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Some contributions to cardiac and pulmonary biomechanical modeling, simulation & estimation

Martin Genet

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Some contributions to cardiac and pulmonary biomechanical modeling, simulation & estimation

Mémoire d'habilitation de l'Institut Polytechnique de Paris
préparé à l'École Polytechnique

École doctorale de l'Institut Polytechnique de Paris (EDIPP)
Spécialité: Mécanique

Mémoire présenté et soutenu à Palaiseau, le 21 juin 2022, par

MARTIN GENET

Composition du Jury :

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Alain Goriely Professeur, University of Oxford, United Kingdom	Rapporteur
Gerhard Holzapfel Professeur, Graz University of Technology, Austria	Rapporteur
Merryn Tawhai Professeure, University of Auckland, New Zealand	Rapporteuse
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Patrick Clarysse Directeur de recherche, CREATIS/CNRS, Lyon, France	Examineur

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Curriculum Vitæ

(Many items are clickable for more information.)

Personal informations

Name: Martin Genet

Citizenship: French

Date of Birth: 28 July 1983

Academic position: Assistant Professor, Mechanics Department, École Polytechnique

Research affiliations: MΞDISIM team, Solids Mechanics Laboratory, École Polytechnique & MΞDISIM team, INRIA

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Education

2022 (expected in June): *École Polytechnique* (France), Accreditation to supervise research.

2010: *École Normale Supérieure de Cachan* (France), *Laboratoire de Mécanique et de Technologie*, Doctor of Philosophy in Mechanics, passed with very honorable distinction. Thesis: “Toward a virtual material for ceramic composites” (in French), Supervision: Pr. Ladevèze.

2006: *École Normale Supérieure de Cachan* (France), Mechanical Engineering Department, Master’s degree, passed with highest honors, first in class. First year thesis: “Investigation of a hydraulic impact—a technology in rock breaking”, Supervision: Dr. Yan & Pr. Allix. Second year thesis: “Using minicomposites for the identification of a lifetime model of ceramic composites” (in French), Supervision: Dr. Lubineau, Dr. Cluzel & Dr. Baranger.

2004: *École Normale Supérieure de Cachan* (France), Mechanical Engineering Department, Bachelor’s degree, passed with honors.

2004: Orsay University (France), Fundamental Physics Department, Bachelor’s degree, passed with great honors.

2003: Admitted to *École Normale Supérieure de Cachan* (France).

Academic positions

Since 2015: Assistant Professor, Mechanics Department & Solids Mechanics Laboratory (M Ξ DISIM team), *École Polytechnique*, Palaiseau, France.

2012–2015: Marie-Curie International Outgoing Fellow, Pr. Guccione’s group, Surgery Department, University of California at San Francisco (UCSF, USA), Pr. Kuhl’s group, Mechanical Engineering Department, Stanford University (USA), and Pr. Kozzerke’s group, Institute for Biomedical Engineering, Swiss Federal Institute of Technology (ETHZ, Zurich, Switzerland).

2010–2012: Postdoctoral research fellow, Dr. Tomsia & Pr. Ritchie’s group, Materials Sciences Division, Lawrence Berkeley National Laboratory (USA).

Summer 2008: Research visitor, Prs. Evans & Zok’s group, Materials Department, University of California at Santa Barbara (UCSB, USA).

Fall 2007: Research visitor, Pr. Lamon’s group, *Laboratoire des Composites Thermostructuraux* (LCTS), Bordeaux I University (France).

2006–2010: Master II and Doctoral research fellow, Pr. Ladevèze’s group, *Laboratoire de Mécanique et de Technologie* (LMT), *École Normale Supérieure de Cachan* (ENSC, France).

Summer 2005: Master I research fellow, Dr. Yan’s group, Computational Engineering and Research Center, University of Southern Queensland (USQ, Toowoomba, Australia).

Scholarships, Grants & Awards

2020–2021: French National Research Agency (ANR) COVID Grant (145,000€): “CT-scan Modeling in COVID-19 Sequelae” (PI: Pr. Brillet, APHP/INSERM).

2019–2023: French National Research Agency (ANR) Young Investigator (JCJC) Grant (383,868€): “Many-scale Modeling of Lung Poromechanics”.

2018: Young Investigator Award from the Francophone Society for Biomechanics (1,000€).

2016–2020: Swiss National Science Foundation Grant (CHF648,688): “Magnetic Resonance Imaging-Guided Computational Mechanics of Growth & Remodeling of the Failing Heart” (PI: Pr. Kozzerke, ETHZ).

2012–2015: Marie-Curie International Outgoing Fellowship (275,362€): “Computational Tools for Cardiac Mechanics”, UCSF (USA) & ETHZ (Switzerland).

2012: NBCR Summer Institute 2012 Scholarship (\$1,200).

2011: Nominee for Best Poster Award, Materials Research Society Fall Meeting, Boston (USA).

2008: *École Normale Supérieure de Cachan* Prize for International Action (800€).

2008: SAMPE French Student: “Toward a virtual material for the lifetime prediction of CMCs”.

2007–2009: DGA/CNRS PhD Scholarship (36,600€): “Toward a virtual material for ceramic composites”, *Laboratoire de Mécanique et de Technologie (LMT), École Normale Supérieure de Cachan* (France).

2003–2007: French National College Scholarship (62,400€): Pupil civil servant, Mechanical Engineering Department, *École Normale Supérieure de Cachan* (France).

Synergistic activities

Journal Editorial Boards:

- Frontiers in Physiology, Computational Physiology and Medicine Section (IF 4.566), Associate Editor
- Frontiers in Bioengineering and Biotechnology, Biomechanics Section (IF 5.890), Review Editor

Journal Papers Reviewing:

- Frontiers in Bioengineering and Biotechnology (IF 5.890) (1 article in 2021)
- Journal of the Mechanical Behavior of Biomedical Materials (IF 3.902) (1 article in 2020)
- Inverse Problems in Science and Engineering (IF 1.950) (1 article in 2019)
- Journal of Elasticity (IF 2.285) (1 article in 2016)
- Journal of Biomechanics (IF 2.712) (1 article in 2015)
- Computer Methods in Biomechanics and Biomedical Engineering (IF 1.763) (1 article in 2015)
- Acta Biomaterialia (IF 8.947) (3 articles in 2014–2019)
- Biomechanics and Modeling in Mechanobiology (IF 2.963) (4 articles in 2013–2021)
- Computers in Biology and Medicine (IF 4.589) (1 article in 2013)
- Mechanics Research Communications (IF 2.254) (1 article in 2012)
- Journal of Computational Physics (IF 3.553) (2 articles in 2011–2021)
- Journal of the American Ceramic Society (IF 3.784) (1 article in 2011)
- Mécanique & Industrie (IF 0.913) (1 article in 2010)
- Composites Science and Technology (IF 8.528) (3 articles in 2009–2011)

Conference Papers Reviewing:

- 46th Congress of the Biomechanics Francophone Society, Saint-Etienne, France, 2021.
- 10th International Conference on Functional Imaging and Modeling of the Heart (FIMH2019), Bordeaux, France, 2019.

Grants Reviewing:

- French National Research Agency (1 proposal in 2022).
- Swedish Foundation for Strategic Research (5 proposals in 2019).

Conference Organization:

- Part of Organization Committee of the 13th French National Conference on Computational Mechanics, Presqu’île de Giens, France, 2017.

Minisymposia Organization:

- “Computational Biomechanics: Advanced Methods and Emerging Areas” (w/ Christian Cyron, Alessio Gizzi, Daniel Hurtado & Michele Marino), 14th World Congress in Computational Mechanics (WCCM), Paris, France, 2020.
- “Lung Biomechanical Modeling and Simulation” (w/ Dominique Chapelle & Daniel Hurtado), 6th International Conference on Computational and Mathematical Biomedical Engineering (CMBE), Sendai City, Japan, 2019.
- “Coupled multi-organ modeling of the cardiopulmonary system” (w/ Lik Chuan Lee), 8th World Congress of Biomechanics (WCB), Dublin, Ireland, 2018.

Workshop Organization:

- Model/Data/AI in Mechanics at Institut Polytechnique de Paris (w/ Christophe Josserand & Benjamin Leclaire), Palaiseau, 2021.

Collective responsibilities

Within MEDISIM:

- 2015–: Maintenance of the team web site.

Within the *Laboratoire de Mécanique des Solides*:

- 2021–: Point of contact for energetic transition.
- 2015–: Implementation and organization of the LMS Journal Club. (Annual budget: *ca.* 1000€.)

