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Project-Team REO

Numerical simulation of biological flows

IN COLLABORATION WITH: Laboratoire Jacques-Louis Lions (LJLL)

RESEARCH CENTER
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THEME
Modeling and Control for Life Sciences

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Creation of the Project-Team: 2005 April 01, end of the Project-Team: 2018 December 31

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2. Overall Objectives

2.1. Overall Objectives

REO is a joint project-team of the Inria Research Center of Paris and the Jacques-Louis Lions Laboratory (LJLL) of the Pierre and Marie Curie University (Sorbonne Université, UPMC Paris 6) and CNRS (UMR7598). Its main objectives are:

- the modeling of blood flow in large vessels, air flow in the respiratory tract, and the cardiac electrophysiology;
- the design and the analysis of efficient and robust numerical methods for these problems;
- the development of numerical software to assist medical decisions and to contribute to the design of medical devices.

REO put a strong effort in working with real data, coming either from clinicians or industrial partners. The development of methods for the interaction of data and simulation is therefore an important aspect of the activity of the team.

3. Research Program

3.1. Multiphysics modeling

In large vessels and in large bronchi, blood and air flows are generally supposed to be governed by the incompressible Navier-Stokes equations. Indeed in large arteries, blood can be supposed to be Newtonian, and at rest air can be modeled as an incompressible fluid. The cornerstone of the simulations is therefore a Navier-Stokes solver. But other physical features have also to be taken into account in simulations of biological flows, in particular fluid-structure interaction in large vessels and transport of sprays, particles or chemical species.

3.1.1. Fluid-structure interaction

Fluid-structure coupling occurs both in the respiratory and in the circulatory systems. We focus mainly on blood flows since our work is more advanced in this field. But the methods developed for blood flows could be also applied to the respiratory system.

Here “fluid-structure interaction” means a coupling between the 3D Navier-Stokes equations and a 3D (possibly thin) structure in large displacements.

The numerical simulations of the interaction between the artery wall and the blood flows raise many issues: (1) the displacement of the wall cannot be supposed to be infinitesimal, geometrical nonlinearities are therefore present in the structure and the fluid problem have to be solved on a moving domain (2) the densities of the artery walls and the blood being close, the coupling is strong and has to be tackled very carefully to avoid numerical instabilities, (3) “naive” boundary conditions on the artificial boundaries induce spurious reflection phenomena.

Simulation of valves, either at the outflow of the cardiac chambers or in veins, is another example of difficult fluid-structure problems arising in blood flows. In addition, very large displacements and changes of topology (contact problems) have to be handled in those cases.

Due to stability reasons, it seems impossible to successfully apply in hemodynamics the explicit coupling schemes used in other fluid-structure problems, like aeroelasticity. As a result, fluid-structure interaction in biological flows raise new challenging issues in scientific computing and numerical analysis : new schemes have to be developed and analyzed.

We have proposed and analyzed over the last few years several efficient fluid-structure interaction algorithms. This topic remains very active. We are now using these algorithms to address inverse problems in blood flows to make patient specific simulations (for example, estimation of artery wall stiffness from medical imaging).

3.1.2. Aerosol

Complex two-phase fluids can be modeled in many different ways. Eulerian models describe both phases by physical quantities such as the density, velocity or energy of each phase. In the mixed fluid-kinetic models, the biphasic fluid has one dispersed phase, which is constituted by a spray of droplets, with a possibly variable size, and a continuous classical fluid.

This type of model was first introduced by Williams [46] in the frame of combustion. It was later used to develop the Kiva code [36] at the Los Alamos National Laboratory, or the Hesione code [41], for example. It has a wide range of applications, besides the nuclear setting: diesel engines, rocket engines [39], therapeutic sprays, *etc.* One of the interests of such a model is that various phenomena on the droplets can be taken into account with an accurate precision: collision, breakups, coagulation, vaporization, chemical reactions, *etc.*, at the level of the droplets.

The model usually consists in coupling a kinetic equation, that describes the spray through a probability density function, and classical fluid equations (typically Navier-Stokes). The numerical solution of this system relies on the coupling of a method for the fluid equations (for instance, a finite volume method) with a method fitted to the spray (particle method, Monte Carlo).

We are mainly interested in modeling therapeutic sprays either for local or general treatments. The study of the underlying kinetic equations should lead us to a global model of the ambient fluid and the droplets, with some mathematical significance. Well-chosen numerical methods can give some tracks on the solutions behavior and help to fit the physical parameters which appear in the models.

3.2. Multiscale modeling

Multiscale modeling is a necessary step for blood and respiratory flows. In this section, we focus on blood flows. Nevertheless, similar investigations are currently carried out on respiratory flows.

3.2.1. Arterial tree modeling

Problems arising in the numerical modeling of the human cardiovascular system often require an accurate description of the flow in a specific sensible subregion (carotid bifurcation, stented artery, *etc.*). The description of such local phenomena is better addressed by means of three-dimensional (3D) simulations, based on the numerical approximation of the incompressible Navier-Stokes equations, possibly accounting for compliant (moving) boundaries. These simulations require the specification of boundary data on artificial boundaries that have to be introduced to delimit the vascular district under study. The definition of such boundary conditions is critical and, in fact, influenced by the global systemic dynamics. Whenever the boundary data is not available from accurate measurements, a proper boundary condition requires a mathematical description of the action of the reminder of the circulatory system on the local district. From the computational point of view, it is not affordable to describe the whole circulatory system keeping the same level of detail. Therefore, this mathematical description relies on simpler models, leading to the concept of *geometrical multiscale* modeling of the circulation [42]. The underlying idea consists in coupling different models (3D, 1D or 0D) with a decreasing level of accuracy, which is compensated by their decreasing level of computational complexity.

The research on this topic aims at providing a correct methodology and a mathematical and numerical framework for the simulation of blood flow in the whole cardiovascular system by means of a geometric multiscale approach. In particular, one of the main issues will be the definition of stable coupling strategies between 3D and reduced order models.

