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Project-Team COMMEDIA

Computational mathematics for bio-medical applications

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

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

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Project-Team COMMEDIA

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Keywords

Computer sciences and digital sciences

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2 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., [73, 74, 71, 76, 64]), 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., [44, 59, 62]). 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 [46, 56, 79]), 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., [81]). 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 [75]). 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 [70]). 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 [52]. 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 [69]). 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 [51]) 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 [68, 66]). 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 [58], 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 [48, 50]. 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 [78, 47, 65, 45]) are known to be inaccurate in space. These difficulties have been recently circumvented by a Nitsche-based cut-FEM methodolgy (see [42, 53]). 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., [63]). 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., [75, 77,

49]). 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 [43]) 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 [72]). 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 [67]). 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 [80]). 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., [76, 57]). 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., [55]). 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 [69]). 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 [61]). 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 [60]).

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5 Highlights of the year

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Céline Grandmont participated to the Inria covid mission project Prelifa.

6 New software and platforms

6.1 New software

6.1.1 FELiScE

Name: 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 initially 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.

URL: https://team.inria.fr/commedia/software/felisce/

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6.1.2 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.

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6.1.3 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

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7 New results

7.1 Fluid flow reconstruction from medical imaging

Participants Felipe Galarce Marin, Damiano Lombardi, Olga Mula
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In [22] we develop a reduced-order approach to perform a fast estimation of hemodynamics quantities of interest based on measurements which can be modelled as linear forms applied to the system state, corrupted by some noise. A prototypical example of application is the estimation of the pressure (or of the wall shear stress) by using data coming from Doppler Ultrasound imaging or 4d-flow MRI.

7.2 Safety pharmacology

Participants Damiano Lombardi, Fabien Raphel.

In [26] we propose to use a double greedy algorithm to approximate the observable-to-parameters map in an electro-physiology model. This approximation is used as a non-linear preconditioner in a parameter estimation problem solved by means of an Unscented Kalman filter. The results shown that the non-linear preconditioning strategy produced a significant speed-up of the filter convergence and reduced the error mean and standard deviation.

7.3 Mathematical analysis of PDEs

Participants Muriel Boulakia, Céline Grandmont.

In [41] we consider a quasi-static fluid-structure interaction problem where the fluid is modeled by the Stokes equations and the structure is an active and elastic medium. More precisely, the displacement of the structure verifies the equations of elasticity with an active stress, which models the presence of internal biological motors in the structure. Under smallness assumptions on the data, we prove the existence of a unique solution for this strongly coupled system. These kind of models describe selfpropelled structures such as cilia and flagella, that are examples of such soft materials that deform themselves using internal biological motors and thus, induce a flow within the surrounding fluid.

7.4 Numerical methods for multi-physics problems

Participants Miguel Ángel Fernández Varela, Fannie Gerosa.

In [36], robust a priori error estimates are derived for the unfitted meshe semi-implicit coupling scheme recently introduced in [20], for the simulation of incompresible fluid-structure interaction involving thinwalled solids. The analysis shows that, under a hyperbolic-CFL condition, the leading term in the energy error scales as $\mathcal{O}(h^{r-\frac{1}{2}})$, where $r = 1,2$ stands for the extrapolation order of the solid velocity in the viscous luid sub-step. The theoretical findings are illustrated via a numerical experiments which show, in particular, that the considered method avoids the spatial non-uniformity issues of standard loosely coupled schemes and that it delivers practically the same accuracy as the fully implicit scheme.

In [35], we consider a fully discrete loosely coupled scheme for incompressible fluid-structure interaction based on the time semi-discrete splitting method introduced in [54]. The splittling method uses a Robin-Robin type coupling that allows for a segregated solution of the solid and the fluid systems, without

inner iterations. For the discretisation in space we consider piecewise affine continuous finite elements for all the fields and ensure the inf-sup condition by using a Brezzi-Pitkäranta type pressure stabilization. The interfacial fluid-stresses are evaluated in a variationally consistent fashion, that is shown to admit an equivalent Lagrange multiplier formulation. We prove that the method is unconditionally stable and robust with respect to the amount of added-mass in the system. Furthermore, we provide an error estimate that shows the error in the natural energy norm for the system is $\mathcal{O}(\sqrt{T(\Delta t + h)})$ where T is the final time, Δt the time-step length and h the space discretization parameter.