Within the Mechanics Department of École Polytechnique:

- 2019–: Responsible for teaching assistants.

Within École Polytechnique:

- 2020–: Member of the steering committee of École Polytechnique’s JupyterHub.

Within Paris-Saclay University:

- 2016–2019: Organization of the monthly Paris-Saclay Biomechanics Seminar. (Annual budget: *ca.* 4000€.)

Collaborations

Within MEDISIM:

- D. Chapelle: 2 ongoing ANR grants, 1 PhD + 1 ongoing PhD, 3 journal papers + 1 conference paper + 1 paper in preparation.
- P. Moireau: 1 ongoing ANR grant, 1 ongoing PhD, 3 journal papers + 1 paper in preparation.
- J.-M. Allain: 1 PhD, 1 journal paper + 1 conference paper + 1 submitted paper.

Within École Polytechnique:

- A. Pierangelo, LPICM (2017–2020): 1 paper.

Within Institut Polytechnique de Paris:

- C. Fetita, Telecom SudParis (2017–): 1 paper + 1 conference paper.

National:

- 2020–: A. Bel-Brunon (LaMCoS, Lyon), 1 ongoing ANR grant, 1 ongoing PhD.
- 2017–: P.-Y. Brillet, H. Nunes, T. Gille & J.-F. Bernaudin (Avicenne Parisian (APHP) Hospital, Bobigny), 2 ongoing ANR grants, 1 paper + 1 conference paper.

International:

- 2019–: D. Hurtado (Pontifical Catholic University, Santiago, Chile), 1 MS, 1 paper.
- 2019–: R. Chabiniok (MΞDISIM then University of Texas Southwestern Medical Center) & T. Hussein (University of Texas Southwestern Medical Center), 2 journal papers + 1 conference paper.
- 2015–: S. Kozerke (ETH, Zurich, Switzerland), 1 Swiss National Science Foundation grant, 1 ongoing PhD, 9 journal papers + 3 conference papers + 1 paper in revision.
- 2015–2019: S. Wall (Simula, Oslo, Norway), 5 journal papers.
- 2015–2019: L. C. Lee (Michigan State University, Lansing, Michigan, USA), 16 journal papers, 2 conference papers.

Invited conferences & workshops

- [8] “Personalized Pulmonary Mechanics in Health and Idiopathic Pulmonary Fibrosis”, 9th World Congress in Biomechanics, July 2022, Taipei, Taiwan.
- [7] “Personalized Pulmonary Mechanics in Health and Idiopathic Pulmonary Fibrosis”, European Mechanics Society Colloquium on Current Challenges in Soft Tissue Mechanics, April 2022, Frankfurt, Germany.
- [6] “Personalized Pulmonary Mechanics in Health and Idiopathic Pulmonary Fibrosis”, 2nd Biomedical Engineering (BME) Symposium, Institut Polytechnique de Paris, June 2021, Palaiseau, France.
- [5] “Mechanical model-based biomedical image processing”, Parisian Workshop on Biomechanics from cells to tissues, October 2019, Gif-sur-Yvette, France.
- [4] “Mechanical challenges in biomedical imaging (in French)”, Parisian Workshop on Mechanics (RFM), Mai 2019, Fontainebleau, France.
- [3] “Medical images registration with finite elements and mechanical regularization”, 90th Annual Meeting of the International Association of Applied Mathematics and Mechanics (GAMM), February 2019, Vienna, Austria.
- [2] “Growth, residual stress and diffusion tensor imaging in the heart”, Simula Laboratory Cardiac Modeling (CaMo) Workshop, November 2014, Oslo, Norway.
- [1] “Toward a virtual material for lifetime prediction of CMCs” (in French), SAMPE technical days, November 2008, Tarbes, France.

Invited seminars

- [13] “Personalized Pulmonary Mechanics in Health and Idiopathic Pulmonary Fibrosis”, Multiscale Modeling and Simulation Laboratory (MSME, CNRS/UPEC/UPEM), Créteil, France (June 2021).
- [12] “Equilibrated Warping—Image Registration using Finite Element Method and Mechanical Regularization—Application to Cardiac MR and US images”, BMEIS Seminar Series, King’s College London, UK (December 2018).
- [11] “Modeling and Simulation in Cardiac Biomechanics” (in French), Mechanical Engineering Department, *École Normale Supérieure*, Cachan, France (December 2016).
- [10] “Personalized Cardiac Mechanics—Computational Tools and Applications”, Mechanics & Living Systems Initiative, *École Polytechnique*, Palaiseau, France (July 2014).
- [9] “Computational Cardiac Mechanics—an overview and preliminary results after nine month”, MΞDISIM team, INRIA, Palaiseau, France (July 2013).
- [8] “Toward virtual ceramic composites”, Tsai Lab, Stanford University, Palo Alto, California, USA (August 2010).
- [7] “Toward virtual ceramic composites”, Kuhl Lab, Stanford University, Palo Alto, California, USA (August 2010).
- [6] “Toward virtual ceramic composites” (in French), *Institut de Mécanique des Fluides et des Solides* (IMFS), Strasbourg, France (May 2010).
- [5] “Mechanical basis of the lifetime prediction tool developed at LMT-Cachan: modeling and simulation” (in French), Lifetime day, Snecma Propulsion Solide, Bordeaux, France (April 2010).
- [4] “Toward virtual ceramic composites” (in French), *Laboratoire de Mécanique et de Technologie* (LMT), Cachan, France (November 2009).
- [3] “Multiscale Modeling and Simulation Tools for Composite Materials at LMT-Cachan”, Teledyne Scientific & Imaging, Thousand Oaks, California, USA (July 2008).
- [2] “Multiscale Modeling and Simulation Tools for Composite Materials at LMT-Cachan”, Materials Department, University of California at Santa Barbara (UCSB), California, USA (June 2008).
- [1] “Investigation of a hydraulic impact—a technology in rock breaking”, Mechanical Engineering Department, University of Southern Queensland, Toowoomba, Australia (July 2005).

Mentoring experience

At *École Polytechnique*:

- 2021–: PhD thesis of A. Peyraut: “Modeling and Estimation of Lung Poromechanics”. Co-supervision: Dr. Moireau.
- 2021–: Postdoc of C. Laville: “Personalized modeling of lung poromechanics in COVID-19”.
- 2020–: PhD thesis of M. Manoochehrtayebi: “Many-scale Modeling of Lung Poromechanics”. Co-supervision: Dr. Bel-Brunon (INSA-Lyon) & Dr. Chapelle.

- 2017–: PhD thesis of E. Berbero glu (ETHZ, defense planned for December 2021): “Image Guided Computational Cardiac Mechanics”. Co-supervision: Pr. Koz-erke (ETHZ).
- 2020: Master II thesis of M. Manoochehrtayebi: “Combined Estimation of Mate-rial Law and Unloaded Configuration—Application to Pulmonary Poromechanics”.
- 2019–2020: Master thesis of F. Álvarez-Barrientos (PUC, Santiago, Chile): “On a variational formulation of pressure-driven poromechanics”. Co-supervision: Pr. Hurtado (PUC).
- 2018: Master II thesis of J. Diaz: “On a reduced cylindrical model of the ventricle”. Co-supervision: Dr. Moireau.
- 2018–2021: PhD thesis of N. Tueni: “ Multiscale experimental and theoretical investigation of the structure-property relationships in the myocardium”. Co-supervision: Pr. Allain.
- 2017–2020: PhD thesis of C. Patte: “Personalized pulmonary mechanics: modeling, estimation and application to pulmonary fibrosis”. Co-supervision: Dr. Chapelle.
- 2017: Master II thesis of N. Tueni: “Multi-scale characterization of passive mechanical properties of cardiac tissue”. Co-supervision: Pr. Allain.
- Since 2015: 7 Master I research projects (12 students).

At the University of California at San Francisco:

- 2013–2014: Master I research internship on patient-specific computational cardiac mechanical modeling (A. Toutain).
- 2012–2014: Undergraduate research volunteer training with patient recruit-ment, scanning, and patient-specific computational cardiac mechanical modeling (R. Nguyen).

At the Lawrence Berkeley National Laboratory:

- 2011: Graduate Summer Internship: “A truss model for the understanding and optimization of robocast scaffolds mechanical properties” (M. Scheb).

At *École Normale Supérieure de Cachan*:

- 2008: Master II thesis of M. Gruin & A. Grux: “3D modeling and simulation of the matrix healing process in a microcomposite” (in French). Co-supervision: Dr. Baranger.
- 2008–2010: 2 Master I research projects (5 students).

