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Activity Report 2019

Project-Team COMMEDIA

Computational mathematics for bio-medical applications

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

RESEARCH CENTER
Paris

THEME
Modeling and Control for Life Sciences

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2. Overall Objectives

2.1. Overall Objectives

COMMEDIA is a joint project-team of the Inria Research Center of Paris and the Jacques-Louis Lions Laboratory (LJLL) of Sorbonne Université and CNRS (UMR7598). The research activity of COMMEDIA focuses on the numerical simulation of bio-fluid flows in the human body, more specifically, blood flows in the cardiovascular system and air flows in the respiratory system. These simulations are intended to complement available clinical data with the following purpose: help clinicians or bio-engineers to enhance the understanding of physiological phenomena, to improve diagnosis and therapy planning or to optimize medical devices. The main main objectives of COMMEDIA are:

- the development of appropriate mathematical models and efficient numerical methods for the simulations and for the interaction of simulations with measured data;
- the mathematical analysis of these models and numerical techniques;
- the development and validation of scientific computing software which implements these numerical techniques.

A distinctive feature of the mathematical models considered in COMMEDIA is that they often couple different types of partial differential equations (PDEs). This heterogeneous character in the models is a mathematical manifestation of the multi-physics nature of the considered problems.

3. Research Program

3.1. Multi-physics modeling and simulation

The research activity in terms of modeling and simulation (i.e., the so-called forward problem) is driven by two application domains related to the cardiovascular and the respiratory systems.

3.1.1. Cardiovascular hemodynamics

We distinguish between *cardiac hemodynamics* (blood flow inside the four chambers of the heart) and *vascular hemodynamics* (blood flow in the vessels of the body).

Cardiac hemodynamics. The numerical simulation of cardiac hemodynamics presents many difficulties. We can mention, for instance, the large deformation of the cardiac chambers and the complex fluid-structure interaction (FSI) phenomena between blood, the valves and the myocardium. Blood flow can be described by the incompressible Navier-Stokes equations which have to be coupled with a bio-physical model of the myocardium electro-mechanics and a mechanical model of the valves. The coupling between the fluid and the solid media is enforced by kinematic and dynamic coupling conditions, which guarantee the continuity of velocity and stresses across the interface. In spite of the significant advances achieved since the beginning of this century (see, e.g., [61], [69], [60], [63], [53]), the simulation of all the fluid-structure interaction phenomena involved in the heart hemodynamics remains a complex and challenging problem.

Heart valves are definitely a bottleneck of the problem, particularly due to their fast dynamics and the contact phenomena at high pressure-drops. Computational cost is recognized as one of the key difficulties, related to the efficiency of the FSI coupling method and the robustness of the contact algorithm. Furthermore, the numerical discretization of these coupled systems requires to deal with unfitted fluid and solid meshes, which are known to complicate the accuracy and/or the robustness of the numerical approximations (see Section 3.3.2 below).

The ultimate goal of the proposed research activity is the simulation of the complete fluid-structure-contact interaction phenomena involved within the heart. Most of this work will be carried out in close collaboration with the M3DISIM project-team, which has a wide expertise on the modeling, simulation and estimation of myocardium electro-mechanics. We will also consider simplified approaches for cardiac hemodynamics (see, e.g., [34], [48], [51]). The objective is to develop mathematically sound models of reduced valve dynamics with the purpose of enhancing the description of the pressure dynamics right after the opening/closing of the valve (traditional models yield spurious pressure oscillations).

Vascular hemodynamics. The modeling and simulation of vascular hemodynamics in large vessels has been one of the core research topics of some members of COMMEDIA, notably as regards the fluid-structure interaction phenomena. Here we propose to investigate the modeling of pathological scenarios, such as the hemorrhage phenomena in smaller vessels. Modeling of hemorrhage is motivated by the medical constatation that, after a primary vessel wall rupture, secondary vessel wall ruptures are observed. Biologists postulate that the mechanical explanation of this phenomena might be in the change of applied stress due to blood bleeding. We propose to model and simulate the underlying coupled system, blood vessel flow through the external tissue, to estimate the effect of the subsequent stress variation.

3.1.2. Respiratory flows

The motivation of the proposed research activities is to develop a hierarchy of easily parametrizable models allowing to describe and efficiently simulate the physical, mechanical and biological phenomena related to human respiration, namely, ventilation, particle deposition, gas diffusion and coupling with the circulatory system.

Ventilation. The current modeling approaches (either 3D–0D coupled models where the 3D Navier-Stokes equations are solved in truncated geometries of the bronchial tree with appropriate lumped boundary conditions, or 0D–3D coupled models where the lung parenchyma is described by a 3D elastic media irrigated by a simplified bronchial tree) provide satisfactory results in the case of mechanical ventilation or normal breathing. Realistic volume-flow phase portraits can also be simulated in the case of forced expiration (see [36], [45], [66]), but the magnitude of the corresponding pressure is not physiological. The current models must be enriched since they do not yet correctly describe all the physiological phenomena at play. We hence propose to extend the 0D–3D (bronchial tree–parenchyma) model developed in the team, by considering a non-linear, viscoelastic and possibly poro-elastic description of the parenchyma with appropriate boundary conditions that describe ribs and adjacent organs and taking into account an appropriate resistive model.