To model the arterial tree, a standard way consists of imposing a pressure or a flow rate at the inlet of the aorta, *i.e.* at the network entry. This strategy does not allow to describe important features as the overload in the heart caused by backward traveling waves. Indeed imposing a boundary condition at the beginning of the aorta artificially disturbs physiological pressure waves going from the arterial tree to the heart. The only way to catch this physiological behavior is to couple the arteries with a model of heart, or at least a model of left ventricle.

A constitutive law for the myocardium, controlled by an electrical command, has been developed in the CardioSense3D project [1]. One of our objectives is to couple artery models with this heart model.

A long term goal is to achieve 3D simulations of a system including heart and arteries. One of the difficulties of this very challenging task is to model the cardiac valves. To this purpose, we investigate a mix of arbitrary Lagrangian Eulerian and fictitious domain approaches or x-fem strategies, or simplified valve models based on an immersed surface strategy.

3.2.2. Heart perfusion modeling

The heart is the organ that regulates, through its periodical contraction, the distribution of oxygenated blood in human vessels in order to nourish the different parts of the body. The heart needs its own supply of blood to work. The coronary arteries are the vessels that accomplish this task. The phenomenon by which blood reaches myocardial heart tissue starting from the blood vessels is called in medicine perfusion. The analysis of heart perfusion is an interesting and challenging problem. Our aim is to perform a three-dimensional dynamical numerical simulation of perfusion in the beating heart, in order to better understand the phenomena linked to perfusion. In particular the role of the ventricle contraction on the perfusion of the heart is investigated as well as the influence of blood on the solid mechanics of the ventricle. Heart perfusion in fact implies the interaction between heart muscle and blood vessels, in a sponge-like material that contracts at every heartbeat via the myocardium fibers.
Despite recent advances on the anatomical description and measurements of the coronary tree and on the corresponding physiological, physical and numerical modeling aspects, the complete modeling and simulation of blood flows inside the large and the many small vessels feeding the heart is still out of reach. Therefore, in order to model blood perfusion in the cardiac tissue, we must limit the description of the detailed flows at a given space scale, and simplify the modeling of the smaller scale flows by aggregating these phenomena into macroscopic quantities, by some kind of "homogenization" procedure. To that purpose, the modeling of the fluid-solid coupling within the framework of porous media appears appropriate.
Poromechanics is a simplified mixture theory where a complex fluid-structure interaction problem is replaced by a superposition of both components, each of them representing a fraction of the complete material at every point. It originally emerged in soils mechanics with the work of Terzaghi [45], and Biot [37] later gave a description of the mechanical behavior of a porous medium using an elastic formulation for the solid matrix, and Darcy's law for the fluid flow through the matrix. Finite strain poroelastic models have been proposed (see references in [38]), albeit with *ad hoc* formulations for which compatibility with thermodynamics laws and incompressibility conditions is not established.

3.2.3. Tumor and vascularization

The same way the myocardium needs to be perfused for the heart to beat, when it has reached a certain size, tumor tissue needs to be perfused by enough blood to grow. It thus triggers the creation of new blood vessels (angiogenesis) to continue to grow. The interaction of tumor and its micro-environment is an active field of research. One of the challenges is that phenomena (tumor cell proliferation and death, blood vessel adaptation, nutrient transport and diffusion, etc) occur at different scales. A multi-scale approach is thus being developed to tackle this issue. The long term objective is to predict the efficiency of drugs and optimize therapy of cancer.

[1] http://www-sop.inria.fr/CardioSense3D/

3.2.4. Respiratory tract modeling

We aim at developing a multiscale model of the respiratory tract. Intraprenchymal airways distal from generation 7 of the tracheabronchial tree (TBT), which cannot be visualized by common medical imaging techniques, are modeled either by a single simple model or by a model set according to their order in TBT. The single model is based on straight pipe fully developed flow (Poiseuille flow in steady regimes) with given alveolar pressure at the end of each compartment. It will provide boundary conditions at the bronchial ends of 3D TBT reconstructed from imaging data. The model set includes three serial models. The generation down to the pulmonary lobule will be modeled by reduced basis elements. The lobular airways will be represented by a fractal homogenization approach. The alveoli, which are the gas exchange loci between blood and inhaled air, inflating during inspiration and deflating during expiration, will be described by multiphysics homogenization.

4. Application Domains

4.1. Blood flows

Cardiovascular diseases like atherosclerosis or aneurysms are a major cause of mortality. It is generally admitted that a better knowledge of local flow patterns could improve the treatment of these pathologies (although many other biophysical phenomena obviously take place in the development of such diseases). In particular, it has been known for years that the association of low wall shear stress and high oscillatory shear index give relevant indications to localize possible zones of atherosclerosis. It is also known that medical devices (graft or stent) perturb blood flows and may create local stresses favorable with atherogenesis. Numerical simulations of blood flows can give access to this local quantities and may therefore help to design new medical devices with less negative impacts. In the case of aneurysms, numerical simulations may help to predict possible zones of rupture and could therefore give a guide for treatment planning.

In clinical routine, many indices are used for diagnosis. For example, the size of a stenosis is estimated by a few measures of flow rate around the stenosis and by application of simple fluid mechanics rules. In some situations, for example in the case a sub-valvular stenosis, it is known that such indices often give false estimations. Numerical simulations may give indications to define new indices, simple enough to be used in clinical exams, but more precise than those currently used.

It is well-known that the arterial circulation and the heart (or more specifically the left ventricle) are strongly coupled. Modifications of arterial walls or blood flows may indeed affect the mechanical properties of the left ventricle. Numerical simulations of the arterial tree coupled to the heart model could shed light on this complex relationship.

One of the goals of the REO team is to provide various models and simulation tools of the cardiovascular system. The scaling of these models will be adapted to the application in mind: low resolution for modeling the global circulation, high resolution for modeling a small portion of vessel.