Teaching experience

At *École Polytechnique*:

- 2020–: 200h of lectures & exercise sessions in numerical methods and model-data interaction (Master I, both courses built from scratch).
- 2015–2020: 600h of exercise sessions in continuum mechanics (Bachelor III, Pr. Marigo and Pr. Le Tallec’s courses), modeling and simulation in mechanics (Bachelor III, Pr. Lorentz and Pr. Charkaluk’s courses), and plasticity and fracture mechanics (Master I, Pr. Marigo’s course).

At the Swiss Federal Institute of Technology (ETHZ):

- 2014–2015: Pr. Kozerke’s course on biomedical engineering (Master I), exercise sessions (4h).

At *École Normale Supérieure de Cachan* (ENSC):

- 2007–2009: Pr. Rey’s course on continuum mechanics (Master I), exercise sessions (64h, with “elite” group in 2008–2009).
- 2007–2009: Pr. Dumontet’s course on mathematics for mechanics (Bachelor III), exercise sessions (64h).
- 2006–2007: Pr. Rey’s course on continuum mechanics (Master I), practical work (16h).

At Versailles University (UVSQ):

- 2006–2007: Pr. Champany’s course on contact modeling and simulation (Master II), practical work (16h).

At Ville d’Avray Technological University:

- 2006–2007: Numerical analysis course, practical work (32h).

Outreach experience

2020: Article on virtual patient in cardiology, in *École Polytechnique Alumni Journal* “La Jaune & La Rouge”, <https://www.lajauneetlarouge.com/la-modelisation-mecanique-en-cardiologie-vers-le-patient-virtuel>.

2018: Lecture on cardiac modeling and simulation for applications in cardiology at *École Polytechnique Research Days*, <https://www.youtube.com/watch?v=5W1rV41r408>.

2014: Lecture on science and scientific computing at the Burton High School, San Francisco, with M. Pearson.

2012–2014: Lectures on science and scientific computing, with practical work, at the San Francisco French High School with Ms. Chambon.

2008–2010: Volunteer work for the NGO *Autremonde* in Paris: teaching French to migrants.

2008: One week replacement of Ms. Ponty’s math classes at Gustave Eiffel High School in Cachan, with lectures on science and scientific computing.

2005–2008: Volunteer work for the quarter association of *La Plaine* in Cachan: giving remedial lessons to pupils (middle and high school), organizing cultural and educational events with the families of the quarter.

Summer 2004: Volunteer work for the NGO *Marins Sans Frontières* in Madagascar: investigating a project to assist health services communication and action with boats.

Summer 2003: Volunteer work with the NGO *Association Jeunesse Solide* in Burkina Faso: teaching mathematics and physics to middle-schools pupils.

Introduction

In this document, I present a summary of my research activities of the past nine years, *i.e.*, since the summer 2012, when I left the world of ceramics (ceramic matrix composites during my PhD at the *Laboratoire de Mécanique et de Technologie* (LMT) of the *École Normale Supérieure de Cachan* (ENS), from 2006 to 2010, under the supervision of Pierre Ladevèze; and then cellular ceramics during my Postdoc at the Lawrence Berkeley National Laboratory (LBNL), from 2010 to 2012, in Antoni Tomsia and Robert Ritchie's groups) and started working on biomechanics and related problems. From 2012 to 2015 I worked, thanks to a Marie Curie fellowship from the European Commission, at the University of California at San Francisco (UCSF) (Julius Guccione's group), Stanford University (Ellen Kuhl's group), and the Swiss Federal Institute of Technology (ETH) of Zurich (Sebastian Kozerke's group). Since 2015 I am an Assistant Professor at École Polytechnique, and I conduct my research within the MΞDISIM team (directed by Dominique Chapelle then Philippe Moireau), jointly held by INRIA and the *Laboratoire de Mécanique des Solides* of École Polytechnique.

My work belongs to the general field of biomedical engineering science, whose objectives are (i) to better understand the phenomenon of life in health and disease, and (ii) to develop and analyze novel concepts and methods for biomedical engineering, *i.e.*, which will be the foundation of objective and quantitative tools for medicine, *i.e.*, for the diagnosis and treatment of patients. More precisely, my research focuses on the development of (i) models of the mechanics of living tissues and organs (exclusively the heart until 2017, then the lungs as well), (ii) methods and tools for the simulation of such models (which can be used as a prediction tool, *i.e.*, prognosis, but also to investigate competing hypothesis), and (iii) methods and tools for the estimation of model parameters based on clinical data (which can be used to estimate quantities that cannot be measured *in vivo*, *i.e.*, augmented diagnosis, and to build personalized models that can be used to design patient-specific therapies, *i.e.*, optimized treatment).

In the manuscript, the presentation of the various works is split into three chapters, based on the main scientific problematic. Each chapter is structured to emphasize my continuous quest for the right balance between theoretical and practical studies. Likewise, I have tried to highlight the balance that I attempt to maintain between purely personal work, collaborations and, for several years now, directions or joint directions of research. Chapter 1 concerns biomechanical modeling, at various spatial (microstructural, tissue, organ) and temporal (function, remodeling) scales. Chapter 2 concerns methodological developments for model personalization based on clinical data, and multiple applications studies. Chapter 3 concerns motion tracking, focusing on mechanical regularization and multiple application studies. In the final chapter, I give some perspectives on ongoing and future research.

Throughout the document, in order to clearly position my work with respect to the literature, I distinguish references to personal contributions, which use a numerical style

(*e.g.*, [J1] for journal papers, [C1] for conference papers, and [B1] for book chapters), and contributions from the literature, which use an author-year style (*e.g.*, [Fung 1993]). Consequently, the bibliography is split into two parts.

Chapter 1

Multiscale biomechanical modeling of soft living tissues and organs

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Introduction

As the classic aphorism says, all models are wrong but some are useful. It is with that in mind that the work described in this chapter has been developed. Of course the notion of usefulness is quite broad, and can vary a lot from one piece of work to another, from purely “physics” models aimed at describing a certain comprehension of a system, to “engineering” models aimed at controlling (in a general sense: estimation, prediction, optimization) some aspect of a system.

Section 1.1 describes models at the organ (heart/lung) spatial scale and functional (beating/breathing) temporal scale. These models are based on known physical mechanisms, my contribution being the formulation and coupling of various submodels into a consistent continuum mechanics framework. The final objective of these models is personalized modeling for clinical applications as detailed in Chapter 2.

Section 1.2 describes growth and remodeling models at the organ (here, the heart) and tissue levels. The former are aimed at better understanding and characterizing the

impact of growth on (and growth-induced residual stresses) the organ function. The latter are aimed at better controlling, in growth models, the amount of growth-induced residual stresses.

Section 1.3 describes microstructural (cardiac sheetlets/pulmonary alveoli) models, which are aimed at better understanding the structure-properties in living tissue. They also represent the foundations of future mechanistic models of tissue remodeling, thus extending the work detailed in Section 1.2. Indeed, even though remodeling has an impact on the macroscopic scale (*e.g.*, change of mass or properties), (i) it is actually driven by microscopic signals, which are often only roughly described by macroscopic models, and (ii) its impact on the macroscopic scale is actually induced by microstructural and micromechanical alterations, which again cannot be precisely described by macroscopic models.

1.1 Organ spatial scale and functional temporal scale modeling

1.1.1 Cardiac modeling

The cardiovascular system is a highly complex system, involving many phenomena belonging to various physics and taking place at various spatial and temporal scales. My work focuses on the heart, especially the (left & right) ventricles, two of its four chambers. The ventricular wall is composed of the myocardium, the cardiac muscle, sandwiched between two thin layers, the endocardium & epicardium. The main revolutions in our understanding of the cardiovascular system are (i) the establishment of the circulation (and therefore the role of mechanical pump of the heart) by Harvey in the early 17th century; then (ii) the discovery of the capillaries (smallest blood vessels linking arteries and veins, site of exchange between blood and the outside of the cardiovascular system) by Malpighi in the late 17th century; (iii) the discovery of the muscle electrical activity by Galvani in the 18th century; followed by (iv) the discovery of the electrocardiogram by Waller & Einthoven at the end of the 19th century; (v) the very coupling mechanisms between electrical excitation and mechanical contraction (the sliding filament principle) being first described simultaneously by A. F. Huxley & Niedergerke and H. Huxley & Hanson in the early 50's.

