RESEARCH CENTRE

Inria Paris Centre
at Sorbonne University

IN PARTNERSHIP WITH:
CNRS, Sorbonne Université

2023
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

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Project-Team COMMEDIA

Creation of the Project-Team: 2019 June 01

Keywords

Computer sciences and digital sciences

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Other research topics and application domains

B2.2.1. – Cardiovascular and respiratory diseases

B2.4.1. – Pharmaco kinetics and dynamics

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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., [69, 70, 67, 72, 60]), 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., [42, 55, 58]). 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 [44, 52, 75]), 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., [77]). 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 [71]). 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 [66]). 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 [65]). 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 [49]) 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 [64, 62]). 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 [54], 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 [46, 48]. 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 [74, 45, 61, 43]) are known to be inaccurate in space. These difficulties have been recently circumvented by a Nitsche-based cut-FEM methodolgy (see [40, 50]). 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., [59]). 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., [71, 73, 47]). 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 [41]) 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 [68]). 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 [63]). 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 [76]). 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., [72, 53]). 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., [51]). 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 [65]). 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 [57]). 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 [56]).

5 New software, platforms, open data

5.1 New software

5.1.1 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

5.1.2 FELiScE-NS

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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5.1.3 DCIMaL

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

5.1.4 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

6 New results

6.1 Reduced Order modelling

Participants: Muriel Boulakia, Céline Grandmont, Fabien Lespagnol, Sébastien Riffaud.

In [32], we propose a reduced model associated to the Poisson problem in a domain with small holes. The reduction method is based on a fictitious domain formulation combined with a projection of Dirichlet boudary constraints on a finite dimensional approximation space. After analyzing the existence of a solution for the reduced problem and its convergence towards the full problem, we propose a numerical discretization which relies on augmented finite elements and allows to achieve optimal convergence properties that are illustrated through numerical illustrations.

In [38], we introduce a hybrid approach that alternates between a high-fidelity model and a reduced-order model to speedup numerical simulations while maintaining accurate approximations. In particular, a residual-based error indicator is developed to determine when the reduced-order model is not sufficiently accurate and the high-fidelity model needs to be solved. Then, we propose an adaptive-extended version of the hybrid approach to update the reduced-order model with the solution snapshots generated by the high-fidelity model when the reduced-order model was not sufficiently accurate. In this way, we

expect the reduced-order model to become more robust for predicting new out-of-sample solutions. The performance of the proposed method is evaluated on parametrized, time-dependent, nonlinear problems governed by the 1D Burgers' equation and 2D compressible Euler equations. The results demonstrate the accuracy and computational efficiency of the adaptive hybrid approach with respect to the high-fidelity model.

6.2 Safety pharmacology

Participants: Muriel Boulakia, Haibo Liu, Damiano Lombardi.

In [33], we study how to regularise, by means of a dataset of existing observations, parameter estimation problems in dynamical systems. Thanks to a representation of the dataset in the form of an encoder-decoder pair, we are able to introduce a Lipschitz stable non-linear change of variables such that the parameter estimation problem can be cast as an optimisation of a convex function. We prove that, given a Hölder regularity $C^{1,\beta}$ of the composition of the encoder and the dynamical system equation, we can have some theoretical guarantees on the convergence. Some encouraging numerical results are shown on the Van der Pol and the FizHugh-Nagumo dynamical systems.

6.3 Mathematical analysis of PDEs

Participants: Marguerite Champion, Miguel Angel Fernández Varela, Céline Grandmont, Fabien Vergnet, Marina Vidrascu.

In [16], we propose and study a new continuum mechanics model for the fluid-structure interaction problem involving active thin structures embedded in a Stokes flow. In particular, this model is able to reproduce the behavior of cilia or flagella betting in a viscous flow. In the context of linear or nonlinear elasticity, the model is based upon the definition of a suitable internal Piola-Kirchoff tensor , which mimics the action of internal biological motors, inducing the motility of the structures. The well-posedness of this coupled system is studied and, for the numerical resolution, an equivalent formulation using Lagrange multipliers is introduced, allowing for the use of standard (fluid and structure) solvers, up to an iterative procedure. Numerical simulations are presented, which illustrate the potential of the proposed active elasticity model.

