IN PARTNERSHIP WITH:
Ecole Polytechnique

Activity Report 2018

Project-Team M3DISIM

Mathematical and Mechanical Modeling with Data Interaction in Simulations for Medicine

IN COLLABORATION WITH: Laboratoire de Mécanique des Solides

RESEARCH CENTER
Saclay - Île-de-France

THEME
Modeling and Control for Life Sciences

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Creation of the Team: 2013 January 01, updated into Project-Team: 2016 June 01

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1. Team, Visitors, External Collaborators

Research Scientists

Dominique Chapelle [Team leader, Inria, Senior Researcher, HDR]
Philippe Moireau [Team leader, Inria, Senior Researcher, HDR]
Radomir Chabiniok [Inria, Starting Research Position]
Frédérique Clément [Inria, Senior Researcher, HDR]
Sébastien Imperiale [Inria, Researcher]

Faculty Members

Jean-Marc Allain [Ecole polytechnique, Professor, HDR]
Martin Genet [Ecole polytechnique, Associate Professor]
Patrick Le Tallec [Ecole polytechnique, Professor, HDR]

PhD Students

Ezgi Berberoglu [ETH Zurich, PhD Student, from May 2017]
Federica Caforio [Inria]

Chloe Giraudet [Ecole polytechnique, from Oct 2018]
Marija Gusseva [Inria]
Ustim Khristenko [Ecole polytechnique, until Jan 2018]
François Kimmig [Ecole polytechnique]
Arthur Le Gall [Assistance publique/Hôpitaux de Paris]
Cécile Patte [Inria]
Frédérique Robin [Inria]
Nicole Tueni [Ecole polytechnique, from Jan 2018]
Florent Wijanto [Ecole polytechnique]

Technical staff

Jerome Diaz [Inria, from Nov 2018]
Gautier Bureau [Inria, REO Team, until Mar 2018]

Interns

Oscar Boyadjian-Braize [Ecole polytechnique, from May 2018 until Jul 2018]
Jerome Diaz [Inria, from Apr 2018 until Sep 2018]
Chloé Giraudet [Ecole polytechnique, from Mar 2018 until Aug 2018]
Jessica Manganotti [Ecole polytechnique, from Sep 2018]
Antoine Olive [Ecole polytechnique, from May 2018 until Aug 2018]

Administrative Assistants

Stephanie Aubin [Inria, until Sep 2018]
Hélèna Kutniak [Inria, from Oct 2018]

Visiting Scientists

Francesco Regazzoni [Ecole polytechnique, from Sep 2018]
Katerina Solovska [Czech Technical University in Prague, Aug 2018]
Animesh Tandon [University of Texas Southwestern Medical School, Oct 2018]

External Collaborators

Matthieu Caruel [Univ Paris-Val de Marne]
Fabrice Vallée [Assistance publique/Hôpitaux de Paris]
Hajer Methenni [CEA]

2. Overall Objectives

2.1. Overall Objectives

The research carried out in the M3DISIM team has a rather global methodological perspective oriented towards biomechanics, encompassing mathematical modeling and analysis, inverse problems arising from model-data coupling, and the formulation and analysis of effective and reliable numerical procedures adapted to this overall program. We are also very keen on demonstrating the effectiveness and relevance of these methods in actual applications, usually by proof-of-concept studies carried out within various collaborations.

3. Research Program

3.1. Multi-scale modeling and coupling mechanisms for biomechanical systems, with mathematical and numerical analysis

Over the past decade, we have laid out the foundations of a multi-scale 3D model of the cardiac mechanical contraction responding to electrical activation. Several collaborations have been crucial in this enterprise, see below references. By integrating this formulation with adapted numerical methods, we are now able to

represent the whole organ behavior in interaction with the blood during complete heart beats. This subject was our first achievement to combine a deep understanding of the underlying physics and physiology and our constant concern of proposing well-posed mathematical formulations and adequate numerical discretizations. In fact, we have shown that our model satisfies the essential thermo-mechanical laws, and in particular the energy balance, and proposed compatible numerical schemes that – in consequence – can be rigorously analyzed, see [6]. In the same spirit, we have formulated a poromechanical model adapted to the blood perfusion in the heart, hence precisely taking into account the large deformation of the mechanical medium, the fluid inertia and moving domain, and so that the energy balance between fluid and solid is fulfilled from the model construction to its discretization, see [7].

3.2. Inverse problems with actual data – Fundamental formulation, mathematical analysis and applications

A major challenge in the context of biomechanical modeling – and more generally in modeling for life sciences – lies in using the large amount of data available on the system to circumvent the lack of absolute modeling ground truth, since every system considered is in fact patient-specific, with possibly non-standard conditions associated with a disease. We have already developed original strategies for solving this particular type of inverse problems by adopting the observer stand-point. The idea we proposed consists in incorporating to the classical discretization of the mechanical system an estimator filter that can use the data to improve the quality of the global approximation, and concurrently identify some uncertain parameters possibly related to a diseased state of the patient. Therefore, our strategy leads to a coupled model-data system solved similarly to a usual PDE-based model, with a computational cost directly comparable to classical Galerkin approximations. We have already worked on the formulation, the mathematical and numerical analysis of the resulting system – see [5] – and the demonstration of the capabilities of this approach in the context of identification of constitutive parameters for a heart model with real data, including medical imaging, see [3].

4. Application Domains

4.1. Clinical applications

After several validation steps – based on clinical and experimental data – we have reached the point of having validated the heart model in a pre-clinical context where we have combined direct and inverse modeling in order to bring predictive answers on specific patient states. For example, we have demonstrated the predictive ability of our model to set up pacemaker devices for a specific patient in cardiac resynchronization therapies, see [11]. We have also used our parametric estimation procedure to provide a quantitative characterization of an infarct in a clinical experiment performed with pigs, see [3].

5. Highlights of the Year

5.1. Highlights of the Year

During the 8th World Congress of Biomechanics in Dublin, Martin Genet received the Young Investigator Award from the Francophone Society of Biomechanics for his talk on “A continuum relaxed growth framework for controlling growth-induced residual stresses in living tissues”.

6. New Software and Platforms

6.1. HeartLab

KEYWORDS: Computational geometry - Image analysis - Cardiac - Health - Simulation

FUNCTIONAL DESCRIPTION: The heartLab software is a library designed to perform both simulation and estimation of the heart mechanical behavior (based on various types of measurements, e.g. images).

Also included are geometric data and tools in the code to define cardiac anatomical models compatible with the simulation requirements in terms of mesh quality, fiber direction data defined within each element, and the referencing necessary for handling boundary conditions and estimation, in particular. These geometries are analytical or come from computerized tomography (CT) or magnetic resonance (MR) image data of humans or animals.

- Participants: Radomir Chabiniok, Gautier Bureau, Martin Genet, Federica Caforio, Ustim Khristenko, Dominique Chapelle and Philippe Moireau
- Contact: Philippe Moireau
- URL: https://raweb.inria.fr/rapportsactivite/RA2013/m3disim/uid14.html

6.2. Verdandi

KEYWORDS: HPC - Model - Software Components - Partial differential equation
FUNCTIONAL DESCRIPTION: Verdandi is a free and open-source (LGPL) library for data assimilation. It includes various such methods for coupling one or several numerical models and observational data. Mainly targeted at large systems arising from the discretization of partial differential equations, the library is devised as generic, which allows for applications in a wide range of problems (biology and medicine, environment, image processing, etc.). Verdandi also includes tools to ease the application of data assimilation, in particular in the management of observations or for a priori uncertainty quantification. Implemented in C++, the library may be used with models implemented in Fortran, C, C++ or Python.