Biomechanical modeling of the heart has attracted a lot of attention for a long time. We focus here on models of the cardiac solid mechanics, though other communities have focuses on the fluid mechanics [Kovács et al. 2001], and there are efforts to build fully coupled fluid-structure interaction models [Watanabe et al. 2004; Astorino et al. 2012]; similarly, there is a whole community devoted to studying the electrical aspect of the heart, and there are efforts to perform fully coupled electromechanical simulations [Chapelle, Fernández, et al. 2009; Trayanova 2011]; finally, there are also efforts toward poromechanical simulations [Huyghe et al. 1992; Chapelle, Gerbeau, et al. 2009; Cookson et al. 2012]. Back to pure solid mechanics, we can cite pioneering models based on simple spherical [Hanna 1973] or cylindrical [Arts et al. 1979; Guccione, McCulloch, and Waldman 1991] geometries and associated constrained kinematics, as well as pioneering finite element models [Hunter 1975; McCulloch 1986]. Developments are still ongoing, on both reduced [Caruel et al. 2014] & finite element [Sainte-Marie et al. 2006; Quarteroni et al. 2017] models, and have reached industry [D'Souza 2015]. These models incorporate various levels of details about the ventricular geometry, passive material behavior (transversely isotropic, orthotropic), active material behavior (temporal evolution, strain & strain rate dependency, *etc.*), boundary conditions (coupling to the circulation, the heart surroundings, *etc.*), *etc.*, depending on

the question of interest.

As mentioned already, my work in organ scale cardiac modeling was mostly aimed at personalized modeling, as described in Chapter 2. Thus, my contribution is to select and combine existing modeling bricks into a unified model that (i) can be identified based on clinical data, and (ii) can help address, once identified, clinically relevant questions through augmented diagnosis or prognosis. More precisely, I initially developed a simple left ventricular (though biventricular models were later considered for instance in [J30] [J18], and four chamber models for instance in [J13] [J24]) model where only end-systolic (or early-diastolic) and end-diastolic phases were considered, and supposed to be in static equilibrium (though dynamical models were later considered for instance in [J13] [J30]). I also assumed that the early-diastolic phase corresponded to the ventricular unloaded configuration. The model focused on solid mechanics, and the blood was considered through a homogeneous pressure applied onto the endocardium (while the epicardium was free of load); other mechanisms such as perfusion or electric charges diffusion & reaction were not taken into account (though the later has been considered for instance in [J23] [J25]). The material behavior was model through the Fung exponential anisotropic passive law [Fung 1993] (though the Holzapfel-Ogden law has been considered for instance in [J13] [J18]), and the Guccione active law [Guccione and McCulloch 1993; Guccione, Waldman, et al. 1993]. All details can be found in [J10] [J14].

1.1.2 Reduced cardiac modeling

The models presented so far have a significant computational cost, in particular because of the complex ventricular geometry. Several approaches have been proposed in the literature to reduce the complexity of models, and therefore the cost of computation. This could serve in a pre-calibration step, to calibrate large finite element models more effectively; it could also be used in applications where computation time is essential, such as critical care patient monitoring. If pure “lumped parameters” models have existed for a long time, it is more interesting to employ reduction approaches that keep a strong link between the reduced model and the original full scale model. These approaches can be split into two families: (i) approaches that consist in deriving a reduced model from a full scale model through algebraic manipulation [Bonomi et al. 2017]; and (ii) approaches that consist in defining reduced geometry and kinematics, but use the general motion and behavior laws [Arts et al. 1979]. The MΞDISIM team, notably, has developed a reduced ventricular model following the second approach, based on spherical geometry and kinematics, allowing to end up with a purely scalar problem, and a resolution in real time [Caruel et al. 2014].

I proposed an alternative reduction, based on the cylindrical geometry and kinematics initially proposed by in [Guccione, McCulloch, and Waldman 1991; Guccione and McCulloch 1993; Guccione, Waldman, et al. 1993], which makes it possible in particular to better represent the distribution of the orientation of muscle fibers through the ventricular wall as well as the ventricular torsion, both absent from the spherical reduced model. The kinematics not being reduced to a set of scalars, it was necessary to write the mechanics of continuous mediums on the manifold generated by the kinematics. Moreover, care was taken to define an energy-consistent integration scheme. This work, started during the Master thesis of Jérôme Diaz, co-supervised with Philippe Moireau, and in collaboration with Dominique Chapelle, is currently being written up [J43].

1.1.3 Pulmonary modeling

The lungs are the primary organs of the respiratory system in humans and many animals, responsible for molecular exchanges between external air and internal blood through mechanical ventilation. It has an extraordinary complex architecture, with the inherent fractal structure of the bronchial and blood vessel trees, as well as the hierarchical structure of the parenchyma (groups of alveoli form acini, lobules, segments, lobes, and finally the whole lungs). It is also host to a very complex physics, involving many phenomena at various temporal and spatial scales, such as air flow, blood flow, tissue deformation, gas exchanges, *etc.* Both this architecture and these mechanisms are crucial to its function. For instance, the hierarchical architecture generate an extraordinary large exchange surface in such a confined volume; and the parenchymal compliance allows for an important gas intake.

Lung biomechanics has been extensively studied by physiologists, experimentally as well as theoretically, from fluid, solid as well as exchanges points of view, laying the ground for our current fundamental understanding of the relationship between function and mechanical behavior [Fry et al. 1960; Mead et al. 1970]. However, many questions remain, notably in the intricate coupling between the multiple constituents—tissue, blood and air—, between the many phenomena taking place at different spatial and temporal scales in health and disease.

My work on lungs started with a collaboration with a team of pulmonologists & radiologists from the Avicenne APHP Hospital in Bobigny, and the PhD thesis of Cécile Patte, co-supervised with Dominique Chapelle. We focuses “Idiopathic”—because the mechanisms of appearance and development of the disease remain poorly understood—Pulmonary Fibrosis (IPF), a progressive form of interstitial lung disease where some alveolar septa get thicker and stiffer while others get completely damaged, remains poorly understood (both in terms of origin and development), poorly diagnosed, and poorly treated (with only a few therapeutic options to slow disease progression [Flaherty et al. 2018], and only one real, but often impossible in practice, cure: lung transplant), with a current median survival rate inferior to 5 years [Tcherakian et al. 2011; Cottin, Hirani, et al. 2018; Lederer et al. 2018]. One fundamental question associated with this disease is the possible existence of a mechanism called “mechanical vicious circle”: the fibrosis leads to tissues stiffening, forcing patients to pull harder to breathe, causing higher stresses in the tissue, promoting fibrosis [Hinz et al. 2016]. In order to provide objective and quantitative elements of answers to this question, we have developed a poromechanical model of the lungs at the breathing time scale and the organ space scale [J40] and an associated clinical data-based model personalization procedure [C8] [J41] (see Section 2.2.2).

There have been many published works on lung modeling, we can cite early analytical [Mead et al. 1970; Karakaplan et al. 1980; Budiansky et al. 1987] and more recent computational [Wiechert et al. 2009; Koshiyama et al. 2015; Concha et al. 2018] models at the alveolar/acinar level; at the organ level, there have been models focused on air flow [Y. Yin et al. 2010], including work focused on aerosols and particle deposition [Boudin et al. 2015; Oakes et al. 2016], as well as models focused on gas exchanges and respiration [Choi et al. 2013; Roth et al. 2017]. Closer to solid mechanics, models have been proposed that focus on breathing motion, notably in the context of radiotherapy [Fuerst et al. 2012; Giroux et al. 2017; Lesage et al. 2020], without the need for detailed material behavior; other models incorporate fully detailed pulmonary mechanical behavior [Burrowes et al. 2008; Berger et al. 2016]. Nevertheless, the field of clinical imaging-based personalized modeling is much less developed than for the heart [Tawhai et al. 2009; Choi et al. 2013; Morton et al. 2018]. The problematic of model-data interaction is very similar to that in

the cardiac context.

Poromechanics was formulated originally by [Biot 1941; Biot 1972] and consolidated by [Coussy 2004]; a very general formulation has been recently proposed in [Chapelle and Moireau 2014]. Note that mostly equivalent formulations for poroelasticity can be obtained from Truesdell’s theory of mixtures [Coussy et al. 1998; Cowin et al. 2012]. Pulmonary poromechanical models have been proposed by [Kowalczyk 1993] & [Berger et al. 2016]. In our model, the “solid” phase is composed of both tissue and blood while the fluid phase is the air, and we consider only the end-exhalation & end-inhalation states, which are assumed to be in static equilibrium. The constitutive behavior allows to reproduce the volumetric response of lungs to a change of pressure as observed in experimental data. Special care was taken to manage the closing of the pores in compression and prevent negative porosities, for both the forward (when computing the loaded state from the known unloaded state) & backward (when computing the unloaded state from the known—for instance from images—loaded state) problems, based on an extension of a previously proposed energetic solution [Chapelle and Moireau 2014], and a novel “contact-like” formulation. Furthermore, we developed specific boundary conditions for the lungs, modeling the effect of diaphragm-induced loading and rib cage: a pressure applied on lung boundary representing pleural pressure, and a frictionless contact with a moving surface representing the thorax. All details can be found in [J40].