In [36] we analyse of the contact capabilities of the fluid-structure interaction (FSI) model with seepage reported in [4]. In the case of a rigid disk moving over a fixed horizontal plane, we show that this model encompasses contact and hence removes the non collision paradox of traditional FSI models which rely on Dirichlet or Dirichlet/Navier boundary conditions. Numerical evidence on the theoretical results is also provided.

6.4 Numerical methods for multi-physics problems

Participants: Daniele Corti, Guillaume Delay, Miguel Angel Fernández Varela, Céline Grandmont, Fabien Lespagnol, Oscar Ruz, Fabien Vergnet, Marina Vidrascu.

One of the main difficulties that has to be faced with fictitious domain approximation of incompressible flows with immersed interfaces is related to the potential lack of mass conservation across the interface. In [15], we propose and analyze a low order fictitious domain stabilized finite element method which mitigates this issue with the addition of a single velocity constraint. We provide a complete a priori numerical analysis of the method under minimal regularity assumptions. A comprehensive numerical study illustrates the capabilities of the proposed method, including comparisons with alternative fitted and unfitted mesh methods.

The numerical simulation of incompressible fluid-structure interaction systems with loosely coupled schemes is a delicate problem. Indeed, the splitting method must both be stable for the full nonlinear system and have sufficient accuracy to be of use in practice. In the case of the coupling of an incompressible fluid with thick-walled solids the error analyses reported in the literature are limited to 1/2-order accuracy in time. In [34] we introduce two important extensions of the analysis of the Robin-Robin loosely coupled scheme recently reported in [Numer. Math., 151(4):807–840, 2022]. First, we give a formulation of the scheme in a general non-linear setting and prove its unconditional energy stability. Then we show that nearly-optimal accuracy can be achieved in the linear case. These theoretical findings are illustrated in a series of numerical examples.

In [11] we analyse the convergence of the full discretization of a generalized poromechanical model resulting from the linearization of an initial model fitted to soft tissue perfusion. Our strategy here is based on the use of energy-based estimates and T-coercivity methods, so that the numerical analysis benefits from the essential tools used in the existence analysis of the continuous-time and continuous-space formulation.

[37] We consider the simulation of slender structures immersed in a three-dimensional (3D) flow. By exploiting the special geometric configuration of the slender structures, this particular problem can be modeled by mixed-dimensional coupled equations (3D for the fluid and 1D for the solid). Several challenges must be faced when dealing with this type of problems. From a mathematical point of view, these include defining wellposed trace operators of codimension two. On the computational standpoint, the nonstandard mathematical formulation makes it difficult to ensure the accuracy of the solutions obtained with the mixed-dimensional discrete formulation as compared to a fully resolved one. We establish the continuous formulation using the Navier-Stokes equations for the fluid and a Timoshenko beam model for the structure. We complement these models with a mixed-dimensional version of the fluid-structure interface conditions, based on the projection of kinematic coupling conditions on a finite-dimensional Fourier space. Furthermore, we develop a discrete formulation within the framework of the finite element method, establish the energy stability of the scheme, provide extensive numerical evidence of the accuracy of the discrete formulation, notably with respect to a fully resolved (ALE based) model and a standard reduced modeling approach.

7 Bilateral contracts and grants with industry

7.1 Bilateral contracts with industry

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.

8 Partnerships and cooperations

8.1 International initiatives

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

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

Participants: Muriel Boulakia, Daniele Carlo Corti, Guillaume Delay, Miguel Ángel Fernández Varela *(coordinator)*.

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

Duration: 2022-2025

Coordinator: Miguel Angel Fernández 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

8.1.2 Visits of international scientists

- Erik Burman (UCL), March and October 2023.
- Mihai Nechita (Tiberiu Popoviciu Institute of Numerical Analysis), May 2023.
- Cecilia Pagliantini (Università di Pisa), February and October 2023.
- Gianluca Ceruti (University of Innsbruck), February and October 2023.

8.2 European initiatives

8.2.1 Horizon Europe

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

Participants: Sara Costa, Miguel Ángel Fernández Varela, 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

8.3 National initiatives

8.3.1 ANR

ADAPT: Adaptive Dynamical Approximations by Parallel Tensor methods

Participants: Maria Fuente-Ruiz, Damiano Lombardi *(coordinator)*, Sébastien Riffaud
.

