RESEARCH CENTRE

Inria Paris Center at Sorbonne University

IN PARTNERSHIP WITH:

CNRS, Sorbonne Université

2022

ACTIVITY REPORT

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

Inria

Contents

Project-Team COMMEDIA

Creation of the Project-Team: 2019 June 01

Keywords

Computer sciences and digital sciences

A6.1.1. – Continuous Modeling (PDE, ODE)

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A6.1.5. – Multiphysics modeling

A6.2.1. – Numerical analysis of PDE and ODE

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A6.3.2. – Data assimilation

A6.3.4. – Model reduction

Other research topics and application domains

B2.2.1. – Cardiovascular and respiratory diseases

B2.4.1. – Pharmaco kinetics and dynamics

1 Team members, visitors, external collaborators

Research Scientists

- Miguel Angel Fernández Varela [Team leader, INRIA, Senior Researcher, HDR]
- Céline Grandmont [INRIA, Senior Researcher, HDR]
- Adrien Lefieux [INRIA, Advanced Research Position, from Oct 2022]
- Damiano Lombardi [INRIA, Researcher, HDR]
- Marina Vidrascu [INRIA, Emeritus, HDR]

Faculty Member

- Fabien Vergnet [SORBONNE UNIVERSITE, Associate Professor]

Post-Doctoral Fellows

- Mihai-Simion Nechita [INRIA, until Feb 2022]
- Frédérique Noël [Inria, until Oct 2022]
- Sebastien Riffaud [INRIA]

PhD Students

- Mocia Agbalessi [CASIS and INRIA, CIFRE, until Nov 2022]
- Marguerite Champion [INRIA]
- Daniele Carlo Corti [INRIA]
- Sara Costa Faya [INRIA]
- Maria Fuente Ruiz [INRIA]
- Gael Le Ruz [SORBONNE UNIVERSITE, from Oct 2022]
- Fabien Lespagnol [Politecnico di Milano]
- Haibo Liu [NOTOCORD]
- Fabien Raphel [NOTOCORD, until Apr 2022]
- Oscar Ruz [ANID Chile]

Administrative Assistant

- Julien Guieu [INRIA]

External Collaborator

- Muriel Boulakia [Versailles Saint-Quentin-en-Yvelines University, HDR]

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., [57, 58, 55, 60, 48]), 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., [30, 43, 46]). 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 [32, 40, 63]), 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., [65]). 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 [59]). 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 [54]). 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 Safety pharmacology

One of the the most important problems in pharmacology is cardio-toxicity (see [53]). 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 [37]) 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 [52, 50]). 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 [42], 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 [34, 36]. 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 [62, 33, 49, 31]) are known to be inaccurate in space. These difficulties have been recently circumvented by a Nitsche-based cut-FEM methodolgy (see [28, 38]). 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., [47]). 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., [59, 61, 35]). 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 [29]) 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 [56]). 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 [51]). 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 [64]). 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., [60, 41]). 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., [39]). 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 [53]). 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 [45]). 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 [44]).

5 Highlights of the year

Hiring of Frédérique Noël as CNRS Junior researcher, LJLL.

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 open source, 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/

Contact: Miguel Angel Fernandez Varela

Participants: Daniele Carlo Corti, Miguel Angel Fernandez Varela, Marina Vidrascu, Sara Costa Faya, Mocia Agbalessi, Mihai-Simion Nechita, Oscar Ruz, Fabien Lespagnol, Vicente Mataix Ferrandiz

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.

Contact: Miguel Angel Fernandez Varela

Participants: Miguel Angel Fernandez Varela, Marina Vidrascu, Daniele Carlo Corti, Mocia Agbalessi, Sara Costa Faya, Vicente Mataix Ferrandiz, Mocia Agbalessi

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

Contact: Damiano Lombardi

Participants: Fabien Raphel, Damiano Lombardi

6.1.4 ADAPT

Name: Adaptive Dynamical Approximation via Parallel Tensor methods

Keywords: Scientific computing, Tensor decomposition, Partial differential equation

Functional Description: ADAPT is a library containing methods for scientific computing based on tensors. In many fields of science and engineering we need to approximate the solution of high-dimensional problems. In this library we propose a collection of methods to parsimoniously discretise high-dimensional problems. These methods are mainly based on tensors.

Contact: Damiano Lombardi

Participants: Virginie Ehrlacher, Maria Fuente Ruiz, Damiano Lombardi, Sebastien Riffaud

7 New results

7.1 Respiratory flows

Participants: Céline Grandmont, Frédèrique Noël.