4.2. Respiratory tracts

Breathing, or “external” respiration (“internal” respiration corresponds to cellular respiration) involves gas transport though the respiratory tract with its visible ends, nose and mouth. Air streams then from the pharynx down to the trachea. Food and drink entry into the trachea is usually prevented by the larynx structure (epiglottis). The trachea extends from the neck into the thorax, where it divides into right and left main bronchi, which enter the corresponding lungs (the left being smaller to accommodate the heart). Inhaled air is then convected in the bronchus tree which ends in alveoli, where gaseous exchange occurs. Surfactant reduces the surface tension on the alveolus wall, allowing them to expand. Gaseous exchange relies on simple diffusion on a large surface area over a short path between the alveolus and the blood capillary under concentration gradients between alveolar air and blood. The lungs are divided into lobes (three on the right, two on the left) supplied by lobar bronchi. Each lobe of the lung is further divided into segments (ten segments of the right lung and eight of the left). Inhaled air contains dust and debris, which must be filtered, if possible, before they reach the alveoli. The tracheobronchial tree is lined by a layer of sticky mucus, secreted by the epithelium. Particles which hit the side wall of the tract are trapped in this mucus. Cilia on the epithelial cells move the mucous continually towards the nose and mouth.

Each lung is enclosed in a space bounded below by the diaphragm and laterally by the chest wall and the mediastinum. The air movement is achieved by alternately increasing and decreasing the chest pressure (and volume). When the airspace transmural pressure rises, air is sucked in. When it decreases, airspaces collapse and air is expelled. Each lung is surrounded by a pleural cavity, except at its hilum where the inner pleura give birth to the outer pleura. The pleural layers slide over each other. The tidal volume is nearly equal to 500 ml.

The lungs may fail to maintain an adequate supply of air. In premature infants surfactant is not yet active. Accidental inhalation of liquid or solid and airway infection may occur. Chronic obstructive lung diseases and lung cancers are frequent pathologies and among the three first death causes in France.

One of the goals of REO team in the ventilation field is to visualize the airways (virtual endoscopy) and simulate flow in image-based 3D models of the upper airways (nose, pharynx, larynx) and the first generations of the tracheobronchial tree (trachea is generation 0), whereas simple models of the small bronchi and alveoli are used (reduced-basis element method, fractal homogenization, multiphysics homogenization, lumped parameter models), in order to provide the flow distribution within the lung segments.

4.3. Cardiac electrophysiology

The purpose is to simulate the propagation of the action potential in the heart. A lot of works has already been devoted to this topic in the literature (see *e.g.* [40], [44], [43] and the references therein), nevertheless there are only very few studies showing realistic electrocardiograms obtained from partial differential equations models. Our goal is to find a compromise between two opposite requirements: on the one hand, we want to use predictive models, and therefore models based on physiology, on the other hand, we want to use models simple enough to be parametrized (in view of patient-specific simulations). One of the goal is to use our ECG simulator to address the inverse problem of electrocardiology. In collaboration with the Macs/M3disym project-team, we are interested in the electromechanical coupling in the myocardium. We are also interested in various clinical and industrial issues related to cardiac electrophysiology, in particular the simulation of experimental measurement of the field potential of cardiac stem cells in multi-electrode arrays.

5. Highlights of the Year

5.1. Highlights of the Year

5.1.1. Awards

Chloé Audebert was awarded the AMIES PhD prize 2018 for her PhD thesis under the supervision of J.-F. Gerbeau and I. Vignon Clementel, in the framework of a collaboration with the SME company Fluoptics and with clinicians from Hôpital Paul Brousse (E. Vibert PUPH, Inserm 1193).

6. New Software and Platforms

6.1. FELiScE

Finite Elements for Life SCiences and Engineering problems
KEYWORDS: Finite element modelling - Cardiac Electrophysiology - Cardiovascular and respiratory systems

FUNCTIONAL DESCRIPTION: FELiScE is a finite element code which the M3DISIM and REO project-teams have decided to jointly develop in order to build up on their respective experiences concerning finite element simulations. One specific objective of this code is to provide in a unified software environment all the state-of-the-art tools needed to perform simulations of the complex respiratory and cardiovascular models considered in the two teams – namely involving fluid and solid mechanics, electrophysiology, and the various associated coupling phenomena. FELISCE is written in C++, and may be later released as an opensource library. FELiScE was registered in July 2014 at the Agence pour la Protection des Programmes under the Inter Deposit Digital Number IDDN.FR.001.350015.000.S.P.2014.000.10000.

- Participants: Axel Fourmont, Benoit Fabreges, Damiano Lombardi, Dominique Chapelle, Irène Vignon-Clementel, Jean-Frédéric Gerbeau, Marina Vidrascu, Matteo Aletti, Miguel Angel Fernandez Varela, Mikel Landajuela Larma, Philippe Moireau and Sébastien Gilles
- Contact: Miguel Angel Fernandez Varela
- URL: http://felisce.gforge.inria.fr

6.2. SHELDDON

SHELls and structural Dynamics with DOmain decomposition in Nonlinear analysis
FUNCTIONAL DESCRIPTION: SHELDDON is a finite element library based on the Modulef package which contains shell elements, nonlinear procedures and PVM subroutines used in domain decomposition or coupling methods, in particular fluid-structure interaction.

- Participants: Dominique Chapelle, Marina Vidrascu and Patrick Le Tallec
- Contact: Marina Vidrascu
- URL: https://gforge.inria.fr/projects/shelddon/

6.3. DCIMaL

KEYWORD: Cardiac Electrophysiology
FUNCTIONAL DESCRIPTION: DCIMaL is a Python and C++ software for safety pharmacology studies and particularly field potentials signals measured with micro-electrode array (MEA). The software includes a solver for field potential simulations and a dictionary of entries corresponding to features which can be extracted from real or simulated potential signals. It also includes an algorithm for drug classification (channel blockade or torsadogenic risk) and a tool for estimating ion channel activity (based on the CMAES library). DCIMaL was registered in 2018 at the Agence pour la Protection des Programmes Inter Deposit Digital Number IDDN.FR.001.270003.000.S.P.2018.000.31230

- Participants: Fabien Raphel, Jean-Frédéric Gerbeau and Damiano Lombardi
- Contact: Damiano Lombardi

6.4. FELiScE-NS

KEYWORDS: Incompressible flows - Thin-walled solids
FUNCTIONAL DESCRIPTION: FELiScE-NS is a set finite elements solvers for incompressible fluids (fractional-step schemes) and non-linear thin-walled structures (3D shells, and 2D curved beams) developed in the framework of the FELiScE library. FELiSCe-NS was registered in 2018 at the Agence pour la Protection des Programmes Inter Deposit Digital Number IDDN.FR.001.270015.000.S.A.2018.000.31200.