The numerical approximation of incompressible fluid-structure interaction problems with Lagrange mul-tiplier is generally based on strongly coupled schemes. This delivers unconditional stability but at the expense of solving a computationally demanding coupled system at each time-step. For the case of the coupling with immersed thin-walled solids, in [31] we introduce a class of semi-implicit coupling schemes which avoids strongly coupling without compromising stability and accuracy. A priori energy and error estimates are derived. The theoretical results are illustrated through numerical experiments in an academic benchmark.

7.5 Statistical learning and mathematical modeling interactions

Participants Damiano Lombardi, Olga Mula, Fabien Raphel.

In [30] the aim is to develop training algorithms that deliver local minima of better quality than the ones obtained with usual training approaches such as stochastic gradient descent. We also attempt to bring new quantitative results on the generalization properties of the constructed networks. For this, we have adopted a recent point of view which connects deep learning with optimal control as a way to define a notion of a continuous underlying learning problem. In this view, neural networks can be interpreted as a discretization of a parametric ordinary differential equation which, in the limit, defines a continuous-depth neural network. The learning task then consists in finding the best ODE parameters for the problem under consideration, and their number increases with the accuracy of the time discretization. Although important steps have been taken to realize the advantages of such continuous formulations, most current learning techniques fix a discretization, which implies that the number of layers is fixed. In this work, we introduce an iterative adaptive algorithm where we progressively refine the time discretization. This, in turn, means that we increase the number of layers and the depth of the network across the iterations. Provided that certain tolerances are met across the iterations, we have proved that the strategy converges to the underlying continuous problem. One salient advantage of such a shallow-to-deep approach is that it helps to benefit in practice from the high approximation properties of deep networks by mitigating over-parametrization issues in the training.

7.6 Tensor approximation and HPC

Participants Damiano Lombardi.

In [40] we develop a method to compress a given tensor into a Canonical Polyadic format. This is known to be in general an ill-posed problem. By suitably modifying the TT-SVD method (used in general to construct a Tensor Train format approximation) we propose a method which can produce a stable CP approximation. The tests show that the proposed approach has encouraging performances, especially in high-dimensional settings, when compared to other methods proposed in the literature, such as ALS or ASVD.

7.7 Miscellaneous

Participants Damiano Lombardi, Olga Mula.

In [23] we propose a reduced-order method for the fast reconstruction of facial muscles from CT-scan images. In this short note we investigate how the information available in the form of points lying on the muscle surface could be exploited in order to obtain a full 3D reconstruction of the muscle.

In [25] we propose a simplified fluid-structure interaction model for arterioles in order to provide a mechanical insight of experimental observations and validate an hypothesis on the biological processes leading to micro-haemorrhages. The simulations performed confirmed the medical doctor hypothesis on the most critical configurations leading to micro-haemorrhages in the nervous system micro-circulation.

In [11] we develop a general forecasting method to predict series of hospitalized and dead people using a model reduction method involving SIR compartmental models. The obtained results seem satisfactory not only to us: eminent French epidemiologists, physicians and virologists with whom we have discussed, recognise that our approach has predictive qualities worthy of interest. They have invited us to deploy our approach by making it available as a platform for predicting the evolution of the disease. Also, as a further step, we are currently starting to enlarge the methodology in order to include interregional population mobillity and information on the viral level concentration which can be extracted from the analysis of wasted waters.

The paper [15] is a contribution on state estimation problems using reduced model algorithms. Here we study the notion of optimality of state estimation algorithms: we define a certain criterion to describe the reconstruction quality and we study what is the optimal reconstruction algorithm that provides it. In general, this optimal algorithm cannot be computed in practice. However, we show that if we restrict ourselves to lineal algorithms, the optimal linear algorithm is computable and we provide a numerical illustration of it.