In [24] we propose an integrated dynamical model for oxygen and carbon dioxide transfer from the lung into the blood, coupled with a lumped mechanical model for the ventilation process, for healthy patients as well as in pathological cases. In particular, we focus on the Bohr and Haldane effects, which induce a nonlinear coupling between the oxygen and the carbon dioxide. We also take into account the dead space volume, which requires a special attention in the pathological cases.

In [26], we develop a mathematical model of infection, inflammation and immune response in an idealized bronchial tree that can predict how the air flows and oxygen exchanges reorganize in the tree during an infection. We highlight the links between the localization of the infection and the amplitude of the loss of oxygen flow to blood and that a compensation phenomena due to the reorganization of the flow exists.

7.2 Mathematical analysis of PDEs

Participants: Céline Grandmont.

In [10], we analyze the linearized version of a poromechanics model developed to simulate soft tissues perfusion. This is a fully unsteady model in which the fluid and solid equations are strongly coupled through the interstitial pressure. As such, it generalizes Darcy, Brinkman and Biot equations of poroelasticity. The mathematical and numerical analysis of this model was initially performed for a compressible porous material. Here, we focus on the nearly incompressible case with a semigroup approach, which also allows us to prove the existence of weak solutions. We show the existence and uniqueness of strong and weak solutions in the incompressible limit case, for which a divergence constraint on the mixture velocity appears. Due to the special form of the coupling, the underlying problem is not coercive. Nevertheless, by using the notion of T-coercivity, we obtain stability estimates and well-posedness results. Our study also provides guidelines to propose stable and robust approximations of the problem with mixed finite elements. In particular, we recover an inf-sup condition that is independent of the porosity. Finally, we numerically investigate the elliptic regularity of the associated steady-state problem and illustrate the sensitivity of the solution with respect to the different model parameters.

7.3 Numerical methods for multi-physics problems

Participants: Daniele Corti, Miguel Ángel Fernández Varela.

In [25] we propose an extension of the unfitted Nitsche-XFEM method of [*Comput. Methods Appl. Mech. Engrg., 301, 300-335, 2016*] to three-dimensional fluid-structure interaction problems with immersed thin-walled elastic solids. The fluid and solid domains are discretized with unfitted unstructured meshes. Discrete weak and strong discontinuities are allowed in the fluid and the coupling is enforced consistently via a fluid-sided Nitsche's type mortaring with suitable stabilization for robustness. Integration over cut-elements is handled via an efficient and robust intersection and subtesselation algorithm. The method includes a new approach for the treatment of partially intersected fluid domains. Several numerical examples are presented and discussed, which illustrate the capabilities of the proposed method.

7.4 Statistical learning and mathematical modeling interactions

Participants: Muriel Boulakia, Sara Costa Faya, Damiano Lombardi, Haibo Liu
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In [21] we propose a comparison between mathematical modelling, statistical and machine learning methods to estimate some quantities of interest arising in *in vivo* haemodynamics monitoring for safety pharmacology experiments. Several tests are proposed to compare, in terms of accuracy and computational cost, different methods, applied to telemetry data.

In [17] we propose a comparison between several Neural Network methods applied to a classification problem arising in electro-physiology. Several tests on a realistic experimental dataset are shown.

In [23], we have seen that Deep learning-based numerical schemes such as Physically Informed Neural Networks (PINNs) are a suitable alternative to classical numerical schemes for solving convection-diffusionPartial Differential Equations (PDEs).

7.5 Tensor approximation and HPC

Participants: Miguel Angel Fernandez Varela, Damiano Lombardi, Maria Fuente Ruiz.

In [27] we propose a numerical method to perform, at once, the numerical simulation of a system of linear parametric time dependent PDEs and parameter estimation given partial noisy observations of it. The method consists in introducing a separated discretisation (space-parameters) and using a low-rank solver (based on an adaptation of the TT-GMRES method). The discretisation of the parameter domain is not fixed in time, but it evolves in a sequential way, as we receive the observations. A Metropolis-Hastings algorithm is used for such a task, enabled by a reduced approximation built by exploiting the low-rank solution. The method has been tested on 2d and 3d test-cases, including linear fluid-structure interaction.

7.6 Miscellaneous

Participants: Damiano Lombardi.

In [22] we investigate the possibility of using the Wasserstein distance to build a reduced-order representation of parametric solutions of a non-linear porous medium model. The main idea consists in building modes which approximate, at best, a set of snapshots solutions in the Wasserstein sense. Several test-cases are proposed in order to assess the method.

