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Mathematical Modelling in Medicine

July 20th – August 28th 2009, Luminy, Marseille, France

List of projects for the research session
(updated June 22, 2009)

Modeling and numerical simulations of nanometric aerosols in the lower part of the bronchial tree

Project proposed by **Laurent Boudin** (Univ. Paris 6, INRIA Rocquencourt) and **Céline Grandmont** (INRIA Rocquencourt)

Framework and goals

The classical model of the bronchial tree is divided into several different regions. Between the 8th and 17th tree generations, the air flow can be described through a Poiseuille law. Beyond, till the 23rd generation, the diffusion (Fick's law for instance) is the main phenomenon, and the convection can be neglected.

Therapeutic aerosols have to go very low in the bronchial tree (e.g. reach the pulmonary alveola). Several modelings are possible with respect to the mean size of the aerosol particles (statistical description with a kinetic equation, full description with a system of ordinary differential equations). The aerosol metrology is a key point, since the size of an aerosol particle has a strong impact on the location where the aerosol mainly deposits inside the airways.

We first aim to give coupled models for the air flow beyond the 8th generation and for an aerosol in which the size of the particles are scaled to the nanometer. Then these models will be coupled to air-aerosols models developed for the proximal part of the bronchial tree and numerically investigated using the solver Freefem++.

The project is strongly related with some experimental studies led in the "Aerosols and bronchopneumonic cancer" team of Pr. Patrice Diot, in Tours.

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

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Multiscale mathematical modeling of tumor growth and angiogenesis

Project proposed by **Thierry Colin** (INRIA, MC2), **Emmanuel Grenier** (INRIA, NUMED), **Benjamin Ribba** (INRIA, NUMED) and **Olivier Saut** (INRIA, MC2)

Framework and goals

The aim of the stage is to operate the coupling between a microscopic model of the molecular pathways involved in the process of tumor angiogenesis and a macroscopic model of tumor growth and treatment efficacy. In particular, a quantitative comparison between the different model dynamics (microscopic and macroscopic) is expected to be achieved through numerical simulations.

The process of tumor growth is very complex and not easy to describe, simulate and predict through mathematical modeling tools. Still, with the appearance of innovative treatment strategies such as the targeted therapies, a predictive computer model of tumor growth process may have a significant impact for optimizing the delivery of anti-cancer treatments. The process of tumor-induced angiogenesis is recognized as a key process of tumor growth and cancer development. Anti-angiogenesis drugs have been developed and have shown their efficacy in several cancer diseases. However, these new medicines are always associated with conventional chemotherapy. The framework of this project is the optimization of anti-angiogenesis drug delivery in combination with conventional chemotherapy.

The candidate(s) will work on an on-going development model of tumor growth and treatment. The main objective is to operate the coupling between a macroscopic layer of the tumor growth model and a microscopic layer which focuses on the refined description of the process of angiogenesis at the molecular level.

Expected background and skills

The candidate(s) should have basics in molecular biology, applied mathematics and numerical analysis.

References

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Modelling the formation of atheromatous plaques

Project proposed by **Vincent Calvez** (ENS Lyon), **Nicolas Meunier** and **Annie Raoult** (Univ. Paris 5)

Framework and goals

Atherosclerosis and its complications are one of the most common causes of death in western societies and in Japan. According to recent works, the lesions of atherosclerosis which take place in the intimal layer constitute a chronic inflammatory response to injury. It is now well accepted that atherosclerosis involves plasma low density proteins cholesterol, monocytes/macrophages, endothelial cells and smooth muscle cells.

The advanced lesions of atherosclerosis are most commonly reported in large or medium arteries which can be considered as thick-walled tubes whose internal surface is exposed to flowing blood and external surface is bounded by tissue.

It appears that local hemodynamics conditions have significant impact on the earliest stages of atherosclerosis lesions. Indeed, low wall shear stress, oscillating shear stress and long residence times have been shown experimentally to influence the formation and the composition of plaques. Furthermore, it appears that the plaque composition is crucial in order to predict its evolution. Plaques with thin fibrous cap are easily seen to fracture and then to give raise to complications.