So far, the motion of the trachea and proximal bronchi has been neglected in the ventilation models (see, e.g., [67]). These features can be critical for the modeling of pathologic phenomena such as sleep apnea and occlusion of the airways. This would be a long-term goal where fluid-structure interaction and the possible contact phenomena will be taken into account, as in the simulation of cardiac hemodynamics (see Section 3.1.1).

Aerosol and gas diffusion. The dynamics of aerosols in the lung have been widely studied from the mathematical modeling standpoint. They can be described by models at different scales: the microscopic one for which each particle is described individually, the mesoscopic (or kinetic) one for which a density of probability is considered, or the macroscopic one where reaction-diffusion equations describing the behavior of the constituant concentration are considered. The objective of COMMEDIA will mainly be to develop the kinetic approach that allows a precise description of the deposition area at controlled computational costs. Part of this study could be done in collaboration with colleagues from the Research Center for Respiratory Diseases at Inserm Tours (UMR1100).

The macroscopic description is also appropriate for the diffusion of gases (oxygen and carbon dioxide) in the bronchial tree (see [62]). Regarding the influence of the carrier gas, if the patient inhales a different mixture of air such as a Helium-Oxygen mixture, the diffusion mechanisms could be modified. In this context, the goal is to evaluate if the cross-diffusion (and thus the carrier gas) modifies the quantities of oxygen diffused. Part of this work will be carried out in collaboration with members of the LJLL and of the MAP5.

As a long term goal, we propose to investigate the coupling of these models to models of diffusion in the blood or to perfusion models of the parenchyma, and thus, have access thanks to numerical simulations to new indices of ventilation efficiency (such as dissolved oxygen levels), depending on the pathology considered or the resting or exercise condition of the patient.

3.2. Simulation with data interaction

The second research axis of COMMEDIA is devoted to the interaction of numerical simulations with measured data. Several research directions related to two specific applications are described below: blood flows and cardiac electrophysiology, for which the mathematical models have been validated against experimental data. This list is not exhaustive and additional problems (related to cardiac and respiratory flows) shall be considered depending on the degree of maturity of the developed models.

3.2.1. Fluid flow reconstruction from medical imaging

A first problem which is currently under study at COMMEDIA is the reconstruction of the flow state from Doppler ultrasound measurements. This is a cheap and largely available imaging modality where the measure can be interpreted as the average on a voxel of the velocity along the direction of the ultrasound beam. The goal is to perform a full-state estimation in a time compatible with a realistic application.

A second problem which is relevant is the flow and wall dynamics reconstruction using 4D-flow MRI. This imaging modality is richer than Doppler ultrasound and provides directly a measure of the 3D velocity field in the voxels. This enables the use of direct estimation methods at a reduced computational cost with respect to the traditional variational data assimilation approaches. Yet, the sensitivity of the results to subsampling and noise is still not well understood.

We also propose to address the issues related to uncertainty quantification. Indeed, measurements are corrupted by noise and the parameters as well as the available data of the system are either hidden or not known exactly (see [59]). This uncertainty makes the estimation difficult and has a large impact on the precision of the reconstruction, to be quantified in order to provide a reliable tool.

3.2.2. Inverse problem in electro-cardiography

The objective of the inverse problem in electro-cardiography is to recover information about the cardiac electrical activity from electrical measurements on the body surface (for instance from electrocardiograms). We propose to investigate approaches based on recent methods for the Cauchy problem reported in [42]. Basically, the idea consists in regularizing the discrete inverse problem using stabilized finite element methods, without the need of integrating a priori knowledge of the solution, only regularity on the exact solution is required.

3.2.3. Safety pharmacology

One of the the most important problems in pharmacology is cardio-toxicity (see [58]). The objective is to predict whether or not a molecule alters in a significant way the normal functioning of the cardiac cells. This problem can be formulated as inferring the impact of a drug on the ionic currents of each cell based on the measured electrical signal (e.g., electrograms from Micro-Electrodes Arrays). The proposed approach in collaboration with two industrial partners (NOTOCORD and Ncardia) consists in combining available realistic data with virtual ones obtained by numerical simulations. These two datasets can be used to construct efficient classifiers and regressors using machine learning tools (see [41]) and hence providing a rapid way to estimate the impact of a molecule on the electrical activity. The methodological aspects of this work are addressed in Section 3.3.3.

3.3. Methodological core

The work described in this section is aimed at investigating fundamental mathematical and numerical problems which arise in the first two research axes.

3.3.1. Mathematical analysis of PDEs

The mathematical analysis of the multi-scale and multi-physics models are a fundamental tool of the simulation chain. Indeed, well-posedness results provide precious insights on the properties of solutions of the systems which can, for instance, guide the design of the numerical methods or help to discriminate between different modeling options.

Fluid-structure interaction. Most of the existing results concern the existence of solutions locally in time or away from contacts. One fundamental problem, related to the modeling and simulation of valve dynamics (see Sections 3.1.1 and 3.3.2), is the question of whether or not the model allows for contact (see [57], [55]). The proposed research activity is aimed at investigating the case of both immersed rigid or elastic structures and explore if the considered model allows for contact and if existence can be proved beyond contact. The question of the choice of the model is crucial and considering different types of fluid (newtonian or non newtonian), structure (smooth or rough, elastic, viscoelastic, poro-elastic), or various interface conditions has an influence on whether the model allows contact or not.