1.2 Remodeling temporal scale modeling

Introduction

Models of Section 1.1 describe the current (acute) mechanical behavior of the cardiac of pulmonary tissue. However, living tissues are constantly evolving, adapting their properties (mass, stiffness, *etc.*) to their environment through processes generally referred to as remodeling [Taber 1995]. Models involving such (chronic) remodeling mechanisms would represent prognosis tools, allowing for better patient classification and treatment optimisation. One interesting remodeling mechanism is growth, which consists in matter addition or removal, with identical material properties [Taber 1995]. Growth can be physiological (*e.g.*, the pregnant woman’s heart [Sanghavi et al. 2014]) or pathological (*e.g.*, during heart failure, where growth is accompanied with other remodeling mechanisms [Cohn et al. 2000; Burchfield et al. 2013; Xie et al. 2013], or pulmonary fibrosis [Hinz et al. 2016]). Models involving growth mechanisms could be used to better understand the diseases involving growth, and ultimately better diagnose and treat patients.

After early attempts at modeling (more precisely simulating) growth [Skalak, Dasgupta, et al. 1982], modern approaches are split into two families: (i) the multiplicative decomposition of the transformation gradient, introduced by [Rodriguez et al. 1994] based on finite plasticity theory [Lee 1969]; and (ii) the constrained mixture theory, introduced in the general setting by Truesdell in the 50’s, and in the specific content of tissue growth by [Humphrey and Rajagopal 2002]. Constrained mixture has the advantage of allowing a more detailed description of the growth mechanisms; it is, however, much more complex to implement numerically than the multiplicative split of the deformation gradient—recent developments proposed simplifications to make the framework trackable numerically, leading to a formulation very similar to the multiplicative decomposition of the deformation gradient [Cyron et al. 2016]; it has, however, not yet been applied to the heart or the lungs.

Interestingly, in the field of growth, modeling is ahead of experiments, and there is a clear lack of data to better understand, *e.g.*, the role of mechanics in growth evolution, the

impact of growth on material properties, *etc.*, as well as to compare the predictive power of existing growth formulations, though attempts have been made notably in the cardiac setting [Witzenburg et al. 2017; Rondanina et al. 2019].

1.2.1 Cardiac growth modeling

My first work on growth was to implement (in Abaqus/Standard) a generic framework based on the multiplicative decomposition of the transformation gradient into growth and elastic parts following [Rodriguez et al. 1994; Göktepe et al. 2010]. I first simulated a ventricle with an inverse growth law formulated by my colleague Lik Chuan Lee, which he had only studied analytically. We were thus able to show that this law predicted well a pathological growth of the ventricle in the event of ventricular overpressure, as well as a decrease in the event of normalization of the pressure [J21]. I then applied this modeling framework to Dassault Systèmes’ Living Heart Human Model¹, and characterized the chronic alteration of several parameters (*e.g.*, chamber size, wall thickness, valve perimeter, distance between papillary muscles, *etc.*) in the case of hypertrophies induced by systemic or pulmonary hypertension [J24].

The growth models presented so far are based on purely mechanical models of the heart. I also carried my growth code inside a cardiac electromechanical code developed by my colleagues Lik Chuan Lee & Samuel Wall, so as to be able to perform coupled electro-mechanical-growth simulations [J23] [J25].

1.2.2 Growth-induced residual stresses and relaxed growth modeling

I was also very interested in the problem of growth-induced residual stresses. Indeed, when some regions grow more than others, pre-strain, and therefore auto-balanced stressed, is needed to bring the post-growth configuration back into a compatible configuration [Rodriguez et al. 1994; Skalak, Zargaryan, et al. 1996]. In particular, an interesting question is to what extent these growth-induced residual stresses are consistent with what is known about actual residual stresses in tissues, notably the experience of the opening angle. This experiment consists in taking a slice of tissue (*e.g.*, of an artery [Chuong et al. 1986] or a left ventricle [Omens et al. 1990]), notching it, and measuring the angle by which it will spring open by unloading its internal stresses [Fung 1993]. So I developed a ventricular model where I could induce different levels of growth and then simulate the opening angle experience [J22]. To be able to compare the different growth levels, I also developed a fixed point algorithm on the geometry itself, stabilized with Aitken relaxation, so as to always get the reference geometry after growth, extracted by MRI—so this is the initial geometry, *i.e.*, pre-growth, and not the final geometry, *i.e.*, post-growth, which varies here from one level of growth to another. I was thus able to show that the method was compatible with experimental values of opening angles and, perhaps more importantly, that the prestressed ventricles were more compliant in terms of blood filling, which indicates that the residual stresses, in addition to the well-known beneficial effect of homogenizing stresses [Fung 1993], could also improve ventricular filling properties.

To better control the residual stresses induced by growth, I recently formulated a new law of so-called relaxed growth, which describes, in addition to the growth itself, the relaxation of residual stresses in the tissue [J26]. Indeed, even if living tissues contain residual stresses, part of the residual stresses induced by growth is necessarily canceled out by mechanisms of microstructural reorganization; thus, if some existing laws conserve all growth-induced residual stresses [Göktepe et al. 2010], others systematically ignore all

¹<https://www.3ds.com/heart>

residual stresses [Kroon et al. 2007]. The new law that I have proposed contains two time constants, one for growth and one for relaxation, and therefore unifies the different choices for modeling the residual stresses induced by growth.

1.3 Microstructural spatial scale modeling

1.3.1 Cardiac modeling

In addition to my work on cardiac modeling at the “structural” scale of the organ, I more recently started “material”-level work on the very behavior of the myocardium, in particular as part of the Doctoral thesis of Nicole Tueni, co-supervised with Jean-Marc Allain (MΞDISIM team, Solid Mechanics Laboratory, École Polytechnique). While a large number of works relate to the microscopic foundations of muscle contraction [Guccione and McCulloch 1993; Bestel et al. 2001; Chapelle, Le Tallec, et al. 2012; Kimmig et al. 2021], the microscopic basis for the passive behavior of heart tissue is far from clear, and no model has yet been proposed. At the cellular level, the tissue has an essentially transverse isotropic structure [Humphrey and F. C. P. Yin 1987], however, at the tissue level the observed behavior is orthotropic [Dokos et al. 2002]. It was postulated that this anisotropy was induced by the sheet structure at an intermediate scale. Initially, we developed, in collaboration with the Biological Optics Laboratory of École Polytechnique, a test combining mechanical testing, macroscopic imaging and microscopic imaging, in order to be able to follow the evolution of the orientation of the sheets during mechanical loading on cardiac samples. We were thus able to demonstrate the affinity of the deformation of the layers, at least until the appearance of cracks, *i.e.*, far from the physiological domain [C1] [J20].

Secondly, I led a modeling study on the microscopic foundations of the passive behavior of the myocardium. The main question was: which microstructure is compatible with the observed macroscopic behavior? We were able to show that taking into account only the muscle fibers did not make it possible to reproduce the behavior observed macroscopically, even if accounting for the variations in orientation of the fibers throughout the ventricular wall. And we found that to reproduce the observed macroscopic behavior, it is necessary to introduce the intermediate scale of the sheets into the model. This theoretical work is being written up [J42]. We are also setting up an associated experimental analysis, since our model predicts a very important size effect in the shear properties of the myocardium, which still need to be verified experimentally.

1.3.2 Pulmonary modeling

Poromechanics is a powerful framework to describe the macroscopic response of porous materials like the lung parenchyma; however, it is limited in its description of microscopic quantities, which are actually important for the study of pulmonary diseases, since they drive remodeling mechanisms. Thus, I started working on micromechanical modeling of the lungs. The objective is (i) to better understand structure-function relationships, (ii) to inform the poromechanical model, and (iii) to build foundations for introducing remodeling mechanisms in our pulmonary model.

A first work has been done during the Master thesis of Felipe Álvarez-Barrientos, co-supervised with Daniel Hurtado (Pontifical Catholic University of Chile) [J39]. We developed a variational framework to calculate the response of porous microscopic cells, loaded with strain and/or pressure. We were notably able to quantify the preponderant role of the microstructure on the global poromechanical response.