- Participants: Benoit Fabreges, Miguel Angel Fernandez Varela, Axel Fourmont, Jean-Frédéric Gerbeau and Marina Vidrascu
- Contact: Miguel Angel Fernandez Varela

7. New Results

7.1. Mathematical and numerical analysis of fluid-structure interaction problems

Participants: Muriel Boulakia, Ludovic Boilevin-Kayl, Chen-Yu Chiang, Miguel Ángel Fernández Varela, Jean-Frédéric Gerbeau, Céline Grandmont, Damiano Lombardi, Marc Thiriet, Marina Vidrascu.

In [31], we consider a system modeling the interaction between a viscous incompressible fluid and an elastic structure. The fluid motion is represented by the classical Navier-Stokes equations while the elastic displacement is described by the linearized elasticity equation. The elastic structure is immersed in the fluid and the whole system is confined into a bounded domain of dimension 3. Our main result is the local in time existence and uniqueness of a strong solution of the corresponding system. This result holds without any restrictive assumptions on the domains geometry.

The numerical simulation of a thin-walled structure immersed in an incompressible fluid can be addressed by various methods. In [16], three of them are considered: the Arbitrary Lagrangian-Eulerian (ALE) method, the Fictitious Domain/Lagrange multipliers (FD) method and the Nitsche-XFEM method. Taking ALE as a reference, the advantages and limitations of FD and Nitsche-XFEM are carefully discussed on three benchmark test cases which have been chosen to be representative of typical difficulties encountered in valves or living cells simulations.

Fictitious domain approximations of fluid-structure interaction problems are generally discretized in time using strongly coupled schemes. This guarantees unconditional stability but at the price of solving a computationally demanding coupled system at each time-step. The design of loosely coupled schemes (i.e., methods that invoke the fluid and solid solvers only once per time-step) is of fundamental interest, especially for three-dimensional simulations, but the existing approaches are known to suffer from severe stability and/or time accuracy issues. In [28], we propose a new approach that overcomes these difficulties in the case of the coupling with immersed thin-walled structures.

In [27], we derive a Nitsche-based formulation for fluid-structure interaction (FSI) problems with contact. The approach is based on the work of Chouly and Hild [SIAM Journal on Numerical Analysis. 2013;51(2):1295-1307] for contact problems in solid mechanics. We present two numerical approaches, both of them formulating the FSI interface and the contact conditions simultaneously in equation form on a joint interface-contact surface. The first approach uses a relaxation of the contact conditions to allow for a small mesh-dependent gap between solid and wall. The second alternative introduces an artificial fluid below the contact surface. The resulting systems of equations can be included in a consistent fashion within a monolithic variational formulation, which prevents the so-called "chattering" phenomenon. To deal with the topology changes in the fluid domain at the time of impact, we use a fully Eulerian approach for the FSI problem. We compare the effect of slip and no-slip interface conditions and study the performance of the method by means of numerical examples.

7.2. Numerical methods for biological flows

Participants: Ludovic Boilevin-Kayl, Miguel Ángel Fernández Varela, Jean-Frédéric Gerbeau, Florian Joly, Alexandre This, Marc Thiriet, Irene Vignon Clementel.

Cirrhosis is the common end-stage of chronic liver disease, with architectural distortion increasing the intrahepatic vascular resistance, leading to portal hypertension and systemic circulatory disorders. In [13] we investigate the impact of the changing vascular resistances on the hepatic and global circulation hemodynamics during cirrhogenesis. Morphological quantification of vascular trees from corosion casts of rats developing the disease provide the input for a lumped parameter model of the liver that was coupled to a model of the entire circulation of the rat. The simulations explain how vascular changes due to cirrhosis severely disrupt both hepatic and global hemodynamics.

Image-based models derived from CT angiography are being used clinically to simulate blood flow in the coronary arteries of individual patients to aid in the diagnosis of disease and planning treatments. However, image resolution limits vessel segmentation to larger epicardial arteries. In [20], we propose an algorithm for the generation of a patient-specific cardiac vascular network from epicardial vessels down to arterioles. We extend a tree generation method based on satisfaction of functional principles, to account for competing vascular trees, with flow-related and geometrical constraints adapting the simultaneous tree growths to patient priors.

Growth and remodeling of the embryo pharyngeal arch artery (PAA) network into the extracardiac great vessels is poorly understood but a major source of clinically serious malformations. In [21] we develop a methodological pipeline from high-resolution nano-computed tomography imaging and live-imaging flow measurements to multiscale pulsatile computational models. We identify local morphological variation along the PAAs and their association with specific hemodynamic changes in embryos of different stages, advancing our understanding of morphogenesis.

In [22] we evaluate atrioventricular valve regurgitation (AVVR) in babies born with an already very challenging heart condition, i.e., with single ventricle physiology. Although the second surgery that single ventricle patients undergo is thought to decrease AVVR, there is much controversy in the clinical literature about AVVR treatment. The effect of AVVR on Stage 1 haemodynamics and resulting acute changes from conversion to Stage 2 circulation in single ventricle patients are analyzed through lumped parameter models. Several degrees of AVVR severity are analyzed, for two types of valve regurgitation: incomplete leaflet closure and valve prolapse.