Fluid–structure mixture. The main motivation to study fluid-solid mixtures (i.e., porous media consisting of a skeleton and connecting pores filled with fluid) comes from the modeling of the lung parenchyma and cerebral hemorrhages (see Sections 3.1.1–3.1.2). The Biot model is the most widely used in the literature for the modeling of poro-elastic effects in the arterial wall. Here, we propose to investigate the recent model proposed by the M3DISIM project-team in [47], which allows for nonlinear constitutive behaviors and viscous effects, both in the fluid and the solid. Among the questions which will be addressed, some of them in collaboration with M3DISIM, we mention the justification of the model (or its linearized version) by means of homogenization techniques and its well-posedness.

Fluid–particle interaction. Mathematical analysis studies on the Navier-Stokes-Vlasov system for fluid-particle interaction in aerosols can be found in [38], [39]. We propose to extend these studies to more realistic models which take into account, for instance, changes in the volume of the particles due to humidity.

3.3.2. Numerical methods for multi-physics problems

In this section we describe the main research directions that we propose to explore as regards the numerical approximation of multi-physics problems.

Fluid-structure interaction. The spatial discretization of fluid-structure interaction (FSI) problems generally depends on the amount of solid displacement within the fluid. Problems featuring moderate interface displacements can be successfully simulated using (moving) fitted meshes with an arbitrary Lagrangian-Eulerian (ALE) description of the fluid. This facilitates, in particular, the accurate discretization of the interface conditions. Nevertheless, for problems involving large structural deflections, with solids that might come into contact or that might break up, the ALE formalism becomes cumbersome. A preferred approach in this case is to combine an Eulerian formalism in the fluid with an unfitted mesh discretization, in which the fluid-structure interface deforms independently of a background fluid mesh. In general, traditional unfitted mesh approaches (such as the immersed boundary and the fictitious domain methods [65], [37], [54], [35]) are known to be inaccurate in space. These difficulties have been recently circumvented by a Nitsche-based cut-FEM methodolgy (see [32], [43]). The superior accuracy properties of cut-FEM approaches comes at a price: these methods demand a much more involved computer implementation and require a specific evaluation of the interface intersections.

As regards the time discretization, significant advances have been achieved over the last decade in the development and the analysis of time-splitting schemes that avoid strong coupling (fully implicit treatment of the interface coupling), without compromising stability and accuracy. In the vast majority these studies, the spatial discretization is based on body fitted fluid meshes and the problem of accuracy remains practically open for the coupling with thick-walled structures (see, e.g., [52]). Within the unfitted mesh framework, splitting schemes which avoid strong coupling are much more rare in the literature.

Computational efficiency is a major bottleneck in the numerical simulation of fluid-structure interaction problems with unfitted meshes. The proposed research activity is aimed at addressing these issues. Another

fundamental problem that we propose to face is the case of topology changes in the fluid, due to contact or fracture of immersed solids. This challenging problem (fluid-structure-contact-fracture interaction) has major role in many applications (e.g., heart valves repair or replacement, break-up of drug-loaded micro-capsules) but most of the available studies are still merely illustrative. Indeed, besides the numerical issues discussed above, the stability and the accuracy properties of the numerical approximations in such a singular setting are not known.

Fluid–particle interaction and gas diffusion.

Aerosols can be described through mesoscopic equations of kinetic type, which provide a trade-off between model complexity and accuracy. The strongly coupled fluid-particle system involves the incompressible Navier-Stokes equations and the Vlasov equation. The proposed research activity is aimed at investigating the theoretical stability of time-splitting schemes for this system. We also propose to extend these studies to more complex models that take into account the radius growth of the particles due to humidity, and for which stable, accurate and mass conservative schemes have to be developed.

As regards gas diffusion, the mathematical models are generally highly non-linear (see, e.g., [62], [64], [40]). Numerical difficulties arise from these strong non linearities and we propose to develop numerical schemes able to deal with the stiff geometrical terms and that guarantee mass conservation. Moreover, numerical diffusion must be limited in order to correctly capture the time scales and the cross-diffusion effects.

3.3.3. Statistical learning and mathematical modeling interactions

Machine learning and in general statistical learning methods (currently intensively developed and used, see [33]) build a relationship between the system observations and the predictions of the QoI based on the *a posteriori* knowledge of a large amount of data. When dealing with biomedical applications, the available observations are signals (think for instance to images or electro-cardiograms, pressure and Doppler measurements). These data are high dimensional and the number of available individuals to set up precise classification/regression tools could be prohibitively large. To overcome this major problem and still try to exploit the advantages of statistical learning approaches, we try to add, to the a posteriori knowledge of the available data an *a priori* knowledge, based on the mathematical modeling of the system. A large number of numerical simulations is performed in order to explore a set of meaningful scenarios, potentially missing in the dataset. This *in silico* database of virtual experiments is added to the real dataset: the number of individuals is increased and, moreover, this larger dataset can be used to compute semi-empirical functions to reduce the dimension of the observed signals.