In [19] we propose a review of the state of the art of reduced-order modelling applied to the context of the haemodynamics. In particular, we propose a classification of the contributions based on the methodology which is used.

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.

Withings

Participants: Miguel Ángel Fernández Varela *(coordinator)*, Adrien Lefieux, Damiano Lombardi, Marina Vidrascu, Fabien Vergent.

This research project has the objective of developing mathematical models of photoplethysmography (PPG) measurements in the wrist and their connection to blood pressure estimation.

9 Partnerships and cooperations

9.1 International initiatives

9.1.1 Associate Teams in the framework of an Inria International Lab or in the framework of an Inria International Program

IMFIBIO

Participants: Mocia Agbalessi, Muriel Boulakia, Marguerite Champion, Daniele Corti, Miguel Ángel Fernández Varela *(coordinator)*, Céline Grandmont, Fabien Vergnet, Marina Vidrascu.

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

Duration: 2022-2025

Coordinator: Miguel Angel Fernandez Varela

Partner:

- University College London London (Royaume-Uni)

UCL contact: Erik Burman

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: team.inria.fr/imfibio

9.2 European initiatives

9.2.1 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 *(coordinator)*
.

Funding: Horizon 2020 - MSCA-ITN

Duration: 2020-2024

Coordinator: University of Antwerp

Local coordinator: Damiano Lombardi

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: 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)*, Sébastien Riffaud
.

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: project.inria.fr/adapt

SIMR: Simulation and Imaging for Mitral Regurgitation

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

Funding: ANR PRC

Duration: 2020-2024

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: project.inria.fr/simr

10 Dissemination

10.1 Promoting scientific activities

10.1.1 Scientific events: organisation

- Miguel Ángel Fernández Varela

  - Co-organizer of the Conference to honor the memory of Roland Glowinski, July 2022, Paris, France

- Céline Grandmont

  - Member of the organizing commitee of a Workshop on fluid-structure interaction, oct. 2022, Bruxelles
  - Member of the organizing commitee of the "Journées Math Bio Santé 2022", oct. 2022, Besaçon.

- Damiano Lombardi

  - Co-organiser of the scientific computing seminar, joint event between Inria and Laboratoire Jacques-Louis Lions.

- Marina Vidrascu

  - Co-organizer of the Conference to honor the memory of Roland Glowinski, July 2022, Paris, France

10.1.2 Journal

Member of the editorial boards

- Céline Grandmont

  - Editorial board of Mathematical Modelling of Natural Phenomena
  - Editorial board of Journal of Mathematical Fluid Mechanics
  - Editorial board of M2AN

10.1.3 Research administration

- Miguel Fernández Varela

  - Head of Science,Inria Paris
  - Member of the Inria Evaluation Committee

- Céline Grandmont

  - Member of the Inria Evaluation Commitee
  - Member of the Inria Parity
  - Member of the scientific commitee of the doctoral school EDMH, Paris-Saclay.
  - Member of the scientific commitee of GDR MathSAv: Mathématiques, Santé, Sciences de la Vie. Commitee

- Damiano lombardi

  - Co-president of CES (Commission Emploi Scientifique), INRIA.

10.2 Conferences

- Daniele Corti
  - Contributed talk in minisymposium, Eccomas Congress, June 2022, Oslo, Norway
- Sara Costa Faya
  - Presentation INSPIRE 2022 summer school and ITN-INSPIRE annual meeting,20-24 June
- Miguel Ángel Fernández Varela
  - Invited speaker, Workshop on Mathematical Theory of Coupling Methods for Partial Differential Equations, November 2022, Online
  - Invited speaker, Workshop on numerical methods for fluid, structure and inter- actions problems, November 2022, Toulouse, France
  - Invited talk in MS, WCB conference, July 2022, Tapiei, Taiwan, Online
  - MS keynote speaker, ECCOMAS conference, June 2022, Oslo, Norway
- Haibo Liu
  - Contributed talk in minisymposium, Eccomas Congress, 6-9 june Oslo, Norway
  - Presentation INSPIRE 2022 summer school and ITN-INSPIRE annual meeting,20-24 June
- Damiano Lombardi
  - Workshop speaker, Reduced-order models at work: industry and medicine, Tensor methods for high-dimensional problems and model reduction, Bordeaux, march 2022.
  - Mini-symposium speaker, Fluid-structure interaction calibration from 4d-flow MRI, ECCOMAS 2022, Oslo, june 2022.
  - Mini-symposium speaker, Low-rank solvers for the Vlasov-Poisson equation, SCICADE 2022, Reykjavik, july 2022.
  - Workshop speaker, Learning and Modelling in electro-physiology, Gdr mecabio, Paris, 12/2022
  - Seminar Aachen University, 12/2022, *Adaptive tensor methods for scientific computing.*
- Frédèrique Noel
  - Seminar, Complex System in Social Sciences (EHESS, Paris), February 2022
  - Poster Session, ERS International Congress, September 2022
  - Invited talk, Journées Maths Bio Santé, October 2022
  - Seminar, Rencontres Inria LJLL, October 2022
- Sébastien Riffaud
  - Contributed talk in minisymposium, 7th International Conference on Computational and Mathematical Biomedical Engineering, June 2022, Milano, Italy.
- Fabien Vergnet
  - Seminar of the Applied Analysis group, University of Graz, May 2022.
- Marina Vidrascu
  - Invited talk in MS, 28th Nordic Congress of Mathematicians, August 2022, Aalto University, Finland