The medical imaging community is eager to define quantitative biophysical parameters. As part of a book addressing this question, in [26], we give a short overview of the mathematical modeling of blood flow at different resolutions, from the large vessel scale (three-dimensional, one-dimensional, and zero-dimensional modeling) to microcirculation and tissue perfusion.

In order to reduce the complexity of heart hemodynamics simulations, uncoupling approaches are often considered for the modeling of the immersed valves as an alternative to complex fluid-structure interaction (FSI) models. A possible shortcoming of these simplified approaches is the difficulty to correctly capture the pressure dynamics during the isovolumetric phases. In [35], we propose an enhanced resistive immersed surfaces (RIS) model of cardiac valves which overcomes this issue. The benefits of the model are investigated and tested in blood flow simulations of the left heart.

7.3. Numerical methods for cardiac electrophysiology

Participants: Muriel Boulakia, Jean-Frédéric Gerbeau, Damiano Lombardi, Fabien Raphel.

In [19] a method to assess the variability of phenomena described by PDEs is proposed. In particular, the probability density distribution of the parameters of a model is estimated, in such a way that the statistics of the model output match the observed ones. The investigated approach is based on a differential entropy regularised moment matching.

In [25] we investigated how, by a semi-empirical design of composite biomarkers, the classification of the action of a drug on the electrical activity of a cell can be improved. The data used are measured with a Micro-Electrodes-Array.

In [33] a method is investigated, to design composite biomarkers by exploiting a database of in silico experiments. In particular, a dictionary approach is proposed. The composite biomarker is expressed as a linear combination of linear and non-linear forms applied to the observable. The coefficients of the combination are determined by solving a ℓ^1 regularised optimisation problem.

7.4. Lung and respiration modeling

Participants: Laurent Boudin, Céline Grandmont, Marina Vidrascu, Marc Thiriet, Irene Vignon Clementel.

In [34] we analyse multiscale models arising in the description of physiological flows such as blood flow in arteries or air flow in the bronchial tree. The fluid in the 3D part is described by the Stokes or the Navier-Stokes system which is coupled to 0D models or so-called Windkessel models. The resulting Navier-Stokes-Windkessel coupled system involves Neumann non-local boundary conditions that depends on the considered applications. We first show that the different types of Windkessel models share a similar formalism. Next we derive stability estimates for the continuous coupled Stokes-Windkessel or Navier-Stokes-Windkessel problem as well as stability estimates for the semi-discretized systems with either implicit or explicit coupling.We exhibit different kinds of behavior depending on the considered 0D model. Moreover even if no energy estimates can be derived in energy norms for the Navier-Stokes-Windkessel system, leading to possible numerical instabilities for large applied pressures, we show that stability estimates for both the continuous and semi-discrete problems, can be obtained in appropriate norms for small enough data by introducing a new well chosen Stokes-like operator. These sufficient stability conditions on the data may give a hint on the order of magnitude of the data enabling stable computations without stabilization method for the problem.

In [17], we consider a multi-species kinetic model which leads to the Maxwell-Stefan equations under a standard diffusive scaling (small Knudsen and Mach numbers). We propose a suitable numerical scheme which approximates both the solution of the kinetic model in rarefied regime and the one in the diffusion limit. We prove some a priori estimates (mass conservation and nonnegativity) and well-posedness of the discrete problem. We also present numerical examples where we observe the asymptotic-preserving behavior of the scheme.

In [30], we are interested in a system of fluid equations for mixtures with a stiff relaxation term of Maxwell-Stefan diffusion type. We use the formalism developed by Chen, Levermore, Liu to obtain a limit system of Fick type where the species velocities tend to align to a bulk velocity when the relaxation parameter remains small.

In [29], we consider the Boltzmann operator for mixtures with cutoff Maxwellian, hard potentials, or hard spheres collision kernels. In a perturbative regime around the global Maxwellian equilibrium, the linearized Boltzmann multi-species operator L is known to possess an explicit spectral gap, in the global equilibrium weighted L^2 space. We study a new operator L_ε obtained by linearizing the Boltzmann operator for mixtures around local Maxwellian distributions, where all the species evolve with different small macroscopic velocities of order $\varepsilon > 0$. This is a non-equilibrium state for the mixture. We establish a quasi-stability property for the Dirichlet form of L_ε in the global equilibrium weighted L^2 space. More precisely, we consider the explicit upper bound that has been proved for the entropy production functional associated to L and we show that the same estimate holds for the entropy production functional associated to L_ε, up to a correction of order ε.

7.5. Miscellaneous

Participants: Damiano Lombardi, Irene Vignon Clementel.

In [32] numerical quadrature schemes for the integration of observable quantities in the Brillouin zone for the periodic Schrödinger operator are investigated.

The indocyanine green (ICG) clearance, presented as plasma disappearance rate is, presently, a reliable method to estimate the hepatic function. However, this technique is not instantaneously available and thus cannot been used intra-operatively (during liver surgery). Near-infrared spectroscopy enables to assess hepatic ICG concentration over time in the liver tissue. In [14], we propose to extract more information from the liver intensity dynamics by interpreting it through a dedicated pharmacokinetics model. Parameters for different liver states are estimated from in-vivo measurements in rabbits (El-Desoky et al. 1999), and their link with liver function is investigated.

The hepatic hemodynamics is an essential parameter in surgical planning as well as in various disease processes. The transit time ultrasound (TTUS) perivascular flow probe technology is widely used in clinical practice to evaluate the hepatic inflow, yet invasive. The phase-contrast-MRI (PC-MRI) is not invasive and potentially applicable in assessing the hepatic blood flow. In [15], we compare the hepatic inflow rates using the PC-MRI and the TTUS probe, and evaluated their predictive value of post-hepatectomy adverse events in a porcine experimental model of partial hepatectomy.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

8.1.1. Philips Research

Participants: Miguel Ángel Fernández Varela, Jean-Frédéric Gerbeau, Alexandre This.

CIFRE convention and contract with Philips Research for the PhD thesis of Alexandre This (January 2016 - December 2018) on fusion data/simulation for the assessment of mitral regurgitation.