Several investigations have to be carried out to systematically set up this framework. First, often there is not a single mathematical model describing a physiological phenomenon, but hierarchies of model of different complexity. Every model is characterized by a model error. How can this be accounted for? Moreover, several statistical estimators can be set up and eventually combined together in order to improve the estimations (see [70]). Other issues have an actual impact and has to be investigated: what is the optimal number of *in silico* experiments to be added? What are the most relevant scenarios to be simulated in relation to the statistical learning approach considered in order to obtain reliable results? In order to answer to these questions, discussions and collaborations with statistics and machine learning groups have to be developed.

3.3.4. Tensor approximation and HPC

Tensor methods have a recent significant development because of their pertinence in providing a compact representation of large, high-dimensional data. Their applications range from applied mathematics and numerical analysis to machine learning and computational physics. Several tensor decompositions and methods are currently available (see [56]). Contrary to matrices, for tensors of order higher or equal to three, there does not exist, in general, a best low rank approximation, the problem being ill posed (see [68]). Two main points will be addressed: (i) The tensor construction and the multi-linear algebra operations involved when solving high-dimensional problems are still sequential in most of the cases. The objective is to design efficient parallel methods for tensor construction and computations; (ii) When solving high-dimensional problems, the tensor is not assigned; instead, it is specified through a set of equations and tensor data. Our

goal is to devise numerical methods able to (dynamically) adapt the rank and the discretization (possibly even the tensor format) to respect the chosen error criterion. This could, in turn, improve the efficiency and reduce the computational burden.

These sought improvements could make the definition of parsimonious discretizations for kinetic theory and uncertainty quantification problems (see Section 3.2.1) more efficient and suitable for a HPC paradigm. This work will be carried out in collaboration with Olga Mula (Université Paris-Dauphine) and the ALPINES and MATHERIALS project-teams.

4. Application Domains

4.1. Cardiovascular hemodynamics

The heart is a double pump whose purpose is to deliver blood to the tissue and organs of the body. This function is made possible through the opening and closing of the heart valves. Cardiac diseases generally manifest by affecting the pumping function of the heart. Numerical simulations of cardiac hemodynamics, in normal and pathological conditions, are recognized as a tool of paramount importance for improving the understanding, diagnosis and treatment of cardiac pathologies, and also for the development of implantable devices (see, e.g., [63], [46]). As an example, we can mention the case of cardiac mitral valve regurgitation, one of the most common heart valve diseases. For this pathology, clinical data are known to be insufficient for determining the optimal timing for surgery, the best surgical strategy and the long-term outcome of a surgical repair. Contrary to imaging techniques, numerical simulations provide local information, such as pressure and stresses, which are of fundamental importance for the prediction of the mechanical behavior of native valves and of implantable devices.

4.2. Respiratory flows

Respiration involves the transport of air through the airways from the mouth to the alveoli of the lungs. These units where diffusion of oxygen and carbon dioxide take place, are surrounded by a viscoelastic medium (the parenchyma) consisting of blood vessels and collagen fibers. Air flows due to the displacement of the diaphragm, which drives the pulmonary parenchyma. Accidental inhalations of foreign bodies or pathologies such as asthma, emphysema and fibrosis might prevent the lung of fulfilling its function. Therapies mostly use aerosols (set of small particles, solid or liquid), which must reach the specific areas of the lung targeted for treatment. Understanding the airflow mechanisms within the respiratory network is a fundamental ingredient for predicting the particles motion and their deposition (see, e.g., [44]). Moreover, understanding of the gas diffusion in the lung is also of major importance since the main fonction of this organ is to deliver oxygen to the blood.

4.3. Safety pharmacology

The problem of safety pharmacology can be summarized as follows: given a molecule which is a candidate to become a drug, is its use dangerous due to side effects? Among all the different problems to be addressed, one of the most relevant questions in pharmacology is cardio-toxicity (see [58]). More precisely, the objective is to determine whether or not a molecule alters in a significant way the normal functioning of the cardiac cells. To answer these questions, the CiPA initiative promotes the introduction of novel techniques and their standardisation (see [50]). One of the proposed tests of the CiPA panel is to measure the the electrical activity using Micro-Electrodes Array: these are microchips that record the electrical activity of an ensemble of cells. The task is to infer the impact of a drug on the ionic currents of each cell based on the electrical signal measured (electrograms) and, in perspective, to be able to assess whether a molecule can induce arrhythmia (see [49]).

5. Highlights of the Year

5.1. Highlights of the Year

- Major results have been obtained on the simulation of fluid-structure interaction [1] and of cardiac hemodynamics [8].

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: Matteo Aletti, Daniele Carlo Corti, Dominique Chapelle, Miguel Ángel Fernández, Benoit Fabreges, Axel Fourmont, Jean-Frédéric Gerbeau, Fannie Gerosa, Sébastien Gilles, Mikel Landajuela Larma, Damiano Lombardi, Philippe Moireau, Irène Vignon-Clementel and Marina Vidrascu
- Contact: Miguel Ángel Fernández
- URL: http://felisce.gforge.inria.fr

6.2. 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 Ángel Fernández, Axel Fourmont, Jean-Frédéric Gerbeau and Marina Vidrascu
- Contact: Miguel Ángel Fernández

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

7. New Results

7.1. Cardiovascular hemodynamics

Participant: Miguel Ángel Fernández Varela.