- Participants: Dominique Chapelle, Gautier Bureau, Nicolas Claude, Philippe Moireau and Vivien Mallet
- Contact: Vivien Mallet
- URL: http://verdandi.gforge.inria.fr/

6.3. CardiacLab

KEYWORDS: Cardiovascular and respiratory systems - Matlab - Real time
FUNCTIONAL DESCRIPTION: CardiacLab is a MATLAB toolbox allowing to perform “real-time” cardiac simulations using 0D models of the cardiovascular systems. Its modular development includes (1) a module integrating the mechanical dynamics of the cavity taking into account its particular geometry, (2) a module allowing to choose a micro-model of the cardiac contraction, (3) a module of phase management, (4) a circulation module based on Windkessel models or more advanced 1D flows models, and (5) a perfusion module. The objective of this code is threefold: (1) demonstrate to students, engineers, medical doctors, the interest of modeling in cardiac applications, (2) unify our original modeling developments with the possibility to evaluate them with previous team developments before integrating them into 3D complex formulations, and (3) explore some avenues pertaining to real-time simulat

- Participants: Sebastien Impériale, Martin Genet, Federica Caforio, Ustim Khristenko, Peter Baumgartner, Radomir Chabiniok, François Kimmig and Arthur Le Gall
- Contact: Philippe Moireau
- URL: https://gitlab.inria.fr/M3DISIM/CardiacLab

6.4. MoReFEM

Modeling Research with the Finite Element Method
KEYWORDS: HPC - Multiphysics modelling - Data assimilation

FUNCTIONAL DESCRIPTION: MoReFEM is a HPC finite element library for simulating multiphysics evolution problems like the ones encounter in cardiac modeling (electrophysiology, structure and fluid mechanics, transport-diffusion, wave equations)

- Participants: Philippe Moireau, Patrick Le Tallec, Antoine Olivier, Dominique Chapelle, Ustim Khristenko, François Kimmig, Gautier Bureau and Sébastien Gilles
- Contact: Sébastien Gilles
- URL: https://gitlab.inria.fr/MoReFEM

7. New Results

7.1. Mathematical and Mechanical Modeling

7.1.1. Microscopic model of collagen fiber

Participants: Florent Wijanto, Matthieu Caruel, Jean-Marc Allain [correspondant].

Our studies on collagen tissues have shown that the collagen fibers are able to elongate inelastically under stretch. In tendon, this effect has been attributed to the non-permanent cross-bridges which connect the different collagen fibrils (to assemble a fiber). This sliding effect appears experimentally to be reversible (at least partially) if the tissue is left long enough at its initial resting length. However, this sliding is classically included as an irreversible plastic response, or as a damage of the tissue. We are building a model based on a stochastic description of the binding and unbinding of the cross-bridges. This approach will enable us to have a microscopically based picture of the sliding, which will be able to explain some alteration in case of ageing or of pathological alterations of the tissue. At the moment, we have shown the importance of the density of cross-bridges in the cooperative response of the system. A publication is in preparation on the topic.

7.1.2. Stochastic modeling of chemical-mechanical coupling in striated muscles

Participants: Matthieu Caruel, Dominique Chapelle [correspondant], Philippe Moireau.

We propose a chemical-mechanical model of myosin heads in sarcomeres, within the classical description of rigid sliding filaments. In our case, myosin heads have two mechanical degrees-of-freedom (dofs) – one of which associated with the so-called power stroke – and two possible chemical states, i.e. bound to an actin site or not. Our major motivations are twofold: (1) to derive a multiscale coupled chemical-mechanical model, and (2) to thus account – at the macroscopic scale – for mechanical phenomena that are out of reach for classical muscle models. This model is first written in the form of Langevin stochastic equations, and we are then able to obtain the corresponding Fokker-Planck partial differential equations governing the probability density functions associated with the mechanical dofs and chemical states. This second form is important, as it allows to monitor muscle energetics, and also to compare our model with classical ones, such as the Huxley'57 model to which our equations are shown to reduce under two different types of simplifying assumptions. This provides insight, and gives a Langevin form for Huxley'57. We then show how we can calibrate our model based on experimental data – taken here for skeletal muscles – and numerical simulations demonstrate the adequacy of the model to represent complex physiological phenomena, in particular the fast isometric transients in which the power stroke is known to have a crucial role, thus circumventing a limitation of many classical models. This work is accepted for publication in BMMB.

7.1.3. The importance of the pericardium for cardiac biomechanics

Participant: Radomir Chabiniok [correspondant].

The human heart is enclosed in the pericardial cavity. The pericardium consists of a layered thin sac and is separated from the myocardium by a thin film of fluid. It provides a fixture in space and frictionless sliding of the myocardium. The influence of the pericardium is essential for predictive mechanical simulations of the heart. However, there is no consensus on physiologically correct and computationally tractable pericardial boundary conditions. Here we propose to model the pericardial influence as a parallel spring and dashpot acting in normal direction to the epicardium. Using a four-chamber geometry, we compare a model with pericardial boundary conditions to a model with fixated apex. The influence of pericardial stiffness is demonstrated in a parametric study. Comparing simulation results to measurements from cine magnetic resonance imaging reveals that adding pericardial boundary conditions yields a better approximation with respect to atrioventricular plane displacement, atrial filling, and overall spatial approximation error. We demonstrate that this simple model of pericardial-myocardial interaction can correctly predict the pumping mechanisms of the heart as previously assessed in clinical studies. Utilizing a pericardial model can not only provide much more realistic cardiac mechanics simulations but also allows new insights into pericardial-myocardial interaction which cannot be assessed in clinical measurements yet. The work was accepted for publication in Biomechanics and Modeling in Mechanobiology [26], and is a joint work with Technical University in Munich, Germany (group of W.A. Wall) and Bernoulli Institute for Mathematics at University of Groningen, The Netherlands (C. Bertoglio).

7.1.4. Solving 2D linear isotropic elastodynamics by means of scalar potentials: a new challenge for finite elements

Participants: Sébastien Imperiale, Patrick Joly [Poems].

In this work we present a method for the computation of numerical solutions of 2D homogeneous isotropic elastodynamics equations by solving scalar wave equations. These equations act on the potentials of a Helmholtz decomposition of the displacement field and are decoupled inside the propagation domain. We detail how these equations are coupled at the boundary depending on the nature of the boundary condition satisfied by the displacement field. After presenting the case of rigid boundary conditions, that presents no specific difficulty, we tackle the challenging case of free surface boundary conditions that presents severe stability issues if a straightforward approach is used. We introduce an adequate functional framework as well as a time domain mixed formulation to circumvent these issues. Numerical results confirm the stability of the proposed approach.

7.1.5. Lung multiscale poromechanical modeling, from breathing to pulmonary fibrosis-induced chronic remodeling

Participants: Cécile Patte [correspondant], Martin Genet, Dominique Chapelle.

Pulmonary diseases are about to become the third cause of death in the world. One on them, Idiopathic Pulmonary Fibrosis (IPF), which involves thickening, stiffening and destruction the alveolar walls, remains poorly understood, diagnosed and treated. It has been hypothesized, however, that IPF involves a mechanical vicious circle, where fibrosis induces higher stresses, which in turns favors fibrosis. In this project, we intend to better understand the role of mechanics in the disease progression, in order to improve diagnosis and prognosis. We model the lung behavior during breathing at organ-scale, based on a poromechanical theory, previously established in the team. Then we estimate the regional mechanical properties of the lung, based on clinical data. In the future, the procedure can be used as a prognostic tool by the clinicians.

7.1.6. Mathematical modelling of transient shear wave elastography in the heart

Participants: Federica Caforio [correspondant], Sébastien Imperiale.

The aim of this work is to provide a mathematical model of the excitation and the resulting shear wave propagation in Acoustic Radiation Force (ARF)-based shear wave cardiac elastography. Our approach is based on asymptotic analysis; more precisely, it consists in considering a family of problems, parametrised by a small parameter inversely proportional to the excitation frequency of the probes, the viscosity and the velocity of pressure wave propagation. We derive a simplified model for the expression of the ARF by investigating the

limit behaviour of the solution when the small parameter goes to zero. By formal asymptotic analysis - an asymptotic expansion of the solution is used - we show that the leading order term of the expansion is the underlying nonlinear cardiac mechanics. Subsequently, two corrector terms are computed. The first is a fast-oscillating pressure wave generated by the probes, solution of a Helmholtz equation at every time instant. The second corrector term consists in an elastic field with prescribed divergence, having a function of the first corrector as a source term. This field corresponds to the shear acoustic wave induced by the ARF. We also confirm that, in cardiac mechanics, the presence of viscosity in the model is essential to derive an expression of the shear wave propagation from the ARF, and that this phenomenon is related to the nonlinearity of the partial differential equation.