This project aims at providing a mathematical model describing in a simplified manner the inflammatory process, the formation of the fibrous cap and at coupling it with blood flow in the arterial lumen. We will perform numerical simulations (with the solver Freefem++) in order to reproduce 2D experiments.

References

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Modelling of active suspensions

Project proposed by **Bertrand Maury**, **Astrid Decoene** and **Sébastien Martin** (Univ. Paris Sud)

Framework and goals

Some bacteria (like *Escherichia coli*) are able to swim in a viscous fluid. This project aims at modelling collective phenomena of (possibly dense) suspensions, by means of direct numerical simulations. In particular, we plan to investigate some phenomena which are well documented experimentally:

- variation of the apparent viscosity
- chemotactical behaviour
- self-organization.

References

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Migraine with aura and cortex circumvolutions

Project proposed by **Franck Boyer**, **Guillemette Chapuisat** and **Florence Hubert** (Univ. Aix-Marseille 1 & 3)

Framework and goals

Migraine with aura is an headache accompanied by visual hallucinations and sometimes also prickling in arms or hands and in some cases by a short aphasia. It is conjectured that migraine aura is linked to the propagation of spreading depressions that would cross several area of the brain (visual areas then somatosensory areas...). The reason why those spreading depressions stop at various positions depending on the patient is still unclear but it as been clearly established that they almost always stop at the bottom of a circumvolution. The aim of this project is to numerically study the influence of the curvature of the cortex on the propagation of spreading depressions.

Spreading depressions are triggered by ionic disturbances in the brain. The complete mecanism of spreading depression is still unclear but they are created by a bistable reaction-diffusion mecanism in the cortex and diffusion and absorption mecanisms in the rest of the brain. Hence we would like to study the following equation

$$\partial_t u - \nu \triangle u = \lambda u(u-\theta)(1-u)\mathbb{1}_\Omega - \alpha u \mathbb{1}_{\Omega^c}$$

where Ω represents the cortex (i.e. a thin curved layer at the periphery of the brain). The existence of generalized travelling fronts will depend on λ, α, θ and on the width and the curvature of the cortex [1]. It has been proved [2] that there exists parameters such that the front stops at the bottom of the Rolando sulkus (a real brain geometry has been used). We would like to estimate the limit curvature that prevent the propagation of the front on the all domain and to study how this limit curvature depends on some parameters that could be therapeutically modified.

References

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[2] E. Grenier, M.A. Dronne, S. Descombes, H. Gilquin, A. Jaillard, M. Hommel, J.P Boissel. A numerical study of the blocking of migraine by Rolando sulcus. Preprint (2008).

Optimal placement of electrodes

Project proposed by **C. Poignard** (INRIA Bordeaux), **F. de Gournay** and **O. Kavian** (UVSQ)

Framework and goals

When submitted to an electric field, the membrane of cells becomes thinner and molecules that could not enter the cell may then pass the membrane. This phenomenon, known as *electroporation*, is used in the treatment of skin cancer where the local toxicity of drugs (here bleomycin) is multiplied.

Teams in INRIA-Bordeaux, UVSQ, IGR are trying to understand and modelize the electroporation in order to design an operative treatment of cancer. The major problem encountered by oncologists when trying to electroporate cancer cells is a restriction on the position and on the number of electrodes the physician can put near the cells (for instance in a deep-brain tumor). Hence the technical need for an optimization algorithm that can place a prescribed number of electrodes in order to electroporate a given cancer map. The problem reads as a control problem where the sources of the current must be placed so that the zone where the electric field (in modulus) is greater than a certain threshold fits a prescriped cancer map.

The aim of the project is to provide a functional algorithm that can place the electrodes in dimension 2. We will perform several simulations with either Freefem++ or built-in C++ code with finite element librairies. Good programming skills are mandatory to achieve this project.