Mitral regurgitation is one of the most prevalent valvular heart disease. Proper evaluation of its severity is necessary to choose appropriate treatment. The PISA method, based on Color Doppler echocardiography, is widely used in the clinical setting to estimate various relevant quantities related to the severity of the disease. In [19], the use of a pipeline to quickly generate image-based numerical simulation of intracardiac hemodynamics is investigated. The pipeline capabilities are evaluated on a database of twelve volunteers. Full pre-processing is achieved completely automatically in 55 minutes, on average, with small registration errors compared to the image spatial resolution. This pipeline is then used to study the intracardiac hemodynamics in the presence of diseased mitral valve. A strong variability among the simulated cases, mainly due to the valve geometry and regurgitation specifics, is found. The results from those numerical simulations is used to assess the potential limitations of the PISA method with respect to different MR types. While the PISA method provides reasonable estimates in the case of a simple circular regurgitation, it is shown that unsatisfying estimates are obtained in the case of non-circular leakage. Moreover, it is shown that the choice of high aliasing velocities can lead to difficulties in quantifying MR.

7.2. Respiratory flows

Participant: Céline Grandmont.

In [21], we propose a coupled fluid-kinetic model taking into account the radius growth of aerosol particles due to humidity in the respiratory system. We aim to numerically investigate the impact of hygroscopic effects on the particle behaviour. The air flow is described by the incompressible Navier-Stokes equations, and the aerosol by a Vlasov-type equation involving the airhumidity and temperature, both quantities satisfying a convection-diffusion equation with a sourceterm. Conservations properties are checked and an explicit time-marching scheme is proposed. Two-dimensional numerical simulations in a branched structure show the influence of the particle size variations on the aerosol dynamics.

7.3. Fluid flow reconstruction from medical imaging

Participants: Muriel Boulakia, Miguel Ángel Fernández Varela, Felipe Galarce Marin, Damiano Lombardi, Olga Mula, Colette Voisembert.

In [22], we are interested in designing and analyzing a finite element data assimilation method for laminar steady flow described by the linearized incompressible Navier-Stokes equation. We propose a weakly consistent stabilized finite element method which reconstructs the whole fluid flow from velocity measurements in a subset of the computational domain. Using the stability of the continuous problem in the form of a three balls inequality, we derive quantitative local error estimates for the velocity. Numerical simulations illustrate these convergences properties and we finally apply our method to the flow reconstruction in a blood vessel.

In [29] a state estimation problem is investigated, that consists in reconstructing the blood flow from ultrasound Doppler images. The method proposed is based on a reduced-order technique. Semi-realistic 3D configurations are tested.

7.4. Safety pharmacology

Participants: Damiano Lombardi, Fabien Raphel.

In [31] a greedy method is used to classify molecules action on cardiac myocites. The method is applied to a realistic dataset: the experiments were performed at Ncardia (Netherlands). The experimental dataset is complemented by a synthetic dataset, obtained by simulating experimental meaningful scenarios. The results obtained are encouraging.

7.5. Mathematical analysis of PDEs

Participants: Muriel Boulakia, Jean-Jerome Casanova, Céline Grandmont.

In [23], we consider a reaction-diffusion equation where the reaction term is given by a cubic function and we are interested in the numerical reconstruction of the time-independent part of the source term from measurements of the solution. For this identification problem, we present an iterative algorithm based on Carleman estimates which consists of minimizing at each iteration strongly convex cost functionals. Despite the nonlinear nature of the problem, we prove that our algorithm globally converges and the convergence speed evaluated in weighted norm is linear. In the last part of the paper, we illustrate the effectiveness of our algorithm with several numerical reconstructions in dimension one or two.

In [25] a coupled system of pdes modelling the interaction between a two–dimensional incompressible viscous fluid and a one–dimensional elastic beam located on the upper part of the fluid domain boundary is considered. A good functional framework to define weak solutions in case of contact between the elastic beam and the bottom of the fluid cavity is designed.It is then prove that such solutions exist globally in time regardless a possible contact by approximating the beam equation by a damped beam and letting this additional viscosity vanishes.

7.6. Numerical methods for multi-physics problems

Participants: Miguel Ángel Fernández Varela, Fannie Gerosa.

In [24] we introduce a mixed dimensional Stokes-Darcy coupling where a d-dimensional Stokes' flow is coupled to a Darcy model on the $d-1$ dimensional boundary of the domain. The porous layer introduces tangential creeping flow along the boundary and allows for the modelling of boundary flow due to surface roughness. This leads to a new model of flow in fracture networks with reservoirs in an impenetrable bulk matrix. Exploiting this modelling capability, we then formulate a fluid-structure interaction method with contact, where the porous layer allows for mechanically consistent contact and release. Physical seepage in the contact zone due to rough surfaces is modelled by the porous layer. Some numerical examples are reported, both on the Stokes-Darcy coupling alone and on the fluid-structure interaction with contact in the porous boundary layer.