In [24], we have made a contribution to the topic of domain decomposition of the time domain. We consider the parareal algorithm which is a predictor-corrector algorithm involving propagations in parallel of an accurate fine solver (which is computationally expensive), and a coarse solver. This algorithm is very popular due to its simplicity of implementation but it suffers from poor parallel efficiency (which is unfortunately a common burden in time parallel algorithms). The main obstacle for better efficiency in parareal is the cost of its fine solver so, in order to improve it, we have developed an adaptive parareal strategy in which the accuracy of the fine solver is increased across the iterations. We prove for an idealized setting that the algorithm would provide full parallel efficiency. In practice, although we show that the fine solver is better handled across iterations with our strategy, the cost of the coarse solver starts to enter into the picture, and this prevented us from obtaining full efficiency. Despite this, our results improved by about a factor 2 the efficiency of the traditional algorithm.

In [16] we develop a fully adaptive strategy to solve the radiative transfer equation, which is a lineal Boltzmann equation. The main importance of the approach is that it comes with certified a posteriori error bounds. For this, we formulate a fixed-point iteration in a suitable, infinite dimensional function space that is guaranteed to converge with a fixed error reduction per step. The numerical scheme is then based on approximately realizing this outer iteration within dynamically updated accuracy tolerances that still ensure convergence to the exact solution. To guarantee that these error tolerances are met, we employ rigorous a posteriori error bounds based on a Discontinuous Petrov–Galerkin (DPG) scheme. These a posteriori bounds are also used to generate adapted angular dependent spatial meshes to signifiicantly reduce overall computational complexity. The scheme also requires the evaluation of the global scattering operator at increasing accuracy at every iteration and its computation is accelerated through low-rank approximation and matrix compression techniques. We illustrate the theoretical findings with numerical experiments involving non-trivial scattering kernels.

In [39] we develop a piecewise affine strategy to build a state estimation algorithm for which we prove that we can asymptotically provide the optimal reconstruction performance.

8 Bilateral contracts and grants with industry

8.1 Bilateral contracts with industry

Notocord Systems

Participants Damiano Lombardi *(coordinator)*, 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.

Casis

Participants Mocia Agbalessi, Miguel Ángel Fernández Varela *(coordinator)*, 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 International initiatives

9.1.1 Inria associate team not involved in an IIL

IMFIBIO: Innovative Methods for Forward and Inverse problems in BIO-medical applications

Participants Muriel Boulakia *(coordinator)*, Daniele Corti, Miguel Ángel Fernández Varela, Fannie Gerosa, Céline Grandmont.

Duration: 2020-2022

Coordinator: Muriel Boulakia

Partner: Department of Mathematics, University College London (UK)

Summary: The purpose of the IMFIBIO Associate Team is to exploit the complementary expertise of both partners in mathematical analysis, numerical analysis, scientific computing and data assimilation in order to develop innovative methods for the study of forward and inverse problems in the context of bio-medical applications.

Web site: https://team.inria.fr/imfibio/

9.1.2 Visits to international teams

Research stays abroad

- Fannie Gerosa
  - One week visit at the Mathematics Department of UCL, February 2020
- Céline Grandmont
  - Member of the research group "Analyse et équations aux dérivées partielles" at ULB Belgium

9.2 European initiatives

9.2.1 FP7 & H2020 Projects

INSPIRE: INnovation in Safety Pharmacology for Integrated cardiovascular safety assessment to REduce adverse events and late stage drug attrition

Participants Muriel Boulakia, Sara Costa Faya, Miguel Ángel Fernández Varela, Céline Grandmont, Haibo Liu, Damiano Lombardi *(local coordinator)*.

Funding: Horizon 2020 - MSCA-ITN

Duration: 2020-2023

Coordinator: University of Antwerp

Local coordinator: Damiano Lombardi

Partners: see the link

Summary: INSPIRE is an European Training Network (ETN) projet funding 15 Early Stage Researchers (ESRs) aimed to exploit innovative techniques for better assessment and prediction of cardiovascular safety liabilities.