Physiological modelling of renal dysfunction

Project proposed by **Marie-Aimée Dronne** (Univ. Lyon 1) and **François Gueyffier** (Univ. Lyon 1)

Framework and goals

This project aims at building integrated sub-models of human pathophysiology of hypertension, and exposure to blood pressure lowering drugs (pharmacokinetics and pharmacodynamics) in particular betablockers. The ultimate goal is to simulate on a virtual population the public health impact of different scenarios to use these drugs.

Cell motility: towards visco-elasto-plastic features

Project proposed by **Vuk Milisic**, **Dietmar Oelz** and **Christian Schmeiser** (Wolfgang Pauli Institute, Vienne)

Framework and goals

From the mathematical point of view, the description of biological systems is a big challenge: typically, processes on different time and spatial scales have to be described simultaneously, and their essential features must be captured correctly by the model without making it unnecessarily complicated. Mathematical models for cell movement fulfilling these requirements are often obtained by a limit procedure: first, a detailed microscopic model is established, then a macroscopic limit is carried out, yielding a macroscopic model which is easier to handle both analytically and numerically. The advantage of this method is that through the limit procedure, information from the microscopic level can be incorporated into the macroscopic equations (cp. [2, 1]).

A major focus should be dedicated to the mathematical description of the Actin cytoskeleton: this network is constantly being reorganized, growing at the front of the cell and contracting at the rear while exerting force to the substrate via particular adhesion proteins [4, 3]. The mathematical description of this process is indeed challenging, as chemical signals inside the cell contribute to changes in the structure of the network as well as external chemical or mechanical stimuli. The equations used in numerical simulations are often only asymptotic limits of more complex epsilon models involving among others specific time delay features.

In this project our goal is to establish clearly several features of the epsilon model and the correct scalings to exhibit such a behaviour at the limit. This approach should be performed both on the continuous theoretical level and the numerical one. The expected deliveries of the project should be a numerical code that should be both accurate and robust for every epsilon, some benchmarks exhibiting various mechanical properties of the fibrous material, and possibly some theoretical results on qualitative/quantitative mathematical features of our approach.

References

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Numerical simulation of biological mucus film in lungs using multi-fluid vorticity formulation of Navier-Stokes equations

Project proposed by **Philippe Poncet** (Institut de Mathématiques de Toulouse) and **Marc Thiriet** (CNRS, INRIA Rocquencourt, Paris 6)

Background

Mucus is a viscoelastic fluid secreted by the respiratory epithelium that protects tracheobronchial tree mucosa from dehydration and traps inhaled particles (allergens, carcinogens, dust, micro-organisms, and inflammatory debris) that come into contact with it. Ciliary motions that are associated with mucus propulsion in the human respiratory tract cleans airways, as it flows from either the tracheobronchial tree or upper airways toward the pharynx, where it is swallowed (or expectorated).

Four main factors determine efficiency of mucociliary clearance: (1) Number of cilia that synchronously beat; (2) Cilium beating frequency; (3) Thickness of mucus layer; and (4) Composition and rheology of mucus. Efficient mucociliary transport requires appropriate mucus composition for optimal flow, adequate numbers of functioning ciliated cells and their coordinated motion for mucus propulsion, as well as respiratory epithelium integrity over long distances.

Goal and Framework

This project aims at modelling and simulating airway surface fluid mobility in lungs. Human respiratory ducts are coated by epithelial cells that yield a carpet of cilia vibrating in the airway surface fluid to propulse the mucus stratum with entrapped particles outside the ventilatory system. Motion of the airway surface fluid also influences air circulation. Many attempts have been made to study separately epithelium, mucus features, and air flow in lungs. Nevertheless, coupling of movements of these interacting compartments has never been investigated and this work aims at bringing new insight in numerical strategies for numerical simulation of this coupling. Lagrangian velocity-vorticity formulation of the Navier-Stokes equations have been proved to lead to very robust schemes [5, 2, 4], and will be used in this work.