Chapter 2

Model personalization

Contents

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Introduction

I work on the heart and lungs because they are fascinating and challenging topics, but also because they are important ones: cardiovascular diseases remain the major cause of death globally¹ as well as in Europe², and an important burden on the health care systems of many countries; similarly, chronic obstructive pulmonary disease (COPD), the most common pulmonary disease, is about to become the third cause of death in the world³, while interstitial lung diseases (ILD) is a rarer group of diseases, but still affecting several million people globally [GBD2013 2015]. Even though most cardiovascular and pulmonary diseases could be prevented by addressing behavioral risk factors (tobacco & alcohol use, unhealthy diet, physical inactivity, obesity, *etc.*), it is still of utmost importance to improve early diagnosis and treatment of such diseases. In this regard, medical practices have seen a revolution with the development of medical imaging, started in the 20th century and continuing nowadays, including radiography & tomography, magnetic resonance imaging, ultrasound imaging, electrocardiography imaging, *etc.* Indeed, these techniques allow for noninvasive *in vivo* imaging of live organs, thus switching from making diagnosis and treatment decisions based on global to regional quantities (biomarkers). This revolution is still ongoing, with progress in imaging modalities (*e.g.*, *in vivo* diffusion tensor imaging [Toussaint et al. 2013], electrocardiogram imaging [Rudy 2017], ultrafast ultrasound [Villemain et al. 2020], *etc.*) but also in imaging data processing. Indeed, going from data

¹[https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))

²<https://ehnheart.org/cvd-statistics.html>

³[https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))

(*e.g.*, an image) to an information (*e.g.*, a biomarker, a diagnosis) require some kind of model, and there is a lot of research aimed at switching from subjective and qualitative to more objective and quantitative models. There are recent developments toward purely statistical data-based models from the machine learning community [Leiner et al. 2019; Santhanam et al. 2021; Chassagnon et al. 2021], but physics-based models have already proven that by incorporating existing knowledge about the system they can be used to efficiently derive robust information from the data. Thus, patient-specific models, built by estimating some of their parameters from data, are seen as potential clinical tools for estimation of quantities (biomarkers) that cannot be measured *in vivo* (augmented diagnosis), and optimization of treatments and procedures [Tawhai et al. 2009; Smith et al. 2011; Krishnamurthy et al. 2013].

The art of modeling, at least in engineering science where the model serves as a quantitative prediction tool for the design or control of the system, is to find a balance between many aspects including the objective, the key mechanisms at play and their modeling, the model implementation and computational cost, the available data for model identification & validation, *etc.*

In the cardiac setting, patient-specific geometry can be obtained from echography, tomography or magnetic resonance imaging, through image segmentation. Manual [Plank et al. 2009] or automatic [Campello et al. 2021] approaches have been proposed. However, even though there are initiatives to create public datasets for the assessment of methods performance [Suinesiaputra et al. 2014], one can regret that the tools are often not publicly available, such that it is not easy for people from other fields (*e.g.*, from mechanical modeling) to use cutting edge segmentation tools. Cardiac motion during beating can be extracted from temporal images obtained from echography or magnetic resonance imaging, through motion tracking/image registration or other techniques. Tracking material points is only possible if there is enough contrast to distinguish them from their neighbors. Some work has been done in directly processing the standard ultrasound or magnetic resonance images [Suffoletto et al. 2006], thus tracking the small intensity variations (often called speckles) in the images, while specific imaging techniques have been proposed for tracking material points, such as spatial modulation of magnetization (SPAMM) [Zerhouni et al. 1988; Ryf et al. 2002], displacement encoding with stimulated echoes (DENSE) [Aletras et al. 1999], *etc.* As with segmentation, public datasets exist to assess methods performance [Tobon-Gomez et al. 2013], but tools are rarely publicly available, slowing down their dissemination among non-experts. Other properties can be extracted from other imaging techniques, such as tissue anisotropy through diffusion tensor imaging (DTI), tissue viability through late gadolinium enhancement (LGE) magnetic resonance imaging, metabolism activity through single-photon emission computed tomography (SPECT) or positron emission tomography (PET), *etc.* Besides geometrical, kinematical and physiological data, pressure and forces are key data for mechanical modeling, but are more difficult to measure *in vivo*. Ventricular pressure can be measured with a catheter, which is minimally but still invasive. Often one has to rely on cuff pressure measurement, which are non invasive but further away from the heart itself. Elastography (based on ultrasound or magnetic resonance) allows to estimate regional stiffnesses (and thus, in combination with strain measurement, to estimate forces) from mechanical waves speed measurement [Bercoff et al. 2004], but it is not straightforward to apply to the beating heart.

In the pulmonary setting, the similar problematics exist. Because of the porous nature of the parenchyma and its localization within the thoracic cage, it is not straightforward to image *in vivo* using ultrasound or magnetic resonance imaging (though there are devel-

opments in that direction [Kolb et al. 2016; Boucneau et al. 2020]), such that X-rays and computed tomography are the most commonly used imaging techniques. The lung geometry can be extracted from computed tomographies, which usually have good resolution and contrast, using various approaches [Hu et al. 2001; Hofmanninger et al. 2020]. Such techniques are also used to segment within the lungs between healthy regions and regions affected by various pathologies [Fetita et al. 2019]. Because of the radiations associated to X-rays, computed tomographies are always performed parsimoniously. For instance, it is only since recently that the Francophone Pulmonology Society recommends two phases (end exhalation & end inhalation) scans for the diagnosis of idiopathic pulmonary fibrosis [Cottin, Crestani, et al. 2013], from which breathing kinematics can be extracted; the full breathing dynamics, however, is still missing. In some situations, for instance to track lung tumors before radiotherapy, full 4D computed tomography scans can be performed, allowing to measure the full breathing dynamics. Nevertheless, thanks to the inherent heterogeneous structure of the lungs, thoracic images show good contrast, such that lung motion can be tracked from standard images, and benchmarks have been propose to test existing methods [Murphy et al. 2011]. Breathing pressures are generally extremely difficult to measure *in vivo*, and very few quantitative data is available [Bates 2009].

The problem of estimating parameters of such biomechanical models based on such data is often very ill-posed, because the data is actually quite scarce with respect to the complexity of the system. For instance, for the heart, even with beating strains & ventricular pressures it is not straightforward to estimate ventricular material parameters, because (i) the myocardium behavior has both passive & active components, (ii) it is anisotropic, (iii) the ventricle is always loaded during the cardiac cycle, so the unloaded configuration is unknown, *etc.*, such that hypotheses have to be made to regularize the problem. Similar problems exist for the lungs. The various estimation approaches proposed in the literature can be decomposed into two families : variational (where patient-specific states and/or parameters are sought as minimizers of some distance function between model and data) and sequential (for dynamic formulations, where the model state and/or parameters are successively filtered based on the temporal data until convergence toward patient-specific values) approaches [Chapelle, Fragu, et al. 2013]. Depending on various aspects (*e.g.*, size of the model, number of parameters, *etc.*), each approach can have advantages and disadvantages in terms of implementation cost, robustness, precision, *etc.*

2.1 Methods

My first work in this field was to develop personalized left ventricular models for a group of healthy humans [J10]. The aim here was to define the reference material behavior for the human myocardium; also to define reference ventricular stress fields that can serve as targets for the *in silico* optimization of cardiac treatments aimed at normalizing ventricular stress.

Available data was standard cine MRI images, from which geometry was extracted, as well as tagged MRI images, from which 3D cardiac strains were extracted. Ventricular pressure data was not available, but all volunteers had normal cuff pressures so normal ventricular pressure was considered. In terms of modeling, as described in Section 1.1.1, only end-diastolic & end-systolic phases were considered; moreover inertia and viscous effects were neglected, such that these phases were assumed to correspond to static equilibria. In order to regularize the ill-posed estimation problem, I made the following additional modeling hypotheses: (i) the early-diastolic configuration could be considered as the unloaded configuration, (ii) the anisotropy of the passive behavior law could be considered

patient-agnostic such that only two passive material parameters (one characterizing the initial stiffness, one for the nonlinearity) needed to be estimated for each subject, and (iii) all but one parameter of the active behavior law could be considered patient-agnostic such that only one active material parameter needed to be estimated for each subject. To be able to identify two passive parameters from only one loading data, I used as additional *a priori* information the Klotz curve, which is a master pressure-volume curve that is consistent across species, age & conditions after proper normalization [Klotz et al. 2006], and designed a nested derivative-free optimization loop for robustness.