7.1.7. Analysis and calibration of a linear model for structured cell populations with unidirectional motion : Application to the morphogenesis of ovarian follicles

Participants: Frédérique Clément, Frédérique Robin [correspondant], Romain Yvinec [INRA].

In [41], we have analyzed a multi-type age dependent model for cell populations subject to unidirectional motion, in both a stochastic and deterministic framework. Cells are distributed into successive layers; they may divide and move irreversibly from one layer to the next. We have adapted results on the large-time convergence of PDE systems and branching processes to our context, where the Perron-Frobenius or Krein-Rutman theorems cannot be applied. We have derived explicit analytical formulas for the asymptotic cell number moments, and the stable age distribution. We have illustrated these results numerically and we have applied them to the study of the morphodynamics of ovarian follicles. We have proven the structural parameter identifiability of our model in the case of age independent division rates. Using a set of experimental biological data, we have estimated the model parameters to fit the changes in the cell numbers in each layer during the early stages of follicle development.

7.1.8. A multiscale mathematical model of cell dynamics during neurogenesis in the mouse cerebral cortex

Participants: Frédérique Clément [correspondant], Marie Postel [Sorbonne Universités].

Work in collaboration with Sylvie Schneider-Maunoury (Sorbonne Universités), Alice Karam (Sorbonne Universités), Guillaume Pézeron (MNHN). Neurogenesis in the murine cerebral cortex involves the coordinated divisions of two main types of progenitor cells, whose numbers, division modes and cell cycle durations set up the final neuronal output. To understand the respective roles of these factors in the neurogenesis process, we have combined experimental in vivo studies with mathematical modeling and numerical simulations of the dynamics of neural progenitor cells [43]. A special focus has been put on the population of intermediate progenitors (IPs), a transit amplifying progenitor type critically involved in the size of the final neuron pool. Our multiscale formalism describing IP dynamics allows one to track the progression of cells along the subsequent phases of the cell cycle, as well as the temporal evolution of the different cell numbers. Our model takes into account the dividing apical progenitors (AP) engaged into neurogenesis, both neurogenic and proliferative IPs, and the newborn neurons. The transfer rates from one population to another are subject to the mode of division (symmetric, asymmetric, neurogenic) and may be time-varying. The model outputs have been successfully fitted to experimental cell numbers from mouse embryos at different stages of cortical development, taking into account IPs and neurons, in order to adjust the numerical parameters. Applying the model to a mouse mutant for Ftm/Rpgrip1l, a gene involved in human ciliopathies with severe brain abnormalities, has revealed a shortening of the neurogenic period associated with an increased influx of newborn IPs from apical progenitors at mid-neurogenesis. Additional information have been provided on cell kinetics, such as the mitotic and S phase indexes, and neurogenic fraction. Our model can be used to study other mouse mutants with cortical neurogenesis defects and can be adapted to study the importance of progenitor dynamics in cortical evolution and human diseases.

7.1.9. Advances in computational modeling approaches of pituitary gonadotropin signaling

Participants: Frédérique Clément [correspondant], Romain Yvinec [INRA].

Work in collaboration with Pascale Crépieux, Anne Poupon and Éric Reiter (INRA). We have reviewed thoroughly the state-of-the-art in computational modeling approaches of pituitary gonadotropin signaling [30]. Pituitary gonadotropins play an essential and pivotal role in the control of human and animal reproduction within the hypothalamic-pituitary-gonadal (HPG) axis. The computational modeling of pituitary gonadotropin signaling encompasses phenomena of different natures such as the dynamic encoding of gonadotropin secretion, and the intracellular cascades triggered by gonadotropin binding to their cognate receptors, resulting in a variety of biological outcomes. We have overviewed historical and ongoing issues in modeling and data analysis related to gonadotropin secretion in the field of both physiology and neuro-endocrinology. We have mentioned the different mathematical formalisms involved, their interest and limits. We have discussed open statistical questions in signal analysis associated with key endocrine issues. We have also reviewed recent advances in the modeling of the intracellular pathways activated by gonadotropins, which yields promising development for innovative approaches in drug discovery. The greatest challenge to be tackled in computational modeling of pituitary gonadotropin signaling is the embedding of gonadotropin signaling within its natural multiscale environment, from the single cell level, to the organic and whole HPG level. The development of modeling approaches of G protein-coupled receptor signaling, together with multicellular systems biology may lead to unexampled mechanistic understanding with critical expected fallouts in the therapeutic management of reproduction.

7.1.10. Structured cell population dynamics applied to the early development of ovarian follicles

Participants: Frédérique Clément, Frédérique Robin [correspondant], Romain Yvinec [INRA].

The ovarian follicles are the basic anatomical and functional units of the ovaries, which are renewed from a quiescent pool all along reproductive life. Follicular development involves a finely tuned sequence of growth and maturation processes, involving complex cell dynamics. Understanding follicular development is a crucial issue for the management of reproduction in a clinical or breeding context, and for the preservation of endangered species. In their early stages of development, ovarian follicles are made up of a germ cell (oocyte), whose diameter increases steadily, and of surrounding proliferating somatic cells, which are layered in a globally spherical and compact structure. We have designed a modeling approach dedicated to the initiation phase of follicle development. The initiation phase is described by joint stochastic dynamics accounting for cell shape transitions (from a flattened to a cuboidal shape) and proliferation of reshaped cells. We have then derived the mean time elapsed before all cells have changed shapes and the corresponding increment in the total cell number, which is fitted to experimental data retrieved from primordial follicles (single layered follicle with only flattened cells) and primary follicles (single layered follicles with only cuboidal cells).

7.1.11. Newton-Krylov method for computing the cyclic steady states of evolution problems in non-linear mechanics

Participants: Ustim Khristenko, Patrick Le Tallec [correspondant].

This work is focused on the Newton-Krylov technique for computing the steady cyclic states of evolution problems in nonlinear mechanics with space-time periodicity conditions. This kind of problems can be faced, for instance, in the modeling of a rolling tire with a periodic tread pattern, where the cyclic state satisfies “rolling” periodicity condition, including shifts both in time and space. The Newton-Krylov method is a combination of a Newton nonlinear solver with a Krylov linear solver, looking for the initial state, which provides the space-time periodic solution. The convergence of the Krylov iterations is proved to hold in presence of an adequate preconditioner. After preconditioning, the Newton-Krylov method can be also considered as an observer-controller method, correcting the transient solution of the initial value problem after each period. Using information stored while computing the residual, the Krylov solver computation time becomes negligible with respect to the residual computation time. The method has been analyzed and tested on academic applications and compared with the standard evolution (fixed point) method. Finally, it has been implemented into the Michelin industrial code, applied to a full 3D rolling tire model.

7.1.12. Delayed feedback control method for computing the cyclic steady states of evolution problems

Participants: Ustim Khristenko, Patrick Le Tallec [correspondant].

This work is focused on fast techniques for computing the cyclic steady states of evolution problems in non-linear mechanics with space–time periodicity conditions. In industrial applications, in order to avoid the inversion of very large matrices, such a cyclic solution is usually computed as an asymptotic limit of the associated initial value problem with arbitrary initial data. However, when the relaxation time is high, convergence to the limit cycle can be very slow. In such cases nonetheless, one is not interested in the transient solution, but only in a fast access to the limit cycle. Thus, in this work we modify the problem, introducing the time-delayed feedback control, which is widely used for stabilization of unstable periodic orbits. In our framework it is applied to an initially stable system in order to accelerate its convergence to the limit cycle. Moreover, the control term, based on the space–time periodicity error, includes both shifts in time and in space. Our main result is the optimal form of the control term for a very general class of linear evolution problems, providing the fastest convergence to the cyclic solution, which has been further extended and studied in the non-linear case. Efficiency of the method increases with the problem's relaxation time. The method has been tested using academic applications and compared to the non-controlled asymptotic convergence as well as to the Newton–Krylov shooting algorithm. Finally, the method has been implemented into the Michelin industrial code, applied to a full 3D rolling tyre model.