10.3 Teaching - Supervision - Juries

10.3.1 Teaching

- Licence:
  - Marguerite Champion
    - Numerical analysis, 24h, L3, Sorbonne University
    - Mathematics for scientific study, 24h, L1, Sorbonne University
  - Fabien Vergnet
    - Numerical analysis and ODE, 58h, L3, Polytech Sorbonne, Sorbonne Université.
    - Nonlinear systems and optimization, 30h, L3, Polytech Sorbonne, Sorbonne Université.
    - Fourier analysis, 39h, L3, Polytech Sorbonne, Sorbonne Université.
    - Dynamical systems, 12h, L3, Polytech Sorbonne, Sorbonne Université.
    - Differential equations, 18h, L2, Polytech Sorbonne, Sorbonne Université.
- Master:
  - Miguel Ángel Fernández Varela
    - Modeling and simulation in life sciences, 20h, M2, Sorbonne Université
  - Damiano Lombardi
    - Lectures, Numerical Methods for PDEs, M2, 21 hours, Sorbonne Université.
    - TP, Numerical Methods, M1, 24 hours, Sorbonne Université.
    - Lecture, 1.5 hours, Modeling the electro-physiology of heart, 11/2022 Ecole des Mines Paristech.
    - Student projects supervision.
      1. Co-supervision of TER (supervised research project) on statistical learning/mathematical modelling interaction, 2.5 months, M1 student.
      2. Co-supervised internship on mathematical modelling in electro-physiology, 2 months, M1 student.

10.3.2 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: Mathieu Barré, Mathematical and numerical study of a poroelastic model.Supevisors: C. Grandmont & P. Moireau (M3DISIM, Inria Saclay)
- PhD in progress: Marguerite Champion, Modeling, analysis and simulation of fluid-structure-contact interaction. Supervisors: M.A. Fernández Varela, C. Grandmont, F. Vergnet & M. Vidrascu
- PhD in progress: Daniele Corti, Modeling and numerical simulation of the mitral apparatus.Since October 2020. Supervisors: M.A. Fernández Varela, G. Delay , F. Vergnet & M. Vidrascu
- PhD in progress: Sara Costa Faya, An in silico approach to monitor and predict haemodynamics during safety pharmacology studies. Since September 2020. Supervisors: M.A. Fernández Varela, C. Grandmont & D.Lombardi
- PhD in progress: Maria Fuente Ruiz, Adaptive tensor methods for scientific computing.Supervisors: D. Lombardi & V. Ehrlacher
- PhD in progress: Fabien Lespagnol, A new computational approach for fluid-structure interaction of slender bodies immersed in three-dimensional 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-throughputs creening in safety pharmacology. Since September 2020. Supervisors: D. Lombardi & M. Boulakia
- PhD in progress: Gaël le Ruz, Observer theory in general constrained spaces – from formulations to applications. Since September 2020. Supervisors: D. Lombardi & P. Moireau
- PostDoc in progress: Sebastien Riffaud.Tensor methods for parametric fluid-structure interaction and data assimilation. Supervisors: D. Lombardi & M.A. Fern ‘’andez Varela
- PostDoc : Fréderique Nöel, Modelling of ventilation and gaz diffusion in the contect of Covid disease. Supervisors: C. Grandmont