Web site: https://www.uantwerpen.be/en/projects/inspire-safety-pharmacology/

9.3 National initiatives

9.3.1 ANR

ADAPT: Adaptive Dynamical Approximations by Parallel Tensor methods

Participants Maria Fuente-Ruiz, Damiano Lombardi *(coordinator)*, Olga Mula
.

Funding: ANR JCJC

Duration: 2018-2022

Coordinator: Damiano Lombardi

Summary: 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.

Web site: https://project.inria.fr/adapt/

SIMR: Simulation and Imaging for Mitral Regurgitation

Participants Daniele Carlo Corti, Miguel Ángel Fernández Varela *(coordinator)*, Fannie Gerosa, Céline Grandmont, Marina Vidrascu.

Funding: ANR PRC

Duration: 2020-2023

Coordinator: Miguel Ángel Fernández Varela

Partners: CREATIS, HCL, LGEF, M3DISIM, TIMC

Summary: The SIMR project aims at evaluating the physical consequences of mitral repair using efficient numerical simulations, advanced imaging techniques and an innovative measurement tools in a clinical study.

Web site: https://project.inria.fr/simr/

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

- Damiano Lombardi
  - Co-organizer of the CEMRACS 2021 summer school.
  - Co-organizer of Inria-LJLL meeting in scientific computing
- Olga Mula
  - Co-organizer of the CEMRACS 2021 summer school.
  - Mini-symposium co-organizer (with B. Després, M. Campos- Pinto and O. Laffite.) Numerical Aspects of Transport, Boltzmann and Kinetic Equations,WCCM-ECCOMAS 2020 conference, Paris

10.1.2 Journal

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
- Olga Mula
  - Member of the editorial board of Calcolo

10.1.3 Scientific expertise

- Olga Mula
  - Member of "Facing the virus", a scientific initiative on Covid-19 launched by researchers from PSL Univ.
  - Member of the "Liaison Committee of SIGMA", the activity group on Signal-Image-Geometry-Modelling-Approximation.

10.1.4 Research administration

- Miguel Ángel Fernández Varela
  - Head of Science, Inria Paris
  - 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
- Damiano Lombardi
  - Member of LJLL Conseil du Laboratoire

10.1.5 Conferences

- Muriel Boulakia
  - Seminar, Workshop on Collective behavior of particles in fluids , December 2020, IHP Paris
  - Seminar MEDISIM-POEMS-DEFI, June 2020, Inria Saclay
- Daniele Corti
  - Contributed talk, WCCM-ECCOMAS 2020 conference, Paris
- Miguel Ángel Fernández Varela
  - Contributed talk, WCCM-ECCOMAS 2020 conference, Paris
  -
- Fannie Gerosa
  - Contributed talk, WCCM-ECCOMAS 2020 conference, Paris
- Céline Grandmont
  - Invited Speaker, Mathematics of Complex Systems in Biology and Medicin conference, Feb 2020, Cirm Marseille
- Damiano Lombardi
  - Seminar, Eindhoven Univ of Technology, September 2020
- Olga Mula
  - Seminar Rencontres INRIA-LJLL, December 2020
  - Seminar of the Jean-Leray Institute, November 2020
  - Seminar of the MaNu activity group, June 2020
  - Seminar MEDISIM-POEMS-DEFI (Inria Saclay), June 2020
  - Working Group at Dauphine on COVID-19, June 2020
  - Seminar ANEDP at Univ de Lille, March 2020
  - Journée des 50 ans du CEREMADE (Univ Paris-Dauphine), January 2020
- Fabien Raphel
  - Math-bio GDT Marseille
- Marina Vidrascu
  - Contributed talk at WCCM-ECCOMAS 2020 conference, Paris