I then focused on infarcted human hearts [J14]. The aim was to quantify the loss of contractility in the infarct and its border zone, in order (i) to better characterize the mechanics of the infarct border zone, and (ii) advance toward automatic, objective & quantitative classification of patients after myocardial infarction. I obtained the data by recruiting & scanning patients from the UCSF Hospital. Besides anatomical and functional images, we also performed viability scans, allowing to localize scar tissue. The viability imaging data was directly (without any need for infarct segmentation) incorporated into the model, within both the passive and active material laws.

Over the following years, I was able to participate in improving various aspects of these personalized modeling methods. In [J22] I proposed to use Aitken relaxation (already used in [J5]) to improve the fixed point used to estimate the unloaded configuration from a loaded configuration extracted from images, improvement which has been studied in detail in [J17]. In [J18] I participated in the implementation of a tool to calculate, thanks to the adjoint problem, the gradient of the cost function of the optimization problem associated with the estimation of the parameters of the models, allowing a minimization more efficient than with the gradient-free methods used for instance in [J10] & [J14].

2.2 Applications

2.2.1 Cardiac applications

Personalized models could be used as objective and quantitative tools for diagnosis, prognosis and treatment optimization; in this sense they potentially represent one of the foundations of biomedical engineering applied to medicine. I participated in several studies on different treatments, existing or potential. In a first study on a treatment based on biopolymer injection into the myocardium, we were able to show the influence of the residual stresses induced by the injections on the ventricular mechanics [J12]. I also participated in the writing of a review article on the use of numerical simulation in cardiac surgery [J11]. I have also participated in studies focusing on the optimization of mitral annuloplasty rings [J13] [J16], as well as on a left respiratory support device [J15]. In a more recent study, we used patient-specific models to characterize the impact of pulmonary hypertension on ventricular mechanics [J19].

2.2.2 Pulmonary applications

Part of the model described in 1.1.3 can be personalized based on routine clinical data. In the *ad hoc* consortium gathered around these questions, Catalin Fetita (Telecom SudParis) is an image processing expert, and provides us with segmentations of lungs and fibrosis extents of the thoracic CT images acquired by Pierre-Yves Brillet (Avicenne APHP Hospital). We also adapted the motion tracking tools described in Chapter 3 to track these

images. The main issue with these images is the important sliding between the lungs and the rib cage [Vandemeulebroucke et al. 2012], which we resolve by using both the images themselves and the segmentations [J41]. We studied both decoupled (where motion tracking and parameter estimation are performed sequentially) and integrated (where they are performed simultaneously) estimation methods. We have first results on patients which are in line with what we know about the disease, *i.e.*, a stiffening of the fibrotic regions. All details are in [C8] & [J41].

Chapter 3

Motion Tracking

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Introduction

As discussed in Chapter 2, motion information is critical for model personalization. If some approaches to parameter estimation consist in working directly with the images, for instance the integrated correlation approach [Hild et al. 2006] [J41], most approaches consist in first extracting motion from images, and then using motion data for model personalization [Chabiniok et al. 2016]. Specific techniques have been proposed to image directly displacements (*e.g.*, displacement encoding (DENSE) magnetic resonance imaging [Aletras et al. 1999], which provide Eulerian displacements) or strains (*e.g.*, strain-encoded (SENC) magnetic resonance imaging [Osman 2003]); however, most approaches consist in obtaining visual images of the object of interest and process them to extract motion data. Standard ultrasound, magnetic resonance or computed tomography images can be used; however, since they usually show little contrast within a given tissue, specific techniques have been developed to create additional contrast, notably in magnetic resonance imaging with spatial modulation of magnetization (SPAMM) [Zerhouni et al. 1988; Ryf et al. 2002], and more recently with with subtly-tagged magnetic resonance imaging [Schrauben et al. 2017]. Extracting motion from images is a classical image processing problem, referred to as motion tracking, nonrigid image registration, or digital image correlation. Interestingly, the literature on the subject is quite confusing, with many approaches developed in various communities and using different vocabulary despite manipulating similar concepts; there are, however, at the scientific community level, remarkable efforts at structuring the literature [Sotiras et al. 2013]. Nevertheless, another regrettable—in my opinion—situation, is that even though benchmarks have been organized to compare the performance of existing methods [Bornert et al. 2009; Tobon-Gomez et al. 2013], the tools are often not openly available, slowing down the progress of science and engineering.

One central question regarding motion tracking is regularization, *i.e.*, the *a priori* knowledge that is used to reduce the ill-posedness of the problem. Many regularizers

have been proposed, some purely mathematical without physical content (such as a simple laplacian smoothing which can be problematic as even though it does not penalize rigid body translations, it does penalize large deformations as well as rigid body rotations), and some based on continuum mechanics (which have the possibility to incorporate more physical content). Mechanical regularizers have been proposed under many forms, *e.g.*, early work of [Bajcsy et al. 1983] included linear elastic regularization, with almost the same limitations as for the laplacian; and extension to hyperelasticity in [Veress, Weiss, et al. 2002; Veress, Gullberg, et al. 2005; Le Guyader et al. 2011], which does not penalize any rigid body motion but still penalizes large deformations. In order to alleviate this problem, [Rabbitt et al. 1995; Christensen et al. 1996] proposed to use a fluid-like regularization, while [Claire et al. 2004] proposed to use the error in equilibrium instead of elastic energy. This later idea solves all above issues as it penalizes only the deviation to an equilibrium solution (with arbitrary tractions on the boundary of the domain), not the magnitude of displacements or strains.

3.1 Methods for motion tracking with mechanical regularization

My contribution to this domain started with formulating an extension of [Claire et al. 2004]’s equilibrium gap regularization principle to finite strain elasticity, and implementing it within a custom finite element image registration tool (based on the FEniCS [Alnæs et al. 2015] and the VTK [Schroeder et al. 2006] libraries) [J31], which I refer to as equilibrated warping. The method and its implementation have been validated on [Tobon-Gomez et al. 2013]’s magnetic resonance [J31] and ultrasound [C6] *in vivo* imaging data.

Then, in particular as part of the thesis of Ezgi Berberoğlu, co-supervised with Sebastian Kozerke (ETH, Zurich, Switzerland), the method has been verified on *in silico* data [J33]. In addition, it allowed us to study the impact of image properties on the measured deformations, and we were able to prove that the reduced radial deformations measured from tagged MRI images, a long-standing problem associated with these images [Tobon-Gomez et al. 2013], is mainly induced by the resolution of *in vivo* images [J38]. One potential solution to this problem, is to combine untagged (which have a better in-plane resolution) and tagged imaged (which have better contrast within the myocardium), which is straightforward in our framework thanks to the flexibility of the finite element approach to motion tracking, and allowed us to get good radial strains, in addition to good circumferential, longitudinal and torsion [J44].

To overcome the problem of reduced deformations extracted from tagged images induced by their low resolution, I started to develop a method of motion tracking based not only on a mechanical model for regularization, but also on a model of the image process itself [C7]. In this work, we therefore model the effect of discretization on the image, *i.e.*, the blur between the pixels, so as not to be biased by it. This is particularly tricky in the case of MRI, where the images are acquired in Fourier space, but the first results are very encouraging—it could be the decisive solution to an old problem in cardiac MRI.

3.2 Applications to the analysis of cardiac pathologies

The tool I developed is quite generic and robust; it is available to everyone at https://gitlab.inria.fr/mgenet/dolphin_warp. I used it for many studies, focused on the heart (see Section 2.2.1) or the lungs (see Section 2.2.2). It has also interested several

colleagues, and has been used in several studies where I was able to provide my expertise [J30] [J32] [J34] [J37]. For example, in a recent study of 76 patients with tetralogy of Fallot at the Children’s Hospital in Dallas, led by Radomir Chabiniok (formerly MΞDISIM team, INRIA, now at University of Texas Southwestern Medical Center, Dallas, USA), we found that the intra- and inter-observer variabilities on the ventricular torsion measurement with my tool were much lower compared to a reference commercial registration tool [J36]—this is an important result, a first step towards the use of this type of data and tools for patient follow-up.

Perspectives

The research themes presented in this manuscript are still active today, and I intend to pursue them in various forms (personal work, collaborative work, supervision) in the future. I present now a few specific axes that I plan to develop.