Unfitted mesh finite element approximations of immersed incompressible fluid-structure interaction problems which efficiently avoid strong coupling without compromising stability and accuracy are rare in the literature. Moreover, most of the existing approaches introduce additional unknowns or are limited by penalty terms which yield ill conditioning issues. In [28], we introduce a new unfitted mesh semi-implicit coupling scheme which avoids these issues. To this purpose, we provide a consistent generalization of the projection based semi-implicit coupling paradigm of [Int. J. Num. Meth. Engrg.,69(4):794-821, 2007] to the unfitted mesh Nitsche-XFEM framework.

7.7. Statistical learning and mathematical modeling interactions

Participants: Damiano Lombardi, Fabien Raphel.

In [30] a greedy dimension reduction method is proposed to deal with classification problems. The method proposed can be seen as a goal oriented dimension reduction method. Elements of a Stiefel manifold (whose dimension is not fixed a priori) are computed in such a way that the classification score is maximised. Several examples are proposed to illustrate the method features and to highlight its differences with classical reduction methods used in classification.

7.8. Tensor approximation and HPC

Participant: Damiano Lombardi.

In [26] a hierarchical adaptive piece-wise tensor decomposition is proposed to approximate high-dimensional functions. Neither the subtensor partitioning nor the rank of the approximation in each of the partitions are fixed a priori. Instead, they are computed to fulfill a prescribed accuracy. Two main contributions are proposed. A greedy error distribution scheme, that allows to adaptively construct the approximation in each of the partitions and a hierarchical tree algorithm that optimise the subtensor partitioning to minimise the storage. Several example on challenging functions are proposed.

7.9. Miscellaneous

Participants: Damiano Lombardi, Olga Mula.

In [20] an approximated formulation of the multi-marginal optimal transport problem (Kantorovich formulation) is proposed. In the formulation, called MCOT, the constraints on the marginal densities are replaced by moments of the densities. This formulation allows to deal simply with a wide spectrum of high-dimensional multi-marginal problems, with non-standard (martingale) constraints.

In [27] a reduced-order modeling framework is proposed, in which a set of model instances is part of a metric space. The introduction of the exponential and logarithmic maps (Riemannian geometry) makes it possible to reduce in an effective way solutions that are classically challenging for standard model reduction methods. Some examples on 1D hyperbolic equations and Wasserstein distance are proposed.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

8.1.1. Notocord Systems

Participants: Damiano Lombardi, Fabien Raphel.

This work is devoted to the investigation on new approaches and efficient algorithms in the context of safety pharmacology and the analysis of biological signals.

8.1.2. Casis

Participants: Mocia Agbalessi, Miguel Ángel Fernández Varela, Damiano Lombardi.

This work is devoted to the combination of 4D-MRI data and fluid-structure interaction models of blood flow to asses indicators of aneurysm rupture.

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. ANR Project "ADAPT"

Participants: Maria Fuente-Ruiz, Damiano Lombardi [coordinator], Olga Mula.

Period: 2018-2022.
Adaptive Dynamical Approximations by Parallel Tensor methods. The main goal of the ANR is to investigate the numerical approximation of the solution of high-dimensional problems. In particular, the applications that motivate this study are the Uncertainty Quantification and the Kinetic theory. The main objective is to construct in an adaptive way parsimonious discretisations starting from arbitrarily chosen separated discretisations.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events: Organisation

- Céline Grandmont
  - Co-organizer of Inria-LJLL meeting in scientific computing
- Damiano Lombardi
  - Co-organisation (with Sanjay Pant, Swansea University) of two mini-symposia: Machine learning methods in biomedical engineering and Uncertainty Quantification and Bayesian inference in biomedical applications at CMBE 2019, June 2019, Sendai, Japan
  - Co-organizer of Inria-LJLL meeting in scientific computing
- Olga Mula
  - Co-organizer of Summer School on Sparity for Physics, Signals and Learning, at Inria Paris, June 2019
  - Co-organiser of the GdT Stat-Num at Paris Dauphine

10.1.1.1. Member of the Organizing Committees

- Céline Grandmont
  - Member of the local organizing comittee of WCCM 2020

10.1.2. Scientific Events: Selection

- Muriel Boulakia
  - Member of the scientific committee of LIA COPDESC and Lions-Magenes Days, LJJL, November 2019, Paris
- Miguel Ángel Fernández Varela
  - Member of the scientific committee of XDMS 2019, July 2019, Lugano

10.1.2.1. Member of the Editorial Boards

- Céline Grandmont
  - Member of the editorial board of Mathematical Modelling of Natural Phenomena
  - Member of the editorial board of Journal of Mathematical Fluid Mechanics (since November 2019)
- Olga Mula
  - Member of the editorial board of Calcolo (since October 2019)

10.1.2.2. Reviewer - Reviewing Activities

- Muriel Boulakia
  - Expert for « Appel à projets générique », ANR 2019

10.1.3. Research Administration

- Miguel Ángel Fernández Varela
  - Head of Science, Inria Paris (from September 2019)
  - Deputy Head of Science, Inria Paris (until August 2019)
  - Member of the Inria Evaluation Committee
- Céline Grandmont
  - Member of the Inria Evaluation Committee
  - Member of the Inria Parity Committee
  - Member of the scientific board of the EDMH, Paris Saclay