8.1.2. Kephalios & Epygon

Participants: Gautier Bureau, Miguel Ángel Fernández Varela, Jean-Frédéric Gerbeau, Ludovic Boilevin-Kayl, Marina Vidrascu.

REO is an academic partner of the industrial project MIVANA, dedicated to the development of new technologies for mitral valve treatment. It is led by the start-up company Kephalios, with the participation of the start-up company Epygon, by the company MDB Texinov and the research institute IFTH. In this framework, REO has two bilateral contracts with Kephalios and Epygon on the modeling and simulation of two medical devices for mitral valve repair.

8.1.3. Instem/NOTOCORD

Participants: Muriel Boulakia, Damiano Lombardi, Jean-Frédéric Gerbeau, Fabien Raphel.

REO partners with the software company NOTOCORD. The collaboration started in 2013 the framework of the LabCom "cardioXcomp". In 2016, the ANR funding came to an end, and NOTOCORD was acquired by the company Instem. Our collaboration with Instem/NOTOCORD continues as a bilateral partnership with the purpose of developing the software cardioXcomp dedicated to the safety pharmacology industry. This project is also supported by a grant by AMIES (Agency for Interaction in Mathematics with Business and Society).

8.1.4. ESIEE-Heartflow

Participant: Irene Vignon Clementel.

Research contract with ESIEE-Heartflow on coronary tree modeling.

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR

9.1.1.1. ANR Project "IFSMACS"

Participants: Muriel Boulakia, Céline Grandmont [local coordinator].

Period: 2015-2019.
The objective of this project, coordinated by Takéo Takahashi (Inria Nancy Grand-Est), is the mathematical analysis of systems involving structures immersed in a fluid. This includes the asymptotic analysis, the study of the controllability and stabilization of fluid-structure interaction systems, the understanding of the motion of self-propelled structures and the analysis and development of numerical methods to simulate fluid-structure systems.

9.1.1.2. Participation to other ANR projects

- Laurent Boudin is a member of the ANR Blanc project Kibord on kinetic models in biology and related domains
- Laurent Boudin is a member of the ANR TecSan Oxhelease
- Céline Grandmont is a member of the ANR TecSan Oxhelease
- Irene Vignon Clementel is a member of the project iLite (09/16-), RHU-santé grant, a large French hospital-medical research consortium that aims at developing innovations for liver and tissue engineering (Inria PI: Dirk Drasdo).

9.2. European Initiatives

9.2.1. Collaborations in European Programs, Except FP7 & H2020

9.2.1.1. SimInhale COST

Participant: Irene Vignon Clementel.

Action MP1404, a pan-European network of experts in the field of inhaled medicine.

9.3. International Research Visitors

9.3.1. Visits of International Scientists

9.3.1.1. Internships

- Charu Mittal, Visiting PhD student, Indian Institute of Technology Bombay, March 2018–August 2018

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. Member of the Organizing Committees

- Laurent Boudin
  - Member of the organizing committee of the 7th "Forum Emploi Maths", December 2018, Paris
  - Member of both Boards of Mathematics Licence and Master, Sorbonne Université
  - Member of the IREM (Institutes for Research on Mathematics Teaching) Scientific Committee
  - Member of the SMAI (French Society for applied and industrial mathematics) Teaching Committee.
- Céline Grandmont
  - Co-organizer of Inria-LJLL meeting in scientific computing
  - Co-organizer of the CEMRACS 2018
- Irene Vignon Clementel
  - Minisymposium with F. Van de Vosse (Eindhoven U.) at WCCB, Dublin, Ireland.
  - Minisymposium at GDR mecabio January, Toulouse, France.
  - Session to foster collaboration between scientists and medical doctors at the Inria/CentraleSupelec/APHP meeting, November 12, Paris, France.

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

- Irene Vignon Clementel
  - Steering committee, multidisciplinary workshop on surgical innovation WIC, 23-25 June, Cabourg, France
  - Programme committee member, Computational and Mathematical Biomedical Engineering Conference
  - Conference steering committee, International Conference on Engineering Frontiers in Pediatric and Congenital Heart Disease

10.1.2.2. Member of the Editorial Boards

- Jean-Frédéric Gerbeau
  - Member of the editorial board of the SIAM Journal of Scientific Computing (SISC).
  - Series editor of "SEMA SIMAI Series", Springer.
  - Member of the editorial board of Journal Advances in Computational Mathematics (ACOM), Springer
  - Member of the editorial board of International Journal for Numerical Methods in Biomedical Engineering (IJNMBE), Wiley.
  - Member of the editorial board of Communications in Applied and Industrial Mathematics, SIMAI/De Gruyter.
  - Member of the editorial board of Journal for Modeling in Ophthalmology, Kugler.
- Céline Grandmont
  - Member of the editorial board of Mathematical Modelling of Natural Phenomena
- Marc Thiriet
  - Member of the editorial board of Digital Medicine
  - Member of the editorial board of Computer Methods in Biomechanics and Biomedical Engineering–Imaging and Visualization
- Irene Vignon Clementel
  - Associate Editor of the International Journal for Numerical Methods in Biomedical Engineering

10.1.3. Leadership within the Scientific Community

- Jean-Frédéric Gerbeau
  - Elected member of the Board of Directors of SMAI (French Society for Industrial and Applied Mathematics), in charge of the SMAI publications (M2AN, COCV, etc.)

10.1.4. Research Administration

- Muriel Boulakia
  - Supervisor of the teaching of mathematics at the engineer school Polytech Sorbonne
- Miguel Ángel Fernández Varela
  - Deputy Head of Science, Inria Paris
  - Member of the Scientific Positions Commission, Inria Paris
  - Member of the Inria Evaluation Committee
- Jean-Frédéric Gerbeau
  - Head of science, Inria Paris (until Sept. 2017)
  - Member of the scientific committee of Labex NUMEV, Montpellier.