10.2 Teaching - Supervision - Juries

10.2.1 Teaching

- Licence:
  - Muriel Boulakia
    - Projects on differential equations, 12h, L3, Polytech Sorbonne, Sorbonne Univ
    - Nonlinear systems and optimization, 36h, L3, Polytech Sorbonne, Sorbonne Univ
    - Mathematics for scientific studies, 50h, L1, Sorbonne Univ
  - Felipe Galarce Marin
    - TD Numerical methods for differential equations, 24h, L3, Sorbonne Univ
  - Fannie Gerosa
    - TD Numerical methods for differential equations, 26h, L3, Sorbonne Univ
  - Damiano Lombardi
    - PGD methods , 3 h, ENPC.
    - TP, Numerical Analysis, L3, 24h, Sorbonne Univ
  - Fabien Raphel
    - TP Numerical Analysis in Python 12h, L3, Sorbonne Univ
- Master:
  - Muriel Boulakia
    - Tutorials on Basis of Functional Analysis (distance learning), 30h, M1, Sorbonne Univ
    - Preparatory course for teaching admission examination “Agrégation”, 60h, M2, Sorbonne Univ
  - Miguel Ángel Fernández Varela
    - Modeling and numerical methods for hemodynamics, 30h, M2, Sorbonne Univ
  - Damiano Lombardi
    - Mini-course Modeling the electrophysiology of heart, 4.5h, M2, Ecole des Mines Paristech
    - TD, Numerical Methods, M1, 15 h, Sorbonne Univ

10.2.2 Supervision

- 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: Marguerite Champion, Modeling and numerical simulation of implantable aortic blood pumps. Since November 2020. Supervisors: M.A. Fernández Varela, C. Grandmont & M. Vidrascu
- PhD in progress: Daniele Corti, Modeling and numerical simulation of the mitral apparatus. Since October 2020. Supervisors: M.A. Fernández Varela, F. Alauzet and G. Delay & M. Vidrascu
- PhD in progress: Sara Costa Faya, An in silico approach to monitor and predict haemodynamics during safety pharmacology studies., since September 2020. M.A. Fernández Varela, C. Grandmont & D.Lombardi
- PhD in progress: Maria Fuente Ruiz , Adaptive tensor methods for scientific computing. Since March 2020. Supervisors: D. Lombardi & V. Ehrlacher
- 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 Lespagnol, A new computational approach for fluid-structure interaction of slender bodies immersed in three-dimen- sional flow. Since September 2020. Supervisors: M. Boulakia, M.A. Fernández Varela, C. Grandmont & Paolo Zunino (MOX, Politechnico de Milano)
- PhD in progress: Haibo Liu, Data assimilation for high-throughput screening in safety pharmacology. Since September 2020. Supervisors: D. Lombardi & M. Boulakia
- 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

- Muriel Boulakia
  - PHD committee: Nicolas Molina, Univ Paris-Dauphine (reviewer), Imene Djebour, IECL Nancy
- Miguel Ángel Fernández Varela
  - Hiring committees: Inria CRCN Paris and CRCN National
  - PHD committee: Daniel Grinberg MD, INSA Lyon (reviewer)
- Céline Grandmont
  - Hiring committee Assistant Professor Univ Orléans
  - Hiring committees: Inria CRCN Lille, Inria DR2
  - PHD committee: Nicola Molinas, Univ Dauphine
  - Blaise Pascal SMAI Prize
- Damiano Lombardi
  - PHD committee: Roman Weinhadl, Otto von Guericke Univ and Max Planck Magdebourg (reviewer) and Sebastien Riffaud, Univ. Bordeaux
- Olga Mula
  - Hiring committee Assistant Professor UTC Compiègne, Univ Stasbourg
  - PHD committee: Antonio Galia, Univ Paris-Saclay

10.3 Popularization

10.3.1 Interventions

- Céline Grandmont
  - Conference Filles et Maths, Villetaneuse, February 2020

11 Scientific production

11.1 Major publications

[1] L. Boilevin-Kayl, M. A. Fernández and 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* 41.2 (Feb. 2019), pp. 351–374. DOI: 10.1137/18M1192779. URL: https://hal.inria.fr/hal-01811290.