10.1.4. Conferences

- Muriel Boulakia
  - Seminar, Modeling and scientific computation, November 2019, LAGA, Univ. Paris 13
  - Invited speaker, Control and stabilization issues for PDE, September 2019, Toulouse
  - Contributed talk in minisymposium, Applied Inverse Problems Conference, July 2019, Grenoble
  - Seminar, Numerical Analysis and PDE, Université Lille, March 2019, Lille
  - Invited speaker, Workshop on fluid-structure interaction, March 2019, Politecnico di Milano, Italy
- Miguel Ángel Fernández Varela
  - Seminar, Laboratoire Mathématiques Jean Leray, Univ Nates, Nantes
  - Contributed talk in minisymposium, ICIAM, July 2019, Valencia, Spain
  - Invited speaker, iHEART conference on Modelling the Cardiac Function, July 2019, Varese, Italy
- Felipe Galarce Marin
  - Seminar at Inria Chile, July 2019, Santiago, Chile
  - Semina at Universidad Técnica Federico Santa Maria, July 2019, Valparaiso, Chile
  - Seminar at Pontificia Universidad Católica de Valparaíso, July 2019, Valparíso, Chile
  - Contributed talk in minisymposium, CSMA, May 2019, Giens
  - Contributed talk in minisymposium, Enumath, September/October 2019, Egmond aan Zee, The Netherlands
- Fannie Gerosa
  - Contributed talk in minisymposium, 9th biennial congress of SMAI, May 2019, Guidel Plages, France
  - Contributed talk in minisymposium, 15th US National Congress on Computational Mechanics, July/August 2019, Austin, Texas
- Céline Grandmont
  - Plenary speaker, International Meeting on Applied Mathematics & Evolution, La Rochelle, April 2019
  - Keynote speaker, PDE 2019: Partial Differential Equations in Fluids and Solids, Berlin, Sep. 2019
  - Invited Speaker, International Conference “Multiscale Modeling in Fluid Mechanics and Fluid-Structure Interaction” , Oct. 2019, Vilnius
  - Seminar, ULB, Bruxelles, Nov. 2019

  - Seminar, CMAP, Ecole Polytechnique, Dec. 2019
- Damiano Lombardi
  - Contributed talk in minisymposium, ICIAM, July 2019, Valencia, Spain
  - Contributed talk at the Lions-Magenes days, November 2019, Paris.
  - Contributed talk at Mortech, November 2019, Paris.
- Olga Mula
  - Contributed talk at Enumath, September/October 2019, Egmond aan Zee, The Netherlands
  - Contributed talk at INdaM workshop on kinetic equations, November 2019, Rome, Italy
  - Contributed talk at Mortech, November 2019, Paris.
- Fabien Raphel
  - Contributed poster at The Safety Pharmacology Society (SPS) annual meeting, September 2019, Barcelona, Spain
  - Contributed talk at The Safety Pharmacology Society (SPS) webinar, November 2019, Paris
  - Invited talk at Math jobs forum University of Nantes, January 2019, Nantes

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Licence:

- Muriel Boulakia
  - Projects on differential equations, 34h, L3, Polytech Sorbonne, Sorbonne Université
  - Nonlinear systems and optimization, 35h, L3, Polytech Sorbonne, Sorbonne Université
  - Numerical approximation of functions, 36h, L3, Sorbonne Université
- Fannie Gerosa
  - Function series, integrals and application to differential equation, 38h, L3, Sorbonne Université
- Damiano Lombardi
  - Cours/TD analysis and scientific computing, 32 h, ENPC, L3.
  - Model reduction in large dimensions, 9h, ENPC, L3.
  - TD, Function approximation, Sorbonne University , 18h, L3

Master:

- Muriel Boulakia
  - Preparatory course for teaching admission examination “Agrégation”, 40h, M2, Sorbonne Université
- Miguel Ángel Fernández Varela
  - Modeling and numerical methods for hemodynamics, 30h, M2, Sorbonne Université
- Damiano Lombardi
  - Mini-cours Modeling of cardiac electrophysiology, 3h, M2, Ecole des Mines Paristech

Others:

- Céline Grandmont
  - Invited Lecturer, Hausdorff School on "Modeling and Analysis of Evolutionary Problems in Materials Science" , 6h, Bonn, Sept. 2019
  - Invited Lecturer, Institut d'Etudes Scientifiques de Cargèse, Summer school : *Why modelling the pulmonary ventilation? Music, exercise and medicine*, 1h30, November 2019

10.2.2. Supervision

PhD: Ludovic Boilevin-Kayl, Modeling of cardiac implantable devices, Sorbonne Université, defended on July 10, 2019. Supervisors: J.-F. Gerbeau & M.A. Fernández Varela

PhD: Alexandre This, Fusion data/simulation for the assessment of mitral regurgitation, Sorbonne Université, defended on May 28, 2019. Supervisors: O. Bonnefous, M.A. Fernández Varela, J.-F. Gerbeau & H. Morales