10.3.3 Juries

- Miguel Ángel Fernández Varela
  - Hiring committees: Inria Saclay and Inria DR2 (pre-selection)
  - PHD committee: Nadine Dirani, Université Côte d’Azur
- Céline Grandmont
  - Member of the PhD thesis prize SMAI-Gamni 2022
  - Member of the scientific commitee of the doctoral school EDMH, Paris-Saclay
  - Member of the scientific commitee of GDR MathSAv : Mathématiques, Santé, Sciences de la Vie.
  - Hiring committees: Inria Lille, Lille University and Inria DR2.
- Damiano Lombardi
  - Hiring committee: MdC Sorbonne Université

10.4 Popularization

- Céline Grandmont
  - Invited lecturer Journées mathématiques X-UPS, 2h lecture for teachers of "classe préparatoire"
- Frédèrique Nöel
  - Rencontres Jeunes Mathématiciennes et Informaticiennes, Inria Paris, October 2022

11 Scientific production

11.1 Major publications

[1] M. Barré, C. Grandmont and P. Moireau. ‘Analysis of a linearized poromechanics model for incompressible and nearly incompressible materials’. In: *Evolution Equations and Control Theory* (2022). URL: https://hal.inria.fr/hal-03501526.

[2] E. Burman, R. Durst, M. A. Fernández and J. Guzmán. ‘Fully discrete loosely coupled Robin-Robin scheme for incompressible fluid-structure interaction: stability and error analysis’. In: *Numerische Mathematik* (5th July 2022). DOI: 10.1007/s00211-022-01295-y. URL: https://hal.science/hal-02893444.

[3] V. Ehrlacher, M. Fuente-Ruiz and D. Lombardi. ‘SoTT: greedy approximation of a tensor as a sum of Tensor Trains’. In: *SIAM Journal on Scientific Computing* (2021). URL: https://hal.inria.fr/hal-03018646.

[4] S. Frei, F. Gerosa, E. Burman and M. A. Fernández. 'A mechanically consistent model for fluid-structure interactions with contact including seepage'. In: *Computer Methods in Applied Mechanics and Engineering* (2022). DOI: 10.1016/j.cma.2022.114637. URL: https://hal.science/hal-03174087.

[5] C. Grandmont and F. Vergnet. 'Existence and uniqueness for a quasi-static interaction problem between a viscous fluid and an active structure'. In: *Journal of Mathematical Fluid Mechanics* 23.45 (27th Mar. 2021). DOI: 10.1007/s00021-020-00552-0. URL: https://hal.archives-ouvertes.fr/hal-02493384.

[6] D. Lombardi. 'State estimation in nonlinear parametric time dependent systems using Tensor Train'. In: *International Journal for Numerical Methods in Engineering* (2022). DOI: 10.1002/nme.7067. URL: https://hal.inria.fr/hal-03375811.

[7] D. Lombardi and F. Raphel. 'A method to enrich experimental datasets by means of numerical simulations in view of classification tasks'. In: *ESAIM: Mathematical Modelling and Numerical Analysis* 55.5 (Sept. 2021), pp. 2259–2291. DOI: 10.1051/m2an/2021060. URL: https://hal.science/hal-03377036.

[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* 36.3 (Feb. 2020), e3223. DOI: 10.1002/cnm.3223. URL: https://hal.inria.fr/hal-01944798.

11.2 Publications of the year

International journals

[9] 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'. In: *IMA Journal of Numerical Analysis* (17th Mar. 2022). DOI: 10.1093/imanum/drac004. URL: https://hal.archives-ouvertes.fr/hal-02893508.

[10] M. Barré, C. Grandmont and P. Moireau. 'Analysis of a linearized poromechanics model for incompressible and nearly incompressible materials'. In: *Evolution Equations and Control Theory* (2022). URL: https://hal.inria.fr/hal-03501526.

[11] E. Burman, R. Durst, M. A. Fernández and J. Guzmán. 'Fully discrete loosely coupled Robin-Robin scheme for incompressible fluid-structure interaction: stability and error analysis'. In: *Numerische Mathematik* (5th July 2022). DOI: 10.1007/s00211-022-01295-y. URL: https://hal.archives-ouvertes.fr/hal-02893444.

[12] E. Burman, R. Durst, M. A. Fernández and J. Guzmán. 'Loosely coupled, non-iterative time-splitting scheme based on Robin-Robin coupling: Unified analysis for Parabolic/Parabolic and Parabolic/Hyperbolic problems'. In: *Journal of Numerical Mathematics* (19th Oct. 2022). URL: https://hal.archives-ouvertes.fr/hal-03381765.