Funding: ANR JCJC

Duration: 2018-2023

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

9 Dissemination

9.1 Promoting scientific activities

9.1.1 Scientific events: organisation

- Guillaume Delay
  - Co-organiser of the scientific computing seminar, joint event between Inria and Laboratoire Jacques-Louis Lions.
  - Organizer of the Workshop on data assimilation, Sorbonne Université, November 2023.
- Miguel Ángel Fernández Varela
  - Co-organizer of an FIMH sateltite workshop, Simulation and Imaging for Mitral Regurgitation, Lyon, June 2023.
- Damiano Lombardi
  - Co-organiser of the scientific computing seminar, joint event between Inria and Laboratoire Jacques-Louis Lions.
  - Mini-symposium organiser, High-Dimensional Approximation and Reduced-Order Models, in SIAM CSE, Amsterdam, March 2023.

9.1.2 Journal

Member of the editorial boards

- Céline Grandmont
  - Mathematical Modelling of Natural Phenomena
  - Journal of Mathematical Fluid Mechanics
  - ESAIM: Mathematical Modelling and Numerical Analysis

9.1.3 Invited talks

- Muriel Boulakia
  - Invited speaker, Workshop ANR Trecos, ENS Rennes, June 2023
  - Invited speaker, Conference Optimization and Control in Burgundy, Dijon, May 2023
  - Mini-symposium keynote speaker, CFC 2023, Cannes, April 2023
- Miguel Angel Fernández Varela
  - Invited talk in MS, ICIAM, Tokyo, August, 2023
- Céline Grandmont
  - Conference in honnor pf Grigory Panasenko, Saint Etienne University, Octobre 2023.
  - Séminaire EDP, Grenoble Rhone Alpes Univ., Sept. 2023.
  - Colloquium Nantes, April 2023
- Damiano Lombardi
  - Keynote speaker, Biophysics-based modeling and data assimilation in medical imaging, Berlin, August 2023.
  - Invited talk in MS, ICIAM, Tokyo, August, 2023
- Fabien Vergnet
  - European Conference on Numerical Mathematics and Advanced Applications (ENUMATH), September 2023, Lisbon, Portugal

9.1.4 Research administration

- Muriel Boulakia
  - Member of the committee of the doctoral school FMJH/LMH Paris-Saclay for the thematics Mathematics of Scientific Computing and Engineering
- 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 Paris.

9.2 Teaching - Supervision - Juries

9.2.1 Teaching

- Licence:
  - Marguerite Champion
    - Numerical analysis, 24h, L3, Sorbonne University
    - Python, 32h, L2, Sorbonne University
  - Guillaume Delay
    - Analyse Numérique L3, (48h)
    - Remise à Niveau en Math à PolyTech Sorbonne L3, (12h)
  - Corrie James
    - Math Tutoring, 9h, L1, Université de Versailles Saint-Quentin-en-Yvelines
  - Gaël le Ruz
    - Linear algebra and ODE, 30h, L3, Polytech Sorbonne, Sorbonne Université.
    - Fourier Analysis, 24h, L3, Polytech Sorbonne, Sorbonne Université.
    - Numerical Analysis for PDE, 12h, L3, Polytech Sorbonne, Sorbonne Université.
  - Fabien Vergnet
    - Numerical analysis and ODE, 58h, L3, Polytech Sorbonne, Sorbonne Université.
    - Nonlinear systems and optimization, 30h, L3, Polytech Sorbonne, Sorbonne Université.
- Master:
  - Guillaume Delay
    - Preparation to Agrégation, 34h, M2, Sorbonne Université
    - Numerical analysis for PDE, 18h, M1,PolyTech Sorbonne
    - Initiation to C++, 27h, M2, Sorbonne Université.
    - C++ projet, 21h, M2, Sorbonne Université.
  - Miguel Ángel Fernández Varela
    - Mathematical models and numerical methods for hemodynamics simulations, 20h, M2, Sorbonne Université.
  - Damiano Lombardi
    - Lecture, 1.5h, Modelling the heart, June 2023, ENPC.
    - Lecture, 1.5h, Modeling the electro-physiology of heart, November 2023, Ecole des Mines Paristech.

9.2.2 Supervision

- PhD Mathieu Barré, Mathematical and numerical study of a poroelastic model.Supevisors: C. Grandmont & P. Moireau (M3DISIM, Inria Saclay defended in October 2023).
- 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, D.Lombardi.