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[3] M. Boulakia, S. Guerrero and T. Takahashi. 'Well-posedness for the coupling between a viscous incompressible fluid and an elastic structure'. In: *Nonlinearity* 32 (2019), pp. 3548–3592. DOI: 10.1088/1361-6544/ab128c. URL: https://hal.inria.fr/hal-01939464.

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[7] N. Pozin, S. Montesantos, I. Katz, M. Pichelin, I. Vignon-Clementel and C. Grandmont. 'Predicted airway obstruction distribution based on dynamical lung ventilation data: a coupled modeling-machine learning methodology'. In: *International Journal for Numerical Methods in Biomedical Engineering* 34.9 (May 2018). DOI: 10.1002/cnm.3108. URL: https://hal.archives-ouvertes.fr/hal-01568065.

[8] A. This, L. Boilevin-Kayl, M. A. Fernández and 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). DOI: 10.1002/cnm.3223. URL: https://hal.inria.fr/hal-01944798.

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11.2 Publications of the year

International journals

[10] A. Alfonsi, R. Coyaud, V. Ehrlacher and D. Lombardi. 'Approximation of Optimal Transport problems with marginal moments constraints'. In: *Mathematics of Computation* (2020). DOI: 10.1090/mcom/3568. URL: https://hal.archives-ouvertes.fr/hal-02128374.

[11] A. Bakhta, T. Boiveau, Y. Maday and O. Mula. 'Epidemiological Forecasting with Model Reduction of Compartmental Models. Application to the COVID-19 Pandemic'. In: *Biology* 10.1 (31st Dec. 2020), p. 22. DOI: 10.3390/biology10010022. URL: https://hal.sorbonne-universite.fr/hal-03117258.

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Doctoral dissertations and habilitation theses

[29] D. Lombardi. 'Contributions to scientific computing for data-simulation interaction in biomedical applications'. Sorbonne Université, 1st July 2020. URL: https://hal.inria.fr/tel-03114756.

Reports & preprints

[30] J. Aghili and O. Mula. *Depth-Adaptive Neural Networks from the Optimal Control viewpoint*. 12th July 2020. URL: https://hal.archives-ouvertes.fr/hal-02897466.

[31] M. Annese, M. A. Fernández and L. Gastaldi. *Splitting schemes for a Lagrange multiplier formulation of FSI with immersed thin-walled structure: stability and convergence analysis*. 8th July 2020. URL: https://hal.archives-ouvertes.fr/hal-02893508.

[32] J. Atif, B. Cabot, O. Cappé, O. Mula and R. Pinot. *Initiative face au virus. Regards croisés sur l'épidemie de Covid-19 apportés par les données sanitaires et de géolocalisation (mars à octobre 2020)*. Université PSL; Inria; CNRS, 21st Dec. 2020. URL: https://hal.archives-ouvertes.fr/hal-03084832.

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[34] L. Brotcorne, A. Canteaut, A. C. Viana, C. Grandmont, B. Guedj, S. Huot, V. Issarny, G. Pallez, V. Perrier, V. Quema, J.-B. Pomet, X. Rival, S. Salvati and E. Thomé. *Indicateurs de suivi de l'activité scientifique de l'Inria*. Inria, 1st Dec. 2020. URL: https://hal.inria.fr/hal-03033764.

[35] E. Burman, R. Durst, M. A. Fernández and J. Gunzmán. *Fully discrete loosely coupled Robin-Robin scheme for incompressible fluid-structure interaction: stability and error analysis*. 8th July 2020. URL: https://hal.archives-ouvertes.fr/hal-02893444.

[36] E. Burman, M. A. Fernández and F. Gerosa. *Error analysis of an unfitted mesh semi-implicit coupling scheme for fluid-structure interaction*. 15th Dec. 2020. URL: https://hal.inria.fr/hal-03065803.

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[41] C. Grandmont and F. Vergnet. *Existence and uniqueness for a quasi-static interaction problem between a viscous fluid and an active structure*. 27th Feb. 2020. URL: https://hal.archives-ouvertes.fr/hal-02493384.

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