[13] E. Burman, M. A. Fernández and F. Gerosa. 'Convergence analysis of an unfitted mesh semi-implicit coupling scheme for incompressible fluid-structure interaction'. In: *Vietnam Journal of Mathematics* (13th July 2022). URL: https://hal.inria.fr/hal-03065803.

[14] C. Dupont, M. Vidrascu, P. Le Tallec, D. Barthès-Biesel and A.-V. Salsac. 'Modelling the fluid-structure interactions of a capsule using a nonlinear thin shell model: effect of wall thickness'. In: *Journal of Fluids and Structures* 113.103658 (2022). URL: https://hal.utc.fr/hal-03409766.

[15] V. Ehrlacher, M. Fuente-Ruiz and D. Lombardi. 'SoTT: greedy approximation of a tensor as a sum of Tensor Trains'. In: *SIAM Journal on Scientific Computing* 44.2 (21st Mar. 2022). DOI: 10.1137/20M1381472. URL: https://hal.inria.fr/hal-03018646.

[16] S. Frei, F. Gerosa, E. Burman and M. A. Fernández. 'A mechanically consistent model for fluid-structure interactions with contact including seepage'. In: *Computer Methods in Applied Mechanics and Engineering* (2022). DOI: 10.1016/j.cma.2022.114637. URL: https://hal.archives-ouvertes.fr/hal-03174087.

[17] H. Liu, T. de Korte, S. Bernasconi, C. Bleunven, D. Lombardi and M. Boulakia. 'Artificial Neural Network Comparison on hERG Channel Blockade Detection'. In: *International Journal of Computer Applications* (May 2022). URL: https://hal.inria.fr/hal-03934224.

[18] D. Lombardi. 'State estimation in nonlinear parametric time dependent systems using Tensor Train'. In: *International Journal for Numerical Methods in Engineering* (2022). DOI: 10.1002/nme.7067. URL: https://hal.inria.fr/hal-03375811.

Scientific book chapters

[19] D. Lombardi. 'Reduced order modelling for direct and inverse problems in haemodynamics'. In: *ROMs for the Biomechanics of Living Organs*. 2022. URL: https://hal.inria.fr/hal-03783921.

Reports & preprints

[20] M. Agbalessi, A. Lalande, O. Bouchot, T. Hayase, J.-J. Christophe, M. A. Fernández and D. Lombardi. *Tracking of blood vessels motion from 4D-flow MRI data*. 23rd Sept. 2022. URL: https://hal.inria.fr/hal-03349442.

[21] E. Ataei, S. C. Faya, H. Liu, D. Lombardi, S. Bernasconi, P.-J. Guns and M. Markert. *Comparison of statistical, machine learning, and mathematical modelling methods to investigate the effect of ageing on dog's cardiovascular system*. 2022. URL: https://hal.inria.fr/hal-03933957.

[22] B. Battisti, T. Blickhan, G. Enchery, V. Ehrlacher, D. Lombardi and O. Mula. *Wasserstein model reduction approach for parametrized flow problems in porous media*. 10th May 2022. URL: https://hal.inria.fr/hal-03664061.

[23] A. Beguinet, V. Ehrlacher, R. Flenghi, M. Fuente-Ruiz, O. Mula and A. Somacal. *Deep learning-based schemes for singularly perturbed convection-diffusion problems*. 10th May 2022. URL: https://hal.inria.fr/hal-03664049.

[24] L. Boudin, C. Grandmont, B. Grec and S. Martin. *A coupled model for the dynamics of gas exchanges in the human lung with Haldane and Bohr's effects*. 3rd Dec. 2022. URL: https://hal.science/hal-03883301.

[25] F. M. Gerosa, D. Corti, F. Alauzet and M. A. Fernández. *3D Nitsche-XFEM method for fluid-structure interaction with immersed thin-walled solids*. 30th Dec. 2022. URL: https://hal.inria.fr/hal-03916638.

[26] F. Noël and B. Mauroy. *Propagation of an idealized infection in an airway tree, consequences of the inflammation on the oxygen transfer to blood*. 6th Jan. 2023. URL: https://hal.science/hal-03669474.

[27] S. Riffaud, M. A. Fernández and D. Lombardi. *A low-rank solver for parameter estimation and uncertainty quantification in linear time dependent systems of Partial Differential Equations*. 20th Dec. 2022. URL: https://hal.inria.fr/hal-03908682.