7.2. Numerical Methods

7.2.1. Numerical analysis for an energy-preserving total discretization of a poromechanics model with inf-sup stability

Participants: Dominique Chapelle [correspondant], Philippe Moireau.

We consider a previously proposed general nonlinear poromechanical formulation, and we derive a linearized version of this model. For this linearized model, we obtain an existence result and we propose a complete discretization strategy – in time and space – with a special concern for issues associated with incompressible or nearly-incompressible behavior. We provide a detailed mathematical analysis of this strategy, the main result being an error estimate uniform with respect to the compressibility parameter. We then illustrate our approach with detailed simulation results and we numerically investigate the importance of the assumptions made in the analysis, including the fulfillment of specific inf-sup conditions. This work is accepted for publication in Acta Mathematicae Applicatae Sinica.

7.2.2. Efficient estimation of personalized biventricular mechanical function employing gradient-based optimization

Participant: Martin Genet [correspondant].

Individually personalized computational models of heart mechanics can be used to estimate important physiological and clinically-relevant quantities that are difficult, if not impossible, to directly measure in the beating heart. Here, we present a novel and efficient framework for creating patient-specific biventricular models using a gradient-based data assimilation method for evaluating regional myocardial contractility and estimating myofiber stress. These simulations can be performed on a regular laptop in less than 2 hours and produce excellent fit between measured and simulated volume and strain data through the entire cardiac cycle. By applying the framework using data obtained from 3 healthy human biventricles, we extracted clinically important quantities as well as explored the role of fiber angles on heart function. Our results show that steep fiber angles at the endocardium and epicardium are required to produce simulated motion compatible with measured strain and volume data. We also find that the contraction and subsequent systolic stresses in the right ventricle are significantly lower than that in the left ventricle. Variability of the estimated quantities with respect to both patient data and modeling choices are also found to be low. Because of its high efficiency, this framework may be applicable to modeling of patient specific cardiac mechanics for diagnostic purposes.

7.2.3. Equilibrated warping: Finite element image registration with finite strain equilibrium gap regularization

Participant: Martin Genet [correspondant].

In this work, we propose a novel continuum finite strain formulation of the equilibrium gap regularization for image registration. The equilibrium gap regularization essentially penalizes any deviation from the solution of a hyperelastic body in equilibrium with arbitrary loads prescribed at the boundary. It thus represents a regularization with strong mechanical basis, especially suited for cardiac image analysis. We describe the consistent linearization and discretization of the regularized image registration problem, in the framework of the finite elements method. The method is implemented using FEniCS & VTK, and distributed as a freely available python library. We show that the equilibrated warping method is effective and robust: regularization strength and image noise have minimal impact on motion tracking, especially when compared to strain-based regularization methods such as hyperelastic warping. We also show that equilibrated warping is able to extract main deformation features on both tagged and untagged cardiac magnetic resonance images.

7.2.4. Thermodynamic properties of muscle contraction models and associated discrete-time principles

Participants: François Kimmig [correspondant], Dominique Chapelle, Philippe Moireau.

Considering a large class of muscle contraction models accounting for actin-myosin interaction, we present a mathematical setting in which solution properties can be established, including fundamental thermodynamic balances. Moreover, we propose a complete discretization strategy for which we are also able to obtain discrete versions of the thermodynamic balances and other properties. Our major objective is to show how the thermodynamics of such models can be tracked after discretization, including when they are coupled to a macroscopic muscle formulation in the realm of continuum mechanics. Our approach allows to carefully identify the sources of energy and entropy in the system, and to follow them up to the numerical applications.

7.2.5. A conservative penalisation strategy for the semi-implicit time discretisation of the incompressible elastodynamics equation

Participants: Federica Caforio [correspondant], Sébastien Imperiale.

The principal aim of this work is to provide an adapted numerical scheme for the approximation of elastic wave propagation in incompressible solids. We rely on high-order conforming finite element with mass lumping for space discretisation and implicit/explicit, second-order, energy-preserving time discretisation. The time step restriction only depends on the shear wave velocity and at each time step a Poisson problem must be solved to account for the incompressibility constraint that is imposed by penalisation techniques.

7.2.6. High-order discrete Fourier transform for the solution of the poisson equation

Participants: Federica Caforio [correspondant], Sébastien Imperiale.

The aim of this work is to propose a novel, fast, matrix-free solver for the Poisson problem discretised with High-Order Spectral Element Methods (HO-SEM). This method is based on the use of the Discrete Fourier Transform to reduce the problem to the inversion of the symbol of the operator in frequency space. The solver proposed is endowed with several properties. First, it preserves the efficiency of standard FFT algorithm; then, the matrix storage is minimised; a pseudo- explicit Singular Value Decomposition (SVD) is used for the inversion of the symbols; finally, it can be easily extended to multiple dimensions and non-periodic boundary conditions. In particular, due to the underlying HO-SEM discretisation, the multi-dimensional symbol of the operator can be efficiently computed from the one-dimensional symbol by tensorisation.

7.3. Inverse Problems

7.3.1. Analysis of an observer strategy for initial state reconstruction of wave-like systems in unbounded domain

Participants: Sébastien Imperiale, Philippe Moireau [correspondant].

We are interested in reconstructing the initial condition of a wave equation in an unbounded domain configuration from measurements available in time on a subdomain. To solve this problem, we adopt an iterative strategy of reconstruction based on observers and time reversal adjoint formulations. We prove the convergence of our reconstruction algorithm with perfect measurements and its robustness to noise. Moreover, we develop a complete strategy to practically solve this problem on a bounded domain using artificial transparent boundary conditions to account for the exterior domain. Our work then demonstrates that the consistency error introduced by the use of approximate transparent boundary conditions is compensated by the stabilization properties obtained from the use of the available measurements, hence allowing to still be able to reconstruct the unknown initial condition. This work is accepted with minor revision for publication in COCV.

7.4. Experimental Assessments

7.4.1. Mathematical modeling and experimental validation of flow through aortic valve

Participant: Radomir Chabiniok [correspondant].

Assessment of the valvular diseases by phase-contrast magnetic resonance imaging (MRI) has known limits due to limited spatial-temporal resolution of MRI and artifacts intrinsic to the method. This problem is addressed by the collaborative work of the Institute for Clinical and Experimental Medicine in Prague (IKEM, participants J. Tintera and R. Galabov) and the mathematical modeling group at the Czech Technical University in Prague (CTU, participants P. Paus, R. Fucik), additionally with the combined clinical cardiovascular MRI & modeling expertise of R. Chabiniok (Inria). A flow phantom was constructed at IKEM and used to perform an extensive experimental study targeted to capture the phenomena in valvular stenosis / regurgitation. The Mathematical modeling group at CTU then performed flow simulations by using the techniques of Lattice-Boltzmann method and their high-performance computing GPU implementations. This work is shedding light into possibly significant factors limiting the direct interpretation of PC MRI and opening the way into interaction of PC MRI data with mathematical model as a “smart filtering” of flow exam.

7.4.2. Skin multiscale mechanics

Participant: Jean-Marc Allain [correspondant].