Regarding the heart, my most recent activities have been focused on the myocardium behavior. The multiscale model of the myocardial anisotropy proposed in [J42] predicts a very strong size effect in the myocardial shear properties, which needs to be validated experimentally, a task already initiated in collaboration with Jean-Marc Allain. We also plan to better understand the sheetlet structure through microimaging at the SOLEIL synchrotron, and propose a more realistic model structure. Another important follow up of this work will be to introduce proper nonlinear behavior to the micromodel constituents, as well as the finite strain elasticity framework, and go from a simple model of the myocardial anisotropy to a full fledge behavior model.

On the longer term, I plan to continue my modeling activities on growth & remodeling at the ventricular level, potentially based on the multiscale behavior law just mentioned, as well as the relaxed growth framework proposed in [J26]. For me the key question here is the available data, as I believe in this field modeling is ahead of experimentation, and lacks validation. Thus, I plan to use the chronic porcine myocardial infarction data generated during the Swiss National Science Foundation (SNF) grant “Magnetic Resonance Imaging-Guided Computational Mechanics of Growth & Remodeling of the Failing Heart” (PI: Sebastian Kozerke, ETH Zurich, Switzerland), part of which was already used in [J44].

Regarding the lungs, my future activities are strongly connected to my ANR JCJC “Computational Lung Biomechanics: Many-Scale Modeling and Estimation” & ANR COVID “In silico modeling of thoracic CT and sequela of covid-19” (PI: Pierre-Yves Brillet, APHP Avicenne Hospital) grants. The first main axe of development targets the micromechanical foundations of the poromechanical behavior law proposed in [J40] for the lung parenchyma. In the context of Mahdi Manoochehrtayebi’s PhD, and in collaboration with Aline Bel-Brunon (LaMCoS, INSA-Lyon) & Dominique Chapelle, we will build a micromechanical model at the alveolar scale together with an upscaling strategy. This model will be validated thanks to thoroughly instrumented inflation tests performed on porcine lung segments at LamCoS [Pallière 2018]. Moreover, it will be the bases for future efforts, notably in the context of Alice Peyraut’s PhD, to actually model remodeling phenomena such as fibrosis, which often have a measurable impact at the macroscale but are driven at the microscale.

The second main are of development focuses on the potential clinical applications of the personalized modeling pipeline introduced in [J41]. This will require methodological developments to make the pipeline more robust and efficient, such that eventually it is usable directly by clinicians, in the clinic. For instance, in the context of Colin Laville’s post-doc,

and in collaboration with Catalin Fetita (Samovar, Telecom SudParis), we are streamlining our approach to clinical image segmentation and meshing. Another improvement in the robustness side, will be to use Bayesian inversion approaches to parameter estimation, in order to establish parameter identifiability in a more rigorous way. On the efficiency side, I plan to apply model reduction techniques, allowing to deport most of the computational cost from the clinic (online) to the lab (offline). These developments will enable to apply our personalized modeling pipeline to a large number of IPF & COVID patients, allowing to further establish potential model-based biomarkers for pulmonary diseases. Moreover, many of these methodological developments will serve future efforts toward personalized modeling in the cardiac context as well.

Even though I do not intend to stay in the motion tracking field for many more years, I still would like to finalize two important ideas. First, my current formulation of [Claire et al. 2004]’s equilibrium gap principle in the finite strain setting is at the continuous level and then confuses equilibrium errors with discretization errors; thus I plan to formulate another regularization term at the discrete level that does not integrate discretization errors, only equilibrium errors. Secondly, I plan to finalize the work initiated in [C7], which consists in using a model of the imaging process within the motion tracking algorithm, in order to alleviate the impact of imaging bias such as partial voluming.

Publications

Journal papers

Submitted & In Preparation

- [J44] E. Berberoglio, C. T. Stoeck, S. Kozerke, and **M. Genet**. “Quantification of Left Ventricular Strain by Joint Analysis of 3D Tagging and Cine MR Images”. *In revision at Medical Image Analysis*.
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Ceramic Matrix Woven Composites

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- [29] **M. Genet**, M. Rausch, L. C. Lee, J. M. Guccione, and E. Kuhl (2014). “Differential Growth-Induced Residual Stress in Arteries and the Heart”. *11th World Congress on Computational Mechanics (WCCM)*. Barcelona, Spain

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- [27] N. Tueni, J. Vizet, **M. Genet**, A. Pierangelo, and J.-M. Allain (2020a). “Investigation of Microstructure Evolution and Mechanical Properties in Cardiac Tissue”. *45ème Congrès de La Société de Biomécanique (SB)*. Metz, France
- [26] **M. Genet**, J. Diaz, D. Chapelle, and P. Moireau (2020). “On a Reduced Cylindrical Model of the Left Ventricular Dynamics”. *Virtual Physiological Human (VPH): When Models, Methods and Experiments Meet the Clinics*. Paris, France
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- [19] B. Baillargeon, I. Costa, L. C. Lee, **M. Genet**, J. F. Wenk, E. Kuhl, J. L. Navia, and J. M. Guccione (2014). “A Whole Heart Simulation of the Effects of a Novel Mitral Sub-Valvular Ring on Regional Mechanics”. *7th World Congress in Biomechanics (WCB)*. Boston, Massachusetts, USA
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- [14] **M. Genet**, A. P. Tomsia, and R. O. Ritchie (2012). “An Homogenized Damage Model for Ceramic Structures Made by Freezecastng”. *10th World Congress on Computational Mechanics (WCCM)*. São Paulo, Brazil
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- [11] C. Fagiano, E. Baranger, P. Ladevèze, and **M. Genet** (2012). “Numerical Tools for the Mesoscale Modeling of Thermostructural Woven Composites”. *15th European Conference on Composite Materials (ECCM)*. Venice, Italy
- [10] E. Baranger, L. Marcin, **M. Genet**, C. Cluzel, P. Ladevèze, and A. Mouret (2011). “Toward a Damage Tolerance Analysis of CMCs with a Self-Healing Matrix”. *3rd International Conference on Self-Healing Materials (ICSHM)*. Bristol, United Kingdom
- [9] L. Marcin, **M. Genet**, E. Baranger, and P. Ladevèze (2011). “Vers La Tolérance Au Dommage Pour Les CMCs: Prédiction de La Durée de Vie de Structures”. *17èmes Journées Nationales Sur Les Composites (JNC)*. Poitiers, France
- [8] **M. Genet** and P. Ladevèze (2010a). “A Family of Prediction Tools for Fine Ceramic Fibers Subcritical Cracking”. *7th International Conference on High Temperature Ceramic Matrix Composites (HTCMC)*. Bayreuth, Germany
- [7] L. Marcin, E. Baranger, P. Ladevèze, **M. Genet**, and L. Barroumes (2010). “Prediction of the Lifetime of Self-Healing Ceramic Matrix Composites: Applications to Structural Computations”. *7th International Conference on High Temperature Ceramic Matrix Composites (HTCMC)*. Bayreuth, Germany
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Titre: titre (en français)

Mots clés: Biomécanique, Modélisation & Simulation, Cœur, Poumon, Croissance & Remodelage, Suivi de mouvement

Résumé: Dans ce document, je présente un résumé de mes activités de recherche des neuf dernières années. Mon travail appartient au domaine général de la science de l'ingénierie biomédicale, dont les objectifs sont (i) de mieux comprendre le phénomène de la vie dans la santé et la maladie, et (ii) de développer et d'analyser de nouveaux concepts et méthodes pour l'ingénierie biomédicale, *i.e.* qui seront la base d'outils objectifs et quantitatifs pour la médecine, *i.e.* pour le diagnostic et le traitement de patients. Plus précisément, mes recherches portent sur le développement (i) de modèles de la mécanique des tissus et organes vivants (exclusivement le cœur jusqu'en 2017, puis également les poumons), (ii) de méthodes et outils de simulation de tels modèles (qui peuvent être utilisés comme outil de prédiction, *i.e.* de pronostic, mais aussi pour étudier des hypothèses concurrentes), et (iii) des méthodes et outils pour l'estimation de paramètres de modèles basés sur des données cliniques (qui peuvent être utilisés pour es-

timer des quantités qui ne peuvent pas être mesurées *in vivo*, *i.e.* le diagnostic augmenté, et de construire des modèles personnalisés qui peuvent être utilisés pour concevoir des thérapies personnalisées pour un patient donné, *i.e.* le traitement optimisé).

Dans le manuscrit, la présentation des différents travaux est découpée en trois chapitres, basés sur la problématique scientifique principale. Le chapitre 1 concerne la modélisation biomécanique, à différentes échelles spatiales (microstructure, tissu, organe) et temporelles (fonctionnelle, remodelage). Le chapitre 2 