11.3 Cited publications

[28] F. Alauzet, B. Fabrèges, M. A. Fernández and M. Landajuela. 'Nitsche-XFEM for the coupling of an incompressible fluid with immersed thin-walled structures'. In: *Comput. Methods Appl. Mech. Engrg.* 301 (2016), pp. 300–335.

[29] E. Alpaydin. *Introduction to machine learning*. MIT press, 2009.

[30] M. Astorino, J. Hamers, S. C. Shadden and J.-F. Gerbeau. 'A robust and efficient valve model based on resistive immersed surfaces'. In: *Int. J. Numer. Meth. Biomed. Engng.* 28.9 (2012), pp. 937–959.

[31] F. Baaijens. 'A fictitious domain/mortar element method for fluid-structure interaction'. In: *Int. Jour. Num. Meth. Fluids* 35 (2001), pp. 743–761.

[32] L. Baffico, C. Grandmont and B. Maury. 'Multiscale modeling of the respiratory tract'. In: *Math. Models Methods Appl. Sci.* 20.1 (2010), pp. 59–93.

[33] D. Boffi, N. Cavallini and L. Gastaldi. 'Finite element approach to immersed boundary method with different fluid and solid densities'. In: *Math. Models Methods Appl. Sci.* 21.12 (2011), pp. 2523–2550.

[34] L. Boudin, L. Desvillettes, C. Grandmont and A. Moussa. 'Global existence of solutions for the coupled Vlasov and Navier-Stokes equations'. In: *Differential Integral Equations* 22.11-12 (2009), pp. 1247–1271.

[35] L. Boudin, D. Götz and B. Grec. 'Diffusion models of multicomponent mixtures in the lung'. In: *CEMRACS 2009: Mathematical modelling in medicine*. Vol. 30. ESAIM Proc. EDP Sci., Les Ulis, 2010, pp. 90–103.

[36] L. Boudin, C. Grandmont and A. Moussa. 'Global existence of solutions to the incompressible Navier-Stokes-Vlasov equations in a time-dependent domain'. In: *J. Differential Equations* 262.3 (2017), pp. 1317–1340.

[37] L. Breiman. *Classification and regression trees*. Routledge, 2017.

[38] E. Burman and M. A. Fernández. 'An unfitted Nitsche method for incompressible fluid-structure interaction using overlapping meshes'. In: *Comput. Methods Appl. Mech. Engrg.* 279 (2014), pp. 497–514.

[39] R. K. Calay, J. Kurujareon and A. E. Holdo. 'Numerical simulation of respiratory flow patterns within human lung'. In: *Respir. Physiol. Neurobiol.* 130.2 (2002), pp. 201–221.

[40] P. Cazeaux and C. Grandmont. 'Homogenization of a multiscale viscoelastic model with nonlocal damping, application to the human lungs'. In: *Math. Models Methods Appl. Sci.* 25.6 (2015), pp. 1125–1177.

[41] K. B. Chandran. 'Role of Computational Simulations in Heart Valve Dynamics and Design of Valvular Prostheses'. In: *Cardiovasc. Eng. Technol.* 1.1 (2010), pp. 18–38.

[42] D. Chapelle and P. Moireau. 'General coupling of porous flows and hyperelastic formulations—From thermodynamics principles to energy balance and compatible time schemes'. In: *Eur. J. Mech. B Fluids*. 46 (2014), pp. 82–96.

[43] C. Chnafa, S. Mendez and F. Nicoud. 'Image-Based Simulations Show Important Flow Fluctuations in a Normal Left Ventricle: What Could be the Implications?' In: *Ann. Biomed. Eng.* 44.11 (2016), pp. 3346–3358.

[44] T. Colatsky, B. Fermini, G. Gintant, J. B. Pierson, P. Sager, Y. Sekino, D. G. Strauss and N. Stockbridge. 'The comprehensive in vitro proarrhythmia assay (CiPA) initiative—update on progress'. In: *J. Pharmacol. Toxicol. Methods* 81 (2016), pp. 15–20.

[45] W. J. Crumb, J. Vicente, L. Johannesen and D. G. Strauss. 'An evaluation of 30 clinical drugs against the comprehensive in vitro proarrhythmia assay (CiPA) proposed ion channel panel'. In: *J. Pharmacol. Toxicol. Methods* 81 (2016), pp. 251–262.

[46] M. Fedele, E. Faggiano, L. Dedè and A. Quarteroni. 'A patient-specific aortic valve model based on moving resistive immersed implicit surfaces'. In: *Biomech. Model. Mechanobiol.* 16.5 (2017), pp. 1779–1803.