Skin is a complex, multi-layered organ, with important functions in the protection of the body. The dermis provides structural support to the epidermal barrier, and thus has attracted a large number of mechanical studies. As the dermis is made of a mixture of stiff fibres embedded in a soft non-fibrillar matrix, it is classically considered that its mechanical response is based on an initial alignment of the fibres, followed by the stretching of the aligned fibres. Using a recently developed set-up combining multiphoton microscopy with mechanical assay, we imaged the fibres network evolution during dermis stretching. These observations, combined with a wide set of mechanical tests, allowed us to challenge the classical microstructural interpretation of the mechanical properties of the dermis: we observed a continuous alignment of the collagen fibres along the stretching. All our results can be explained if each fibre contributes by a given stress to the global response. This plastic response is likely due to inner sliding inside each fibre. The non-linear mechanical response is due to structural effects of the fibres network in interaction with the surrounding non-linear matrix. This multiscale interpretation explains our results on genetically-modified mice with a simple alteration of the dermis microstructure. Our previous works have led us to write this year one review article and one chapter of book on multiscale skin biomechanics, to be published next year.

7.4.3. Cornea biomechanics

Participants: Chloé Giraudet, Jean-Marc Allain [correspondant], Patrick Le Tallec.

Cornea is the outer part of the eye. It is a curved transparent organ, which gives 2/3 of the focalisation capacity of the eye. Microscopically, it is made mostly of collagen fibres (as skin) organised in cristal-like lamellae of few micrometers of height and a hundred micrometers in length and width. The lamellae are piled up in a plywood structure, creating a millimetre-thick tissue. Between the lamellae, some cells are present to repair and regenerate the tissue. However, this simple image of the organisation of the collagen is in fact too simple and a more complex heterogeneous organisation has been recently described, with in particular some striae (called the Vogt striae). In C. Giraudet's PhD, we propose to explore the link between microstructure organisation of the collagen in the cornea and mechanical properties. To do so, we will first start by proposing an extension of classical mechanical models (such as Holzapfel's law or others) to the specific case of the cornea. This model will be tested against mechanical assays made under advanced optical microscopes to test first if the model can correctly predict the strain field in volume, and secondly if it correctly predicts the evolution of the lamellae microstructure at different stretch levels. At the moment, we have developed the tools to mechanically test the cornea, but also to build a finite element simulation using the real shape of the cornea we are looking at.

7.4.4. Multiscale properties of the passive cardiac muscle

Participants: Nicole Tueni, Jean-Marc Allain [correspondant], Martin Genet.

We are interested in understanding the effect of the remodelling of cardiac tissues after a disease. Cardiac tissues are mostly made of muscle cells. They can remodel themselves in response to an alteration of their normal response by modifying the sizes and the geometries of the cells in the tissue. Nowadays, we are able to describe the active and passive response of a cardiac tissue, assuming we know the main orientation of the cells inside. However, we do not have models which include explicitly the microstructural cellular organization. Such complex models will be strongly beneficial to determine the consequences of local alterations of the muscle behaviour. In N. Tueni's PhD, we are investigating this multi-scale relationship. To do so, we are imaging the organization at the microscale, while measuring the mechanical properties. These results will be the building block to test and develop mechanical models of the cardiac tissues.

7.4.5. Mechano-perception at the cell level

Participant: Jean-Marc Allain [correspondant].

All cells and organisms experience mechanical forces. Plants along their life are submitted from their environment to long lasting sustained stresses and to recurrent cyclic loading/unloading due to wind or water stream. Mechanical stimulations induce short-term cellular responses, leading to mechanoresponsive gene activation followed by long-term responses permitting structural reinforcement at the whole-plant level. We show that the Mechanosensitive channel Small conductance-Like 10 (MSL10) contributes to oscillation perception at the cell level. This channel responds to pulsed membrane stretching with rapid activation and relaxation. Furthermore, oscillatory pressure stimulation modulates its activity, with increased open probability upon oscillatory than during sustained stimulation. Combined with the adequate localization of MSL10 in plant shoot and leaves, its ability to detect oscillatory deformation at the molecular-scale is relevant for a function of this channel in oscillatory perception in plant.

7.5. Clinical Applications

7.5.1. Exploring kinetic energy as a new marker of cardiac function in the single ventricle circulation

Participants: Radomir Chabiniok [correspondant], Tarique Hussain [ToFMOD].

Ventricular volumetric ejection fraction (VV EF) is often normal in patients with single ventricle circulations despite them experiencing symptoms related to circulatory failure. We sought to determine if kinetic energy (KE) could be a better marker of ventricular performance. KE was prospectively quantified using four-dimensional flow MRI in 41 patients with a single ventricle circulation (aged 0.5-28 yr) and compared with 43 healthy volunteers (aged 1.5-62 yr) and 14 patients with left ventricular (LV) dysfunction (aged 28-79 yr). Intraventricular end-diastolic blood was tracked through systole and divided into ejected and residual blood

components. Two ejection fraction (EF) metrics were devised based on the KE of the ejected component over the total of both the ejected and residual components using 1) instantaneous peak KE to assess KE EF or 2) summating individual peak particle energy (PE) to assess PE EF. KE metrics are markers of healthy cardiac function. PE EF may be useful in grading dysfunction. The work was published in Journal of Applied Physiology (J Appl Physiol 125: 889-900, 2018), [29]. The work represents a collaboration with King's College London (J. Wong, K. Pushparajah, R. Razavi) and with UT Southwestern Dallas (T. Hussain, the member of Inria Associate team ToFMOD).

7.5.2. Using a patient-specific biomechanical cardiovascular model to estimate continuously Left Ventricular Pressure Volume Loop: A proof of concept study

Participants: Arthur Le Gall, Fabrice Vallée, Philippe Moireau, Dominique Chapelle, Radomir Chabiniok [correspondant].

Pressure Volume loops (PV loops) could contribute to optimise haemodynamic managements. While the invasiveness of PV loop acquisition prevents it from being routinely used during surgery, cardiovascular modelling could represent an alternative. Using continuous recording of aortic pressure and flow, we aimed at calibrating a patient-specific model and at interpreting the simulated PV loop during administration of noradrenaline (NOR). This study is the first to allow continuous PV loop monitoring during general anaesthesia. The work was pursued in the collaboration with Lariboisiere Hospital in Paris (A. Le Gall and F. Vallée, both dually affiliated at Inria and at AP-HP, "poste d'accueil").

7.5.3. Augmenting the interpretation of cardiac MRI by biomechanical modeling: Application to Tetralogy of Fallot

Participants: Marija Gusseva, Philippe Moireau, Tarique Hussain [ToFMod], Gerald Greil [ToFMod], Animesh Tandon [ToFMOD], Dominique Chapelle, Radomir Chabiniok [correspondant].

The particularity of the mixed-valve disease – pulmonary regurgitation often combined with a stenosis – requested to extend our model-representation of the valve to allow the backflow during the heart relaxation. For each patient, biomechanical models of their left and right ventricles (LV, RV) were set up. These models then allowed to investigate the functional properties of dilated right ventricles (RV) with incompetent pulmonary valves and of the pulmonary circulation, properties not directly visible in the clinical data. In particular, immediately after deploying the new valve we could observe a decrease of RV contractility by 15%, while the output of RV into pulmonary circulation has increased. This suggests a positive immediate outcome, as the energy needs for function of RV will decrease. The higher cardiac output also suggests an increase of the filling of LV (preload), which could contribute to an improvement of LV function. The model also uncovered a decrease of resistance in the pulmonary circulation. This very preliminary result might suggest some pathophysiological changes, which are typically not thought of in clinics.

This work is pursued under the objectives of the Inria Associate Team ToFMod (T. Hussain, G. Greil, A. Tandon are members of ToFMOD and affiliated at UT Southwestern Medical Center Dallas, USA), the work was accepted for a conference of International Society of Magnetic Resonance in Medicine 2018 and is in preparation for publication.

7.5.4. Longitudinal study of ventricular remodeling and reverse-remodeling in tetralogy of Fallot patients using CMR coupled with biomechanical modelling

Participants: Marija Gusseva, Tarique Hussain [ToFMod], Animesh Tandon [ToFMod], Dominique Chapelle, Radomir Chabiniok [correspondant].