- 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, Politecnico 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.
- PhD defended (March 2023): Maria Fuente Ruiz, Adaptive tensor methods for scientific computing. Supervisors: D. Lombardi & V. Ehrlacher.
- PostDoc: Cyril Karamaoun (CNRS, Sorbonne Université), Until dec 2023, Modelling of gas transport and exchange in the lung. Supervisors: L. Boudin (Sorbonne Univ.) & C. Grandmont.
- PostDoc: Sebastien Riffaud. Tensor methods for parametric fluid-structure interaction and data assimilation. Supervisors: D. Lombardi & M.A. Fernández Varela.
- PostDoc in progress: Lamis Sabbagh (ARC-ULB, hosted by ULB), Mathematical analysis of fluid-structure interactions problems. Supervisor: C. Grandmont.
- Internship Marloes Coolen. Supervisor: M.A. Fernández Varela.
- Internship Corrie James. Supervisors: M. Boulakia & D. Lombardi.
- Internship Riccardo Bianchi. Supervisors: D. Lombardi & Stefano Pagani (Politecnico di Milano)

9.2.3 Juries

- Muriel Boulakia
  - Hiring committees: MdC at GEMaC laboratory, UVSQ ; Professor at Laboratoire de Mathématiques, Université du Littoral Côte d'Opale
- Céline Grandmont
  - Member of the PhD thesis prize SMAI-Gamni 2023
  - Member of the scientific commitee of SMAI 2023.
  - Hiring committees: Inria CR/IFSP Nancy, "Repyramidage PR" La Rochelle University, Inria DR2, and "Chaire de Professeur Junior", Sorbonne Université.
- Miguel Ángel Fernández Varela
  - Hiring committe: Inria CR/IFSP Saclay.

9.3 Popularization

- Marguerite Champion
  - Co-organizer of "Rencontres Jeunes Mathématiciennes et Informaticiennes", Inria Paris, October 2023

10 Scientific production

10.1 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.

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10.2 Publications of the year

International journals

[9] 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'. In: *Cardiovascular Engineering and Technology* 14 (14th Aug. 2023), pp. 577–604. DOI: 10.1007/s13239-023-00677-z. URL: https://inria.hal.science/hal-03349442.

[10] 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* 43.2 (2023), pp. 881–919. DOI: 10.1093/imanum/drac004. URL: https://hal.science/hal-02893508.

[11] M. Barré, C. Grandmont and P. Moireau. 'Numerical analysis of an incompressible soft material poromechanics model using T-coercivity'. In: *Comptes Rendus. Mécanique* 351.S1 (2023), pp. 1–36. DOI: 10.5802/crmeca.194. URL: https://hal.science/hal-04098153.

[12] 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'. In: *Journal of Theoretical Biology* (2023), p. 111590. DOI: 10.1016/j.jtbi.2023.111590. URL: https://hal.science/hal-03883301.

[13] 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* 31.1 (2023), pp. 59–77. DOI: 10.1515/jnma-2021-0119. URL: https://hal.science/hal-03381765.

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[15] D. Corti, G. Delay, M. A. Fernández, F. Vergnet and M. Vidrascu. 'Low-order fictitious domain method with enhanced mass conservation for an interface Stokes problem'. In: *ESAIM: Mathematical Modelling and Numerical Analysis* (18th Dec. 2023). DOI: 10.1051/m2an/2023103. URL: https://inria.hal.science/hal-04084162.

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Invited conferences

[18] D. Lombardi. 'Data assimilation problems in haemodynamics'. In: Workshop on Biophysics-based modeling and data assimilation in medical imaging. Berlin, Germany, 30th Aug. 2023. URL: https://inria.hal.science/hal-04392374.

[19] D. Lombardi, V. Ehrlacher and M. Fuente-Ruiz. 'SoTT: a greedy construction of a sum of Tensor Trains'. In: ICOSAHOM 2023 - International Conference on Spectral and High Order Methods. Seoul, South Korea, 14th Aug. 2023. URL: https://inria.hal.science/hal-04392369.

International peer-reviewed conferences

[20] M. A. Fernández, D. Lombardi and S. Riffaud. 'Parametric solvers for simulation of blood flows'. In: CFC 2023 - IACM Computational Fluids Conference. Cannes, France, 25th Apr. 2023. URL: https://inria.hal.science/hal-04010559.