[47] M. A. Fernández and J. Mullaert. 'Convergence and error analysis for a class of splitting schemes in incompressible fluid-structure interaction'. In: *IMA J. Numer. Anal.* 36.4 (2016), pp. 1748–1782.

[48] H. Gao, L. Feng, N. Qi, C. Berry, B. Griffith and X. Luo. 'A coupled mitral valve-left ventricle model with fluid-structure interaction'. In: *Med. Eng. Phys.* 47 (Sept. 2017), pp. 128–136.

[49] R. Glowinski, T. Pan, T. Hesla and D. Joseph. 'A distributed Lagrange mutiplier/fictitious domain method for particulate flows'. In: *Int. J. of Multiphase Flow* 25 (1999), pp. 755–794.

[50] C. Grandmont and M. Hillairet. 'Existence of global strong solutions to a beam-fluid interaction system'. In: *Arch. Ration. Mech. Anal.* 220.3 (2016), pp. 1283–1333.

[51] L. Grasedyck, D. Kressner and C. Tobler. 'A literature survey of low-rank tensor approximation techniques'. In: *GAMM-Mitt.* 36.1 (2013), pp. 53–78.

[52] M. Hillairet. 'Lack of collision between solid bodies in a 2D incompressible viscous flow'. In: *Comm. Partial Differential Equations* 32.7-9 (2007), pp. 1345–1371.

[53] H. M. Himmel. 'Drug-induced functional cardiotoxicity screening in stem cell-derived human and mouse cardiomyocytes: effects of reference compounds'. In: *J. Pharmacol. Toxicol. Methods* 68.1 (2013), pp. 97–111.

[54] J. Kaipio and E. Somersalo. *Statistical and computational inverse problems*. Vol. 160. Applied Mathematical Sciences. Springer-Verlag, New York, 2005.

[55] D. Kamensky, M.-C. Hsu, Y. Yu, J. A. Evans, M. S. Sacks and T. J. R. Hughes. 'Immersogeometric cardiovascular fluid-structure interaction analysis with divergence-conforming B-splines'. In: *Comput. Methods Appl. Mech. Engrg.* 314 (2017), pp. 408–472.

[56] M. J. van der Laan and S. Rose. *Targeted learning*. Springer Series in Statistics. Springer, New York, 2011.

[57] M. C. Lai and C. S. Peskin. 'An immersed boundary method with formal second-order accuracy and reduced numerical viscosity'. In: *J. Comp. Phys.* 160.2 (2000), pp. 705–719.

[58] R. van Loon, P. D. Anderson, J. de Hart and F. P. T. Baaijens. 'A combined fictitious domain/adaptive meshing method for fluid–structure interaction in heart valves'. In: *International Journal for Numerical Methods in Fluids* 46.5 (2004), pp. 533–544.

[59] S. Martin and B. Maury. 'Modeling of the oxygen transfer in the respiratory process'. In: *ESAIM Math. Model. Numer. Anal.* 47.4 (2013), pp. 935–960.

[60] R. Mittal, J. H. Seo, V. Vedula, Y. J. Choi, H. Liu, H. H. Huang, S. Jain, L. Younes, T. Abraham and R. T. George. 'Computational modeling of cardiac hemodynamics: current status and future outlook'. In: *J. Comput. Phys.* 305 (2016), pp. 1065–1082.

[61] J. M. Oakes, S. C. Shadden, C. Grandmont and I. E. Vignon-Clementel. 'Aerosol transport throughout inspiration and expiration in the pulmonary airways'. In: *Int. J. Numer. Methods Biomed. Eng.* 33.9 (2017).

[62] C. S. Peskin. 'The immersed boundary method'. In: *Acta Numer.* 11 (2002), pp. 479–517.

[63] C. J. Roth, M. Ismail, L. Yoshihara and W. A. Wall. 'A comprehensive computational human lung model incorporating inter-acinar dependencies: Application to spontaneous breathing and mechanical ventilation'. In: *Int. J. Numer. Method. Biomed. Eng.* 33.1 (2016). e02787.

[64] V. de Silva and L.-H. Lim. 'Tensor rank and the ill-posedness of the best low-rank approximation problem'. In: *SIAM J. Matrix Anal. Appl.* 30.3 (2008), pp. 1084–1127.

[65] L. Yoshihara, C. J. Roth and W. A. Wall. 'Fluid-structure interaction including volumetric coupling with homogenised subdomains for modeling respiratory mechanics'. In: *Int. J. Numer. Method. Biomed. Eng.* 33.4 (2016). e2812.