A preliminary study was performed with the patient-specific models for RV and pulmonary circulations set up from three datasets including the 6-months post-PVR follow-up exams obtained in late 2018 from King's College London. Clinical data analyses show a positive result of pulmonary replacement therapy (PVR) and normalization of the RV size, i.e. the so-called reverse-remodeling of the pathologically dilated RV, in all three patients. The biomechanical modeling suggests a further reduction of the active stress needed to be developed by RV (contractility), i.e. a long-term unloading of the previously overloaded ventricle.

This work is pursued under the objectives of the Inria Associate Team ToFMOD (T. Hussain, A. Tandon are members of ToFMOD and affiliated at UT Southwestern Medical Center Dallas, USA). The main partner in this task is King's College London ("Other Participant" in the ToFMOD Associate team, K. Pushparajah, M. Jones, S. Qureshi) who provided unique clinical data of patients with a long-term follow-up after PVR. The work was submitted to the conference of International Society of Magnetic Resonance in Medicine 2019 – the world-wide major scientific & clinical event when MR data are involved.

7.5.5. Optical flow-based non-rigid registration of cardiac MR images

Participant: Radomir Chabiniok [correspondant].

This work deals with non-rigid registration of cardiac MR images, particularly the MOLLI sequences. MOLLI sequence consists of 11 heart images acquired over 17 cardiac cycles. The images of MOLLI sequence are used for pixel-wise estimation of T1 relaxation time values. In this case the registration is necessary to correct the deformations that occur because of the patient's imperfect breath-holding during the acquisition. The main characteristics of the MOLLI sequence is the evolving intensity of the tissues and also large variations of the image contrast. This characteristics of the sequence make the registration process challenging and make the use of intensity-based registration method impossible. For this purpose, we propose a method based on optical flow, using information obtained by image segmentation. The first step of the registration process, is segmentation of the regions of interest, using the level set method. The segmented objects are represented by distance maps. The transformation between original images is determined by applying the optical flow method to the distance maps. The registration process is independent of the varying intensity and takes into account only the shape and position of the segmented areas, such as the myocardium or the ventricles. The implementation of the proposed method is described and the method is tested on several MOLLI sequences. The results are compared to the results of methods based on maximisation of mutual information, and the proposed method performs better for the images with significant changes in intensity.

The work represents a collaborative project with Institute for Clinical and Experimental Medicine (IKEM) Prague (J. Tintera) and with Czech Technical University in Prague (K. Solovska, T. Oberhuber).

7.5.6. Quantification of biventricular strains in heart failure with preserved ejection fraction using hyperelastic warping method

Participant: Martin Genet.

Heart failure (HF) imposes a major global health care burden on society and suffering on the individual. About 50% of HF patients have preserved ejection fraction (HFpEF). More intricate and comprehensive measurement-focused imaging of multiple strain components may aid in the diagnosis and elucidation of this disease. Here, we describe the development of a semi-automated hyperelastic warping method for rapid comprehensive assessment of biventricular circumferential, longitudinal, and radial strains that is physiological meaningful and reproducible. We recruited and performed cardiac magnetic resonance (CMR) imaging on 30 subjects [10 HFpEF, 10 HF with reduced ejection fraction patients (HFrEF) and 10 healthy controls]. In each subject, a three-dimensional heart model including left ventricle (LV), right ventricle (RV), and septum was reconstructed from CMR images. The hyperelastic warping method was used to reference the segmented model with the target images and biventricular circumferential, longitudinal, and radial strain–time curves were obtained. The peak systolic strains are then measured and analyzed in this study. The ROC analysis indicated LV peak systolic circumferential strain to be the most sensitive marker for differentiating HFpEF from healthy controls. Our results suggest that the hyperelastic warping method with the CMR-derived strains may reveal subtle impairment in HF biventricular mechanics, in particular despite a "normal" ventricular ejection fraction in HFpEF.

7.5.7. Extra corporeal life support for cardiac arrest patients with post-cardiac arrest syndrome: the ECCAR study

Participant: Arthur Le Gall.

Purpose: Post-Cardiac Arrest Shock (PCAS) occurring after resuscitated cardiac arrest (CA), is a main cause of early death. Extra-Corporeal Life Support (ECLS) could be useful pending recovery of myocardial failure. We aimed to describe our PCAS population, and factors associated with ECLS initiation. Materials and Methods: This analysis included 924 patients admitted in two intensive care units (ICU) between 2005 and 2014 for CA and PCAS, and, of those patients, 43 patients for whom an ECLS was initiated. Neurological and ECLS-related outcomes were gathered retrospectively. Conclusions: ECLS, as a salvage therapy for PCAS, could represent an acceptable alternative for highly selected patients.

7.5.8. Evaluation of cardiac output variations with the peripheral pulse pressure to mean arterial pressure ratio.

Participant: Arthur Le Gall.

Cardiac output (CO) optimisation during surgery reduces post-operative morbidity. Various methods based on pulse pressure analysis have been developed to overcome difficulties to measure accurate CO variations in standard anaesthetic settings. Several of these methods include, among other parameters, the ratio of pulse pressure to mean arterial pressure (PP/MAP). The aim of this study was to evaluate whether the ratio of radial pulse pressure to mean arterial pressure (ΔPPrad/MAP) could track CO variations (Δ CO) induced by various therapeutic interventions such as fluid infusions and vasopressors boluses [phenylephrine (PE), norepinephrine (NA) or ephedrine (EP)] in the operating room. Trans-oesophageal Doppler signal and pressure waveforms were recorded in patients undergoing neurosurgery. CO and PPrad/MAP were recorded before and after fluid challenges, PE, NA and EP bolus infusions as medically required during their anaesthesia. ΔPPrad/MAP tracked ΔCO variations during PE and NA vasopressor challenges. However, after positive fluid challenge or EP boluses, ΔPPrad/MAP was not as performant to track ΔCO which could make the use of this ratio difficult in current clinical practice.

7.5.9. Perioperative management of patients with coronary artery disease undergoing non-cardiac surgery: Summary from the French Society of Anaesthesia and Intensive Care Medicine 2017 convention

Participant: Arthur Le Gall.

This review summarises the specific stakes of preoperative, intraoperative, and postoperative periods of patients with coronary artery disease undergoing non-cardiac surgery. All practitioners involved in the perioperative management of such high cardiac risk patients should be aware of the modern concepts expected to decrease major adverse cardiac events and improve short- and long-term outcomes. A multidisciplinary approach via a functional heart team including anaesthesiologists, cardiologists and surgeons must be encouraged. Rational and algorithm-guided management of those patients should be known and implemented from preoperative to postoperative period.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

- Contract with start-up 3c-industry for quantitative imaging of their printed product (1.5keuros)
- Contract with L'Oreal for the development of an experimental set-up (29.8keuros)

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. Other funding

IPM-MS project (for Imagerie Polarimétrique de Mueller pour la réalisation d'un système original de caractérisation des propriétés mécaniques des Matériaux Structurés). 50k€ funded by the LABEX Lasips. This project, which involves the LPICM laboratory (Ecole Polytechnique, CNRS), the LMS (Ecole Polytechnique, CNRS, Mines ParisTech) and the Centre des Matériaux (Mines ParisTech), aims at developing an optical tool to study the link between the mechanical properties of a material and its hierarchical organization. Despite the development of new methods to observe the microstructure, one of the limitations is the number of observations that can be obtained on a given sample in a realistic experimental time. To overcome this difficulty, we are planning to use the Mueller polarimetry to obtain at a fast rate (a few frames per second, compared to a few frames per half-hour) relevant information on the local anisotropy of biological (heart, skin) and composite (short fibers composite) samples.

G. Bureau, software engineer in the team, was funded by an Inria Reo industrial contract with Kephalios, a startup working on innovative artificial valves devices.