The configuration considered is a two-phase flow (air and mucus), with oscillatory moving boundaries modeling the epithelium motion and the far field condition in air. The present topic will involve three points :

- Give a vorticity formulation of multi-fluids inspired by fluid-structure formulations [3, 1].
- Implement 1D and 2D basic algorithms able to compute air and mucus dynamics.
- Indentify dominant stiffness generators among several possilibities.

References

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Oxygen diffusion during human breathing

Project proposed by **Bertrand Maury** (Univ. Paris Sud), **Sébastien Martin** (Univ. Paris Sud) and **Céline Grandmont** (INRIA Rocquencourt)

Framework and goals

Among all systems in medical modelling, the respiratory one certainly holds a pole position for complexity. The aim is to obtain simple but representative models to describe the behavior of the air flow coupled to the oxygen diffusion.

In [2] a simple $0D$ model has been developed to describe the coupling between the air flow and the oxygen diffusion in the blood. The first aim of the project will be to determine an optimal strategy which, on several respiratory cycles, maximizes the oxygen diffusion. In a second step one could elaborate more sophisticated diffusion models throught the alveolar wall to take into account the fact that this diffusion is not optimal for normal breathing.

Futhermore in [1] a multiscale model based on the Navier-Stokes equations coupled with an ODE representing the motion of the diaphragm muscle has been elaborated. One possible goal will then be to coupled these oxygen difussion models to this tridimensional model.

References

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Parareal algorithms for solving nonlinear stochastic systems in biology

Project proposed by **Adel Blouza** (Univ. Rouen) and **Karyn Sutton** (North Carolina State Univ.)

Framework and goals

We seek to develop fast and efficient methods for computing solutions of systems of nonlinear stochastic differential equations (SDEs) as they arise in a number of biological applications. Specifically, we are interested in stochastic differential equation models in biochemical, cellular, and gene networks in the field of systems biology. Also of interest are parameter estimation studies in label-structured models of cell proliferation dynamics (similar in structure to the well-known age or size-structured population models), which are special cases of the Fokker-Planck equation, which have an equivalent SDE formulation. The estimation of parameters requires computing the numerical solution over several iterations, a process that can be considerably time consuming. The parareal algorithm is known to be efficient and stable for systems of differential equations and has been applied to some Fokker-Planck systems successfully. We seek to establish the application of these methods to the nonlinear SDE models of biological networks and cell proliferation dynamics.

References

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Biophysical modelling of Prion self-replication processes

Project proposed by **Vincent Calvez** (ENS Lyon), **Marie Doumic** (INRIA Rocquencourt) and **Laurent Pujo-Menjouet** (Univ. Lyon 1)

Framework and goals

There have been recent efforts to address mathematically the issue of Prion replication both *in vivo* and *in vitro*. According to the "protein-only" hypothesis, Prion self-replication is modelled as a biophysical process involving polymerisation, by conversion of the normal PrP form, and fragmentation, by breakage of large polymers. A now well-established model consists in an integro-partial differential equation for the population of Prion aggregates, coupled with an ODE for the quantity of normal PrP.

This project is part of a collaboration between mathematicians and biologists which aims to model amyloid diseases (Prion diseases, Alzheimer) and to establish a link between microscopic features (size distribution of aggregates) and macroscopic observables. Indeed there have been recent experimental evidence that the size distribution contains the signature of a Prion strain. In particular, such a modelling can help to design carefully experimental protocols for *in vitro* amplification of infectious Prion aggregates (PMCA = Protein Misfolding Cyclic Amplification). PMCA is a crucial tool for diagnosis since it is able to quickly amplify undetectable doses of infectious Prion. This protocol alternates incubation phases (where polymerization process occurs) with sonication phases (which induces strong fragmentation of Prion aggregates).