Conferences without proceedings

[21] M. Boulakia, M. A. Fernández, D. Lombardi, M. Nechita and M. Agbalessi. 'Fluid-structure interaction calibration from 4D-flow MRI data'. In: CFC 2023 - IACM Computational Fluids Conference. Cannes, France, 25th Apr. 2023. URL: https://inria.hal.science/hal-04397115.

[22] H. Liu, D. Lombardi and M. Boulakia. 'Lipschitz Stabilised Autoencoders in Parameter Identification of Dynamical Systems'. In: 10th International Congress on Industrial and Applied Mathematics (ICIAM 2023). Tokyo, Japan, 20th Aug. 2023. URL: https://hal.science/hal-04398536.

[23] H. Liu, D. Lombardi and M. Boulakia. 'Lipschitz Stabilised Autoencoders to Study the Intrinsic Dimensionality of Dynamical Systems and Build Data-driven Models'. In: Math 2 Product (M2P): Emerging Technologies in Computational Science for Industry, Sustainability and Innovation. Taormina, Italy, 30th May 2023. URL: https://hal.science/hal-04398549.

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Edition (books, proceedings, special issue of a journal)

[29] B. Battisti, T. Blickhan, G. Enchery, V. Ehrlacher, D. Lombardi and O. Mula, eds. *Wasserstein model reduction approach for parametrized flow problems in porous media*. CEMRACS 2021 - Data Assimilation and Reduced Modeling for High Dimensional Problems. Vol. 73. EDP Sciences, 30th Aug. 2023, pp. 28–47. DOI: 10.1051/proc/202373028. URL: https://hal.science/hal-04390131.

Doctoral dissertations and habilitation theses

[30] M. Agbalessi. 'State estimation in fluid-structure interaction from 4D-flow MRI data'. Sorbonne Université, 3rd Apr. 2023. URL: https://inria.hal.science/tel-04072648.

[31] M. Fuente Ruiz. 'Adaptive tensor methods for high dimensional problems'. Sorbonne Université, 31st Mar. 2023. URL: https://theses.hal.science/tel-04082601.

Reports & preprints

[32] M. Boulakia, C. Grandmont, F. Lespagnol and P. Zunino. *Numerical approximation of the Poisson problem with small holes, using augmented finite elements and defective boundary conditions*. 30th Jan. 2023. URL: https://inria.hal.science/hal-03501521.

[33] M. Boulakia, H. Liu and D. Lombardi. *Parameter identification through gradient flow on latent variables*. 26th Dec. 2023. URL: https://inria.hal.science/hal-04364114.

[34] E. Burman, R. Durst, M. A. Fernández, J. Guzmán and O. Ruz. *Robin-Robin loose coupling for incompressible fluid-structure interaction: non-linear setting and nearly-optimal error analysis*. 25th Oct. 2023. URL: https://inria.hal.science/hal-04258861.

[35] A. Canteaut, M. Serrano, C. Grandmont, G. Pallez, V. Perrier, X. Rival and E. Thomé. *Bilan de la mandature 2019-2023 de la Commission d'Évaluation Inria*. Inria, 31st Aug. 2023. URL: https://inria.hal.science/hal-04193082.

[36] M. Champion, M. A. Fernández, C. Grandmont, F. Vergnet and M. Vidrascu. *On the analysis of a mechanically consistent model of fluid-structure-contact interaction*. 4th Oct. 2023. URL: https://hal.science/hal-04229012.

[37] F. Lespagnol, C. Grandmont, P. Zunino and M. A. Fernández. *A mixed-dimensional formulation for the simulation of slender structures immersed in an incompressible flow*. 1st Dec. 2023. URL: https://inria.hal.science/hal-04318526.

[38] S. Riffaud. *Accurate and robust predictions for model order reduction via an adaptive, hybrid FOM/ROM approach*. 22nd Dec. 2023. URL: https://inria.hal.science/hal-04361506.

Other scientific publications

[39] S. C. Faya, M. Coolen, C. Wesley, M. Vidrascu, P.-J. Guns, M. A. Fernández and D. Lombardi. 'An in silico approach to monitor and predict haemodynamics during safety pharmacology studies'. In: SPS Annual Meeting. Brussels, Belgium, 18th Sept. 2023. URL: https://hal.science/hal-04394917.

10.3 Cited publications

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[53] 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.

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