9.2. European Initiatives

9.2.1. Collaborations with Major European Organizations

Partner 1: Division of Biomedical Engineering & Imaging Sciences (BMEIS), St Thomas' Hospital, King's College London, UK

clinical-modeling topics mostly encompassing congenital heart diseases (BMEIS acts as "Other participant" in the Inria Associate team ToFMOD, and R. Chabiniok additionally performs clinical MRI exams at St Thomas' hospital 0.5 days / week.

Partner 2: Department of Mathematics, Faculty of Nuclear Sciences and Physical Engineering, Czech Technical University in Prague, Czech Republic

model-constrained image registrations, trans-valvular flow in pathological valves.

Partner 3: Institute for Clinical and Experimental Medicine in Prague

Cardiovascular MRI

9.3. International Initiatives

9.3.1. Inria Associate Teams Not Involved in an Inria International Labs

9.3.1.1. ToFMod

Title: Cardiac Biomechanical Modeling of Chronic Right Ventricular Loading

International Partner (Institution - Laboratory - Researcher):

UT Southwestern Medical Center, Dallas,Texas (United States), Mohammad Tarique Hussain

Start year: 2018

See also: https://m3disim.saclay.inria.fr/associated-team/

This collaboration aims at addressing a crucial issue in cardiology of congenital heart diseases, namely, the optimal timing of pulmonary valve replacement (PVR) in patients with surgically repaired tetralogy of Fallot (ToF) prone to chronic pulmonary regurgitation or right ventricular outflow tract stenosis. Our strategy consists in exploiting the predictive power of biomechanical modeling to shed light in the decision process. We will start by a detailed proof-of-concept study, based on datasets that will be acquired in patients indicated for percutaneous PVR, prior to the procedure, and in the follow-up at 3- and 12-months post-PVR. These datasets will be first used to calibrate the Inria M3DISIM patient-specific heart model simulating a cardiac cycle (at each follow-up time point) to access the myocardial properties – namely, the active contractility and passive stiffness. The instantaneous tissue properties will be statistically analyzed and compared with the level of reverse remodeling – i.e. the positive outcome of PVR. Secondly, the data at each time point will be used to calibrate and further develop the models of long-term tissue remodeling created by the M3DISIM researchers. It is only by combining such invaluable longitudinal data with biomechanical modeling expertise that progress can be achieved in the above objective, indeed.

9.4. International Research Visitors

9.4.1. Invited researchers

- T. Hussain, A. Tandon (Senior researchers at UTSW Medical Center Dallas): joint work in the scope of the Inria Associate team ToFMOD
- F. Regazzoni (3rd year PhD student from MOX, Milan, Italy): From Sept 2018, joint work on model learning and data assimilation coupling.

9.4.2. Internships

- K. Solovska (Czech Technical University and IKEM Prague): 1-30 August 2018, collaborative work with M. Genet and R. Chabiniok in the scope of the Inria Associate team ToFMOD

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific events organisation

10.1.1.1. General chair, scientific chair

R. Chabiniok, Organization of "MRI & Modelling workshop" related to the Inria Associate Team ToFMOD at Inria Paris-Saclay where hosting 14 international speakers from France, UK, USA, Switzerland, Chile, Czech Republic from the domains of MRI, cardiology and modelling (June 21)

R. Chabiniok, Co-chair of the section"Groupe de recherche en imagerie cardiaque" at French Congress of Radiology (Journées Francophones de Radiologie, JFR), Paris (October 12-15)

D. Chapelle, Co-chair of organising committee for VPH2020 Conference (Paris, August 2020)

D. Chapelle, Session co-chair in VPH18 Conference

M. Genet, Session co-chair at the 8th World Congress on Biomechanics, Dublin (July)

F. Clément, Session *Methodological developments for Systems Biology (A)*, ICSB 2018

P. Moireau, Session co-chair in VPH18 Conference

10.1.1.2. Member of organizing committees

M. Genet, Co-organizer of the Paris-Saclay University Biomechanics Seminar Series

A. Le Gall, Member of the organizing committee of WEARe 2018

A. Le Gall, Member of the organizing committee of the youth session of the national congress of the french society anesthesiology, intensive care, and peri-operative medicine

A. Le Gall, Member of the organizing committee of the youth days of teaching of the national congress of the french society anesthesiology, intensive care, and peri-operative medicine

P. Moireau, Member of the a organizing committee of the VPH2020 conference (Paris, August 2020)

P. Moireau, Member of the organizing committee of the Inria-Saclay teams (Poems-M3disim-Defi) scientific computing seminar

10.1.2. Scientific events selection

10.1.2.1. Reviewer

F. Clément *American Control Conference* 2019

P. Moireau, reviewer for VPH18

10.1.3. Journal

10.1.3.1. Member of editorial boards

D. Chapelle, Member of the editorial board of journal *Computers & Structures*

D. Chapelle, Member of the editorial board of journal *ESAIM: M2AN*

10.1.3.2. Reviewer - Reviewing activities

J.M. Allain, reviewer for "Acta Biomateriala", "Journal of the Mechanical Behavior of Biomedical Materials" and "Journal of Applied Mathematics and Mechanics"

R. Chabiniok, reviewer for "Biomechanics and Modeling in Mechanobiology", "Transations Of Society For Modeling And Simulations" and "Journal of Imaging"

D. Chapelle, reviewer for "Biomechanics and Modeling in Mechanobiology", "Computers & Structures", "International Journal for Numerical Methods in Biomedical Engineering", "Meccanica"

F. Clément, Reviewer for "Journal of Mathematical Biology", "PLOS Computational Biology"and "Endocrinology"

M. Genet, Reviewer for "Biomechanics and Modeling in Mechanobiology"

S. Imperiale, reviewer for "Journal of Mathematical Analysis", "Journal of Computational Acoustics", "SIAM Journal on Scientific Computing" and "SIAM Journal on Numerical Analysis"

P. Moireau, reviewer for "AMSES" and "IEEE Control Systems Letters"

F. Robin, Reviewer for "Journal of Mathematical Biology"

10.1.4. Invited talks

J. M. Allain, invited seminar at Century institut, France.

F. Caforio, seminar tours at the School of Biomedical Engineering and Imaging Sciences, King's College London, UK, Simula Research Laboratory, Oslo, Norway and KFU university, Graz, Austria

R. Chabiniok, seminar tours at Institute for Clinical and Experimental Medicine, Mathematical Institute of Charles University and Children's Heart Center at Motol University Hospital, Prague, Czech Republic

R. Chabiniok, invited lectures at Journées Francophones de Radiologie diagnostique et interventionnellle), France and at International Symposium on Modeling, Simulation and Optimization of the Cardiovascular System, Lukasklause Magdeburg, Germany

D. Chapelle, invited seminars at Politecnico di Milano (MOX), and for Dassault-Systèmes' Living Heart Project

M. Genet, invited seminar at the School of Biomedical Engineering and Imaging Sciences, King's College London, UK

S. Imperiale, invited lecture at ICERM, Brown University, USA

P. Le Tallec, seminar tours at University of Michigan, Michigan State University, Notre Dame University and University of Wisconsin at Madison, USA

P. Le Tallec, invited lecture at Charif University, Iran

P. Moireau, invited lectures at VPH18, CEMRACS2018 Luminy and FoMICS Summer School

P. Moireau, invited seminars at MOX, Politecnico di Milano, Italy and LMT, ENS Cachan, France

F. Robin invited seminar at Institut Élie Cartan de Lorraine, Nancy

10.1.5. Leadership within the scientific community

D. Chapelle, Member of the board of directors of the VPH Institute

D. Chapelle, Member of the steering committee of the BioMedical Engineering Institute coordinated by Ecole Polytechnique

F. Clément, member of the direction and scientific board of GdR REPRO

A. Le Gall, Chair of youth committee of SFAR (French Society of Anesthesia and Reanimation)

P. Le Tallec, Director of LMS (Solid Mechanics Laboratory) Ecole Polytechnique

P. Le Tallec, President of the Mechanics department at University Paris-Saclay

P. Moireau, Member of the steering committee of Department of Mathematics of Université Paris Saclay and Jacques Hadamard Foundation

10.1.6. Scientific expertise

R. Chabiniok, Honorary medical consultant at Saint-Thomas hospital (King's College London)

R. Chabiniok, scientific consultant for the joint project of Institute for Clinical and Experimental Medicine in Prague (IKEM) and Czech Technical University

F. Clément, Reviewer for ANR

F. Clément, expert of the BCDE (Cell Biology, Development and Evolution) ITMO (Multi OrganizationThematic Institute) of the French National Alliance for Life and Health Sciences Aviesan.