The objectives of this project are twofold. First, investigate and numerically compute the time-optimization problem starting with a simplified toy model mimicking polymerisation/fragmentation. The dynamics of this simple problem should be well understood before designing an efficient strategy to optimize the whole PMCA protocol. Second, apply the methodology of Prion modelling and the improvement of microscopic description to the modelling of APP peptides in the development Alzheimer disease.

Asymptotic modelling and numerical simulations of blood flows in arteries with wired multi-layer stents

Project proposed by **Eric Bonnetier** (Univ. Grenoble), **Didier Bresch** (Univ. Chambéry) and **Vuk Milisic** (Wolfgang Pauli Institute, Vienne)

Framework and goals

The aim of this project is to investigate the bio-compatibility *in-vivo* features of certain multi-layered wired stents when inserted in arteries of human cardio-vascular network. A stable layer of endothelial cells grows in regions where the flow is tangential to the artery wall integrating the device in a living tissue. Nevertheless in connected arteries or bifurcations, flow is not perturbed, it is even improved in terms of flow-rate. The main scope of this work is to justify mathematically this multi-physics and multi-scale phenomenon.

This work is embedded in an industrial contract with Cardiatis, a company designing and commercializing wired metallic stents.

The blood flow is Newtonian and laminar in large and medium arteries of the cardio-vascular network. The thickness of the stent is small wrt to the diameter of the vessel. It can be seen as a periodic singular perturbation: a boundary roughness. We approximate the flow and the pressure by means of multi-scale boundary layers. Then one should derive wall-laws defined on a smooth boundary included inside the rough domain [3, 2, 1, 4]. Until now, these results concern the 2D case in an idealized geometry. We focus here on more realistic geometries in 3D. Namely we target the specific case of a junction between a main stented artery and a secondary vessel not containing any device. We aim to describe quantitatively the shear-stress, the pressure and the velocity wrt to the various parameters of the problem (geometry, boundary conditions, etc). The major concern is the influence of the stent when the flow is either tangential or normal to it.

Expected background and skills

The candidate should have basics in functional and numerical analysis in order to tackle homogenization and boundary layer theories from theoretical and applicative sides.

References

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Hormonal control of coupled and structured cell population dynamics

Project proposed by **Frédérique Clément** (INRIA Rocquencourt) and **Philippe Michel** (Ecole Centrale de Lyon)

Framework and goals

This project is part of a large scale program (AE INRIA REGATE: REgulation of the GonAdoTropE axis) devoted to the multiscale and multilevel modelling and control of the neuro-endocrine (hypothalamo-hypophyseo-gonadal) reproductive axis.

The project aims at extending a multiscale model for the selection of ovarian follicles (spheroidal structures sheltering the oocytes) basing on structured cell population dynamics. This model consists of coupled PDES (conservation laws with integro-differential velocity and source terms). It is suitable for large cell populations. However, it cannot be used to describe the earliest stages of follicular development, since they involve only few numbers of cells. The main project objective is to build both a discrete and probabilistic formalism to investigate these early stages, and to assess the validity limit of the continuous (deterministic) approximation with respect to the cell number.

Inflammation during ischemic stroke

Project proposed by **Guillemette Chapuisat** (Univ. Aix-Marseille 3) and **Marie-Aimée Dronne** (Univ. Lyon 1)

Framework and goals

Inflammation is the response of vascular tissues to harmful stimuli. It is a protective attempt by the body to remove the injurious stimuli by recruiting cells of the immune system that can progressively eliminate the damage. Inflammation is one of the mechanisms involved in ischemic stroke but the effect of inflammation on the evolution of the infarct is still unclear. It has a beneficial effect by eliminating necrotic cells that could further damage the other cells but it has also a deleterious effect by releasing harmful substances to recruit other inflammation cells. A first model of inflammation during stroke has been established to explore its effects [1], but this model is local and does not take into account the spatial dimension.