PhD in progress: Mocia Agbalessi, Modeling and patient specific fluid-structure interaction simulations of aortic pathological configurations. Since April, 2019, Supervisors: M.A. Fernández Varela & D. Lombardi

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

PhD in progress: Fannie Gerosa, Immersed boundary methods for fluid-structure interaction with topological changes, since January 2018. Supervisor: M.A. Fernández Varela

PhD in progress: Fabien Raphel, Mathematical modeling and learning of biomedical signals for safety pharmacology. Since April 2019. Supervisors: J.-F. Gerbeau & D. Lombardi

10.2.3. Juries

- Miguel Ángel Fernández Varela
  - Hiring committees: Inria Paris (CRCN, Vice-président), Université de Franche-Comté (MdC)
  - PHD committee: P. Quemar, Université Paris-Nord (reviewer), D. Nolte, Groningen University, The Netherlands (reviewer), R.J. Rebolledo Cormack, Universidad de Concepción, Chile (reviewer)
- Céline Grandmont
  - Member of the "agrégation" jury in mathematics
  - Hiring committees: Inria CRCN, Inria DR2
  - PHD committee: N. Lauzeral, Ecole centrale de Nantes (reviewer), F. Vergnet, Paris Sud Univ (member), A. Dekkers, Centrale Suppelec (reviewer)
  - HDR committee: A. Decoene, Paris-Sud Univ (reviewer)

10.3. Popularization

10.3.1. Interventions

- Céline Grandmont
  - Meeting with junior high school students, Collège Iqbal Masih, Saint-Denis. Interview: https://www.youtube.com/watch?v=eJVaVB7z8tU&t=12s

11. Bibliography

Major publications by the team in recent years

[1] L. BOILEVIN-KAYL, M. A. FERNÁNDEZ, J.-F. GERBEAU. *A loosely coupled scheme for fictitious domain approximations of fluid-structure interaction problems with immersed thin-walled structures*, in "SIAM Journal on Scientific Computing", February 2019, vol. 41, n^{o} 2, pp. 351-374 [*DOI :* 10.1137/18M1192779], https://hal.inria.fr/hal-01811290

[2] M. BOULAKIA. *Quantification of the unique continuation property for the nonstationary Stokes problem*, in "Mathematical Control and Related Fields", March 2016, https://hal.inria.fr/hal-01094490

[3] M. BOULAKIA, S. GUERRERO, T. TAKAHASHI. *Well-posedness for the coupling between a viscous incompressible fluid and an elastic structure*, in "Nonlinearity", 2019, vol. 32, pp. 3548-3592 [*DOI :* 10.1088/1361-6544/AB128C], https://hal.inria.fr/hal-01939464

[4] C. GRANDMONT, M. HILLAIRET. *Existence of global strong solutions to a beam-fluid interaction system*, in "Archive for Rational Mechanics and Analysis", 2016 [*DOI :* 10.1007/S00205-015-0954-Y], https://hal.inria.fr/hal-01138736

[5] M. LANDAJUELA, M. VIDRASCU, D. CHAPELLE, M. A. FERNÁNDEZ. *Coupling schemes for the FSI forward prediction challenge: comparative study and validation*, in "International Journal for Numerical Methods in Biomedical Engineering", 2017, vol. 33, n° 4, e02813 p. [*DOI :* 10.1002/CNM.2813], https://hal.inria.fr/hal-01239931

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[8] A. THIS, L. BOILEVIN-KAYL, M. A. FERNÁNDEZ, J.-F. GERBEAU. *Augmented Resistive Immersed Surfaces valve model for the simulation of cardiac hemodynamics with isovolumetric phases*, in "International Journal for Numerical Methods in Biomedical Engineering", May 2019, forthcoming [*DOI :* 10.1002/CNM.3223], https://hal.inria.fr/hal-01944798

[9] E. TIXIER, F. RAPHEL, D. LOMBARDI, J.-F. GERBEAU. *Composite biomarkers derived from Micro-Electrode Array measurements and computer simulations improve the classification of drug-induced channel block*, in "Frontiers in Physiology", 2018, vol. 8, n° 1096, pp. 1-30 [*DOI :* 10.3389/FPHYS.2017.01096], https://hal.archives-ouvertes.fr/hal-01570819

Publications of the year

Doctoral Dissertations and Habilitation Theses

[10] L. BOILEVIN-KAYL. *Modeling and numerical simulation of implantable cardiovascular devices*, Sorbonne Université, July 2019, https://hal.inria.fr/tel-02217259

[11] A. THIS. *Image/Model Fusion for the Quantification of Mitral Regurgitation Severity*, Sorbonne Université, May 2019, https://hal.inria.fr/tel-02176167

Articles in International Peer-Reviewed Journals

[12] L. BOILEVIN-KAYL, M. A. FERNÁNDEZ, J.-F. GERBEAU. *A loosely coupled scheme for fictitious domain approximations of fluid-structure interaction problems with immersed thin-walled structures*, in "SIAM Journal on Scientific Computing", February 2019, vol. 41, n° 2, pp. 351-374 [*DOI :* 10.1137/18M1192779], https://hal.inria.fr/hal-01811290

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