F. Clément, expert for the INRA scientific prospective on predictive approaches in biology and ecology

S. Imperiale, Consultant for CEA

P. Le Tallec, Consultant for CEA

P. Le Tallec, Consultant for Michelin

P. Moireau, Reviewer for ANR

10.1.7. Research administration

J.M. Allain, Scientific Advisory Board, chair BioMecAM

R. Chabiniok, in charge of the objectives of Inria Associate team ToFMOD (with UT Southwestern Medical center Dallas, USA)

R. Chabiniok, in charge of coordination of clinical-modeling projects in the MΞDISIM team, Inria Saclay

D. Chapelle, Head of Science of Inria Saclay-Ile-de-France, and member of the Inria Evaluation Committee

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Bachelor: J.M. Allain, "Introductory Projects in Physics", 10h, (L1), École Polytechnique, France

Bachelor: J.M. Allain, "Classical Mechanics", 32h, (L2), École Polytechnique, France

Bachelor: F. Caforio,"PEIP1 S2 M2 – Mathematical analysis in two and three dimensions, linear algebra in Rn", 22h, (L1), Polytech Paris-Sud, France

Bachelor: F. Caforio,"Math 255 – Differential calculus for physics (mathematical analysis in two and three dimensions)", 42h, (L2), Université Paris-Sud, France

Bachelor: M. Genet, "Continuum Mechanics I", 40h, (L3), École Polytechnique, France

Bachelor: M. Genet, "Modeling and Simulation in Industrial Mechanics", 36h, (L3), École Polytechnique, France

Bachelor: S. Imperiale, "MA102 – Analyse pour les EDP", 24h, (L3), ENSTA ParisTech, France

Bachelor: F. Kimmig, "Modeling and simulation in industrial mechanics", 32h, (L3), École Polytechnique, France

Bachelor: P. Le Tallec, "MEC 431 – Mécanique des Milieux Continus 2", (L3), École Polytechnique, France

Bachelor: P. Le Tallec, "Continuum mechanics", 32h, (L3), Shanghai ParisTech, China

Bachelor: P. Moireau, "MAP 431 – Analyse variationnelle", 40 h, (L3), Ecole Polytechnique, France

Bachelor: P. Moireau, “MODAL 472 – Expérimentation numérique pour les EDP”, 40 h, (L3), Ecole Polytechnique, France

Bachelor: F. Robin, “General mathematics”, 13h, (L1), Sorbonne Universités, France

Bachelor: F. Robin, “Probability and differentiel equation”, 22h (L2), Sorbonne Universités, France

Bachelor: F. Robin, “Power series and integral with parameters”, 20, (L2), Sorbonne Universités, France

Master: J.M. Allain, “Projects in Mechanics”, 6h, (M1), École Polytechnique, France

Master: J.M. Allain, “Cellular motility”, 32h, (M2), École Polytechnique, France

Master: J.M. Allain, “Supervision of the Experimental Center”, 45h, (M1), École Polytechnique, France

Master: D. Chapelle: “Biomechanical Modeling of Active Tissues”, 33h, (M2), Université Paris-Saclay, France

Master: M. Genet, “Plasticity and Fracture”, 18h, (M1), École Polytechnique, France

Master: S. Imperiale, “MA2610 Calcul Scientifique – Mécanique des solides”, 4h, (M1), Centrale/Supelec, France

Master: S. Imperiale, “Simnum – Programmation C++”, 18h, (M1), ENSTA ParisTech, France

Master: P. Le Tallec, “Nuclear Energy on Continuum Mechanics”,15h, (M2), INSTN, France

Master: P. Moireau, “Biomechanical Modeling of Active Tissues”, 12h, (M2), Université Paris-Saclay, France

Master: P. Moireau, “Méthodes et problèmes inverses en dynamique des populations”, 12h, (M2), UPMC, France

Master: P. Moireau, “AMS305 – Complétion de données et identification dans les problèmes gouvernés par des équations aux dérivées partielles”, 16h, (M2), Université Paris-Saclay, France

10.2.2. Supervision

PhD in progress: E. Berberoglu (ETHZ, Switzerland), “Image Guided Computational Cardiac Mechanics”, started February 2017, supervisors: M. Genet and S. Kozerke (ETHZ, Switzerland)

PhD in progress: F. Caforio, “Modélisation mathématique et numérique de la propagation d’ondes élastique dans le coeur”, started: Nov. 2015, supervisors: D. Chapelle and S. Imperiale

PhD in progress: C. Della Valle, “Modélisation et estimation des dynamiques d’assemblage de proteines”, supervisors: M. Doumic and P. Moireau, Université Paris Sciences et Lettres,

PhD in progress: C. Giraudet, “Cornea biomechanics”, started 10/2018; supervisors: J.M. Allain and P. Le Tallec

PhD in progress: M. Gusseva, “Cardiac Biomechanical Modeling for Chronic Ventricular Loading”, supervisors: R. Chabiniok, D. Chapelle, T. Hussain, Université Paris-Saclay, started in December 2017

PhD: U. Khristenko, Université Paris-Saclay, P. Le Tallec, defended Jan 17th

PhD in progress: F. Kimmig, “Multi-scale modeling of muscle contraction – From stochastic dynamics of molecular motors to continuum mechanics, in interaction with experimental assays”, supervisors: M. Caruel and D. Chapelle, Université Paris-Saclay, started in September 2016

PhD in progress: A. Le Gall, “Cardiac modelling for monitoring purposes during general anaesthesia and at Intensive Care Unit”, supervisors: R. Chabiniok, D. Chapelle, E. Gayat, Université Paris-Saclay, started in November 2016

PhD in progress: C. Patte, “Lung multiscale poromechanical modeling: from breathing to pulmonary fibrosis-induced chronic remodeling”, started November 2017, supervisors: M. Genet and D. Chapelle

PhD in progress: F. Robin “Multiscale modeling of the morphodynamics in ovarian follicles”, started October 2016, supervisors: F. Clément & Romain Yvinec [INRA]

PhD in progress: N. Tueni, “Multiscale modeling of cardiac mechanics”, started January 2018, supervisors: M. Genet and J.-M. Allain

PhD in progress: F. Wijanto, “Modélisation multi-échelle des fibres de collagènes”, started: Sept. 2015, supervisors: J.-M. Allain and M. Caruel

Supervision of a project research in CEMRACS 2018 “ Multiscale population dynamics : interactions between scales in developmental and reproductive biology” (F. Clément, M. Postel and R. Yvinec)

10.2.3. Juries

D. Chapelle, PhD Jury of A. Marboeuf, Ecole Polytechnique, March 8

P. Le Tallec, PhD reviewer of R. Mlika, INSA Lyon, Jan 24

P. Le Tallec, PhD Jury of Q. Pierron, ENSTA ParisTech, May 18

P. Le Tallec, PhD reviewer of L. Poirel, Inria Bordeaux, Nov 28

P. Moireau, PhD Jury of U. Khristenko, Université Paris-Saclay, Jan 17th

P. Moireau, PhD Jury of T. Kritter, Bordeaux University, Oct 1st

10.3. Popularization

J.M. Allain, Co-authored a popularization paper in the “Reflets de la Physique” journal (january-february 2018)

D. Chapelle, Interview in *Sciences et Avenir* (November issue)

M. Genet, Presentation at JeudiX—Research Days at École Polytechnique

C. Patte, Fête des Sciences day, organized by Inria. October 11th

11. Bibliography

Major publications by the team in recent years

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