The aim of this project is to establish the most simple model of inflammation during stroke that would take into account the spatial dimension. Inflammatory cells enter the brain tissue through the vessel around the infarct and then follow a chemotactic mecanism to reach the infarcted core. A numerical study of the behaviour of the solutions will be made to understand which parameters influence the beneficial effect of inflammation and which ones influence the deleterious effect. The influence of reperfusion that allows the inflammatory cells to enter the tissue in the middle of the infarct will also be investigated.

References

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Modelling the evolution of sutures in the cranial vault

Project proposed by **Didier Bresch** (Univ. Chambéry), **Vincent Calvez** (ENS Lyon) and **Paul Vigneaux** (ENS Lyon)

Framework and goals

Sutures are fibrous tissues that separate two bone ends of the skull. They are indeed sites where osteogenesis takes place (both proliferation and differentiation). From a morphological point of view, they are convoluted junctions for which complexity evolves with time, before fusion. The precise mechanisms which lead to such an interdigitation pattern are unclear, and we propose to address this issue from the modelling viewpoint.

This project's goal is to design an accurate numerical code based on a suitable model for the development of craniofacial sutures, and henceforth to study the influences of mechanical forces on the sutures' geometry. The model is a mixture of biochemical (reaction-diffusion) and biomechanical (visco-plastic fluid) features. Numerical methods will follow recent works by D. Bresch and P. Vigneaux for Bingham fluids, and will consists in a coupling between finite volumes and augmented Lagrangian methods.

Data assimilation and cardiac valves simulation

Project proposed by **Jean-Frédéric Gerbeau** (INRIA Rocquencourt)

Framework and goals

The numerical simulation of cardiac valves is an extremely challenging fluid-structure interaction problem (large displacements, multi-body contact, very fast dynamics, *etc.*). In this project, we are interested in the estimation of uncertain mechanical parameters of the valve in various simplified 2D configurations. We will use data assimilation techniques and synthetic non-invasive measurements of the system. In the future, such a methodology might be use as a diagnosis tool to estimate valve calcification or stenosis.

Electrical stimulation of a coupled His/ventricular system

Project proposed by **Yves Coudière** (Univ. Nantes), **Jean-Frédéric Gerbeau** (INRIA Rocquencourt) and **Rodolphe Turpault** (Univ. Nantes)

Framework and goals

The His bundle and Purkinje fibers constitute the special conduction network in the heart, that is distinct from the muscle. It is responsible for the initial spread of the electrical excitation through the ventricles. In a healthy configuration, conductivity is significantly higher there as compared to the heart muscle.

Some pathologies (e.g. Bundle branch block) are due to anomalous conductivities in the His bundle. Recovering can be achieved through pointwise stimulations. However this technique is mainly heuristic so far. This project aims at designing a numerical code for the optimization of electrodes' locations. This code will be built upon an existing scheme modelling the electrical signal's propagation in the His bundle and the ventricle.

Multiscale modeling of virus infection and interferon-based immune response

Project proposed by **Anna Marciniak-Czochra** (Univ. Heidelberg)

Framework and goals

The project is devoted to modeling of spread of viral infection in a cell system, including production of interferon and development of resistance. As indicated in the series of experimental works of the group of Karen Duca [1, 3], there are two types of *in vitro* experiments: (1) one-step growth experiments with homogeneously infected cell monolayers, and (2) focal infection experiments, where, initially, only exposed cells are inoculated with virus solution. In both cases, strong anti-viral effects of interferon synthesis are observed. However, there exist experimental observations, which indicate a significant qualitative difference between the dynamics of infection in the two types of experiments.

The aim of this project is to develop models addressing these aspects, including diffusion of virus and interferon particles, and to compare them to the dynamics of spatially homogeneous models proposed in [2]. In addition to the effects of spatial dimension, the project will address the role of intracellular heterogeneity, in particular infection-age structure of infected cells and its stabilizing and destabilizing effects. The models will consist of reaction-diffusion equations and structured population equations coupled to the ordinary differential equations.

References

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