  - Service activity abroad: member of the Reference Committee of the PhD program Mathematical Models and Methods in Engineering (Politecnico di Milano, Italy).
- Céline Grandmont
  - Member of the Inria Evaluation Committee
  - Member of the Inria Parity Committee
- Irene Vignon-Clementel
  - Technology grant committee (Commission de développement technologique), Inria Paris center
  - Committee member for PhD students at Inria "Commission consultative des doctorants", since July 2016.
  - Mediator between PhD students and their supervisors for Inria Paris

10.1.5. Conferences

- Ludovic Boilevin-Kayl
  - Contributed talk in minisymposium, 13th World Congress on Computational Mechanics, July 22th – 27th, 2018, New York City, USA.
  - Seminar, Jacques-Louis Lions Laboratory In-House Day, Sorbonne Université, April 5, 2018, Paris, France.
- Laurent Boudin
  - Seminar, Lab. de mathématiques appliquées du Havre, Univ. Le Havre Normandie, February 2018, Le Havre, France
  - Seminar, Cemracs 2018, August 2018, Marseille, France
  - Seminar of Partial Differential Equations, IRMA, Univ. Strasbourg, November 2018, Strasbourg, France
- Muriel Boulakia
  - congres Inverse Problems, Modeling and simulation, Malta, May 2018
  - Inria-LJLL meeting in scientific computing, October 2018
- Miguel Ángel Fernández Varela
  - Keynote talk in minisymposium, 13th World Congress on Computational Mechanics, July 22-27, 2018, New York City, USA.
- Felipe Galarce Marin
  - Contributed talk in minisymposium, 8th World Congress of Biomechanics, July 8-12, 2018, Dublin, Ireland
- Jean-Frédéric Gerbeau
  - Contributed talk in minisymposium, 8th World Congress of Biomechanics, July 8-12, 2018, Dublin, Ireland
  - Keynote talk in minisymposium, 6th European Conference on Computational Mechanics, June 11-15, 2018, Glasgow, UK
- Céline Grandmont
  - Seminar EDP, Nice, Jan. 2018
  - Seminar, Nantes, May 2018
  - Colloquium, Paris 5 Univ., Nov. 2018
  - Invited Speaker, Workshop Interfaces entre mathématiques et biologie, Nancy Univ., Nov. 2018
- Florian Joly

  - Weekend d'Innovation Chirugicale, Cabourg, Jun. 2018
  - Journées du GDR MécaBio à Montpellier, Nov. 2018
- Damiano Lombardi
  - CMM-Fields-Inria Workshop on Mathematics for Medicine, Toronto (Canada)
  - VPH 2018 Zaragoza (Spain), minisymposium of data assimilation
  - Workshop of matematics for biomedicine, Roma (Italy)
  - Ncardia workshop, Cologne (Germany)
- Marc Thiriet
  - Invited lecture, 15th International Symposium Computer Methods in Biomechanics and Biomedical Engineering and 3rd Conference on Imaging and Visualization March 27th – 30th, 2018, Lisbon, Portugal
  - Invited lecture, 2nd International Conference on Digital Medicine, May 25–27, 2018, Guangzhou, China
  - Invited lecture, France–Taiwan Science Festival, Sept. 14, 2018, Taipei, Taiwan
- Alexandre This
  - INdAM Workshop "Mathematical and Numerical Modeling of the Cardiovascular System",April 16 - 19, 2018, Rome, Italy.
  - Contributed talk in minisymposium, 8th World Congress of Biomechanics, July 8 - 12, 2018, Dublin, Ireland.
- Marina Vidrascu
  - Contributed talk in minisymposium, 13th World Congress on Computational Mechanics, July 22th – 27th, 2018, New York City, USA.
- Irene Vignon Clementel
  - Seminar (biomechanics), Ecole Polytechnique, Nov 16th, Palaiseau, France
  - Keynote lecture at the Workshop on Advanced Computational Biomechanics in Cardio-Vascular Surgery, Nov 8th, Saint-Etienne, France
  - Talk and poster, World conference of biomechanics, July 15-19 2018, Dublin, Ireland
  - Keynote, SBMC (systems biology in mammalian cells) conference, July 4-6, Brehmen, Germany
  - Invited talk, Weekend de l'innovation chirurgicale (WIC), Jun 22-24, Cabourg, France.
  - Invited talk, MRI and modeling workshop, June 22nd, Saclay, France
  - Poster presentation, EASL international conference (clinical liver conf.), April 11-15, Paris, France
  - Invited talk, GDR MecaBio (national biomechanics conference), Jan 10-12th, Toulouse, France

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Licence:

- Laurent Boudin
  - Introduction to series for signal theory, 18h, L2, UPMC
  - Calculus, 38.5h, L1, UPMC
  - Numerical methods for ODE, 53h, L3, UPMC
- Muriel Boulakia

  - Projects on differential equations, 34h, L3, Polytech Sorbonne, Sorbonne University
  - Nonlinear systems and optimization, 35h, L3, Polytech Sorbonne, Sorbonne University
  - Numerical approximation of functions, 36h, L3, Sorbonne University
- Jean-Frédéric Gerbeau
  - Control of dynamical systems, 32h, L3, Ecole Polytechnique.
- Damiano Lombardi
  - Analysis and Scientific Computing, 32h, L3, ENPC
  - Numerical Methods, 48h, L3, Polytech'Paris
  - Reduced models for problems in high dimension, 18h, ENPC, L3
- Irene Vignon Clementel
  - Numerical Methods for Ordinary Differential Equations, 24h ETD, L3, UPMC
  - Numerical simulations of blood flow, 2h30, as part of the undergraduate "continuum mechanics", AgroParisTech

Master:

