of mathematics at ENS Lyon. He is now responsible for first year master students. He is a former associate professor at Ecole Polytechnique (till 2010).

7.2.2. Supervision

HdR: Benjamin Ribba, Université de Grenoble, 2013.

7.3. Popularization

- Vincent Calvez is responsible for regular actions towards high school students (regular talks in high schools).
- Paul Vigneaux:

  Paul Vigneaux has a significant activity in the official dissemination website of CNRS: "Images des Mathematiques". He is a member of its Editorial Board since the beginning in 2009, in particular responsible of the "Billets" section (60% of the total reading flux of the website). Nonetheless, he also edited most of the applied mathematics articles of the site and made several articles contributions. Among others a translated/commented article on Richard Courant and his Institute, as well as a series, with the authorization of the EMS, of 20 articles on "Success Stories of Mathematics in Industry" in 2012-2013. Cf: http://images.math.cnrs.fr/Vigneaux-Paul.html In 2013, he was one of the editors of the series of 40 books published by the association of *Le Monde* (top national newspaper), *Institut Henri Poincaré* (Head: Cedric Villani) and *Images des mathematiques*. This series was supported by Cedric Villani and aims at broadcasting mathematics to a general public. Vincent Calvez was also one of the editors of the series. Currently still under publication, it is already an editorial success in terms of selling (20 book issued).

8. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

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