- Laurent Boudin
  - Basics for numerical methods, 29h, M1, UPMC
  - Student advising for orientation and professional insertion, 20h, M1, UPMC
- Muriel Boulakia
  - Preparatory course for teaching admission examination "Agrégation", 40h, M2, Sorbonne University
- Miguel Ángel Fernández Varela
  - Modeling and numerical methods for hemodynamics, 30h, M2, UPMC
- Irene Vignon Clementel
  - MEC 550 - Biofluid Mechanics and Mass Transport, M2, 1h30, Ecole Polytechnique (engineering school), France
  - Annual ZCCE workshop, M2, 1h30, College of Engineering, Swansea University
  - Innovations thrapeutiques: du fondamental à l'appliqué, bioengineering module, M2, 1h, Paul Brousse Hospital, France
  - IFSBM (Institut de Formation Supérieure BioMédicale), M2, 1h30, Marie Lannelongue Hospital, France
  - M2 Sciences Chirurgicales de l'Université Paris Sud, 1h30, France

10.2.2. Supervision

PhD in progress: Ludovic Boilevin-Kayl, Modeling of cardiac implantable devices, since February 2016. Supervisors: J.-F. Gerbeau & M.A. Fernández Varela

PhD in progress: Alexandre This, Fusion data/simulation for the assessment of mitral regurgitation, since January 2016. Supervisor: J.-F. Gerbeau

PhD in progress: Chen-Yu Chiang, Transport on biological systems and some applications, since February 2016. Supervisor: M. Thiriet

PhD in progress: Felipe Galarce, Enhancing hemodynamics measurements with mathematical modeling, since December 2017. Supervisors: J.-F. Gerbeau & D. Lombardi.

PhD in progress: Fannie Maria Gerosa, Immersed boundary methods for fluid-structure interaction with topological changes, since January 2018. Supervisor: M.A. Fernández Varela
PhD in progress: David Michel, Mathematical analysis of fluid-kinetic coupled models, since September 2018. Supervisors: L. Boudin & A. Moussa
PhD in progress: Nicolas Golse, Contributions of anatomical and hemodynamic modeling of the liver in the anticipation, realization and teaching of liver surgery, since November 2018. Supervisors: E Vibert and I. Vignon-Clementel.

10.2.3. Juries

- Laurent Boudin
  - PhD committee: Nisrine Outada, Sorbonne Université & Caddi Ayad University, Gentien Marois, Insa Toulouse, Onera & CEA
  - HDR committee: Ayman Moussa, Sorbonne Université
- Muriel Boulakia
  - PhD committee: Pierre-Elliott Bécue, Inria Bordeaux Sud-Ouest; Guillaume Delay, Univ Toulouse (referee); Sourav Mitra, Univ. Toulouse; Josef Kolumban, Univ. Dauphine; Fabien Wahl, Inria Paris
  - Hiring committee: CDI researcher, Univ. Bordeaux
- Miguel Angel Fernández Varela
  - PhD committee: Rabii Mlika, INSA Lyon (president), Guillaume Delay, Universtié de Toulouse (member), Karol Cascavita, ENPC (member)
  - Hiring committee: Inria (DR2).
- Céline Grandmont
  - Member of the “agrégation” jury in mathematics.
  - Hiring committees: Inria Rennes (CR2), Inria CRCN.
  - PHD committee: J.-C. Casanova, Toulouse University (referee), J. Kolomban, Dauphine Univ. (president), S. Girel, Lyon Univ. (referee), C. Taing, Sorbonne Univ.
  - HDR committee: A. Moussa, Sorbonne Univ.
- Irene Vignon Clementel
  - Hiring committee: Nice University (MdC), Inria (CRCN), Inria (DR2, admission).
  - PHD committee: Clara Jaquet, ESIEE (member), Jules Dichamp, IMFT (referee) Noémie Boissier, UPMC (co-advisor) Mohamed Bekheit, U. Paris-Saclay (president).

10.3. Popularization

10.3.1. Interventions

- Céline Grandmont
  - Conference “Métier”: Master Maths students, UPMC, Oct 2018
  - Conference at "Rendez-vous des Jeunes Mathématiciennes et Informaticiennes", Inria Oct. 2018
  - High school discussion on scientific career, 18th January, Blanche de Castille, Le Chesnay, France
  - High school conference, 9th January, Blanche de Castille, Le Chesnay, France

11. Bibliography

Major publications by the team in recent years

[1] L. BOUDIN, L. DESVILLETTES, C. GRANDMONT, A. MOUSSA. *Global existence of solutions for the coupled Vlasov and Navier-Stokes equations*, in "Differential and integral equations", November 2009, vol. 22, n^{o} 11-12, pp. 1247-1271, https://hal.archives-ouvertes.fr/hal-00331895

[2] L. BOUDIN, B. GREC, F. SALVARANI. *A mathematical and numerical analysis of the Maxwell-Stefan diffusion equations*, in "Discrete and Continuous Dynamical Systems - Series B", 2012, vol. 17, n° 5, pp. 1427-1440 [*DOI :* 10.3934/DCDSB.2012.17.1427], https://hal.archives-ouvertes.fr/hal-00490511

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[5] J. CHRISTOPHE, T. ISHIKAWA, N. MATSUKI, Y. IMAI, K. TAKASE, M. THIRIET, T. YAMAGUCHI. *Patient-specific morphological and blood flow analysis of pulmonary artery in the case of severe deformations of the lung due to pneumothorax*, in "Journal of Biomechanical Science and Engineering", 2010, vol. 5, n° 5, pp. 485-498, https://hal.inria.fr/inria-00543090

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[9] P. MOIREAU, C. BERTOGLIO, N. XIAO, C. A. FIGUEROA, C. TAYLOR, D. CHAPELLE, J.-F. GERBEAU. *Sequential identification of boundary support parameters in a fluid-structure vascular model using patient image data*, in "Biomechanics and Modeling in Mechanobiology", July 2012, vol. 12, n° 3, pp. 475-496 [*DOI :* 10.1007/S10237-012-0418-3], https://hal.inria.fr/hal-00760703

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"Journal of Pharmacological and Toxicological Methods", 2018, vol. 89, pp. 59-72, https://hal.inria.fr/hal-01562673

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[30] L. BOUDIN, B. GREC, V. PAVAN. *Diffusion models for mixtures using a stiff dissipative hyperbolic formalism*, May 2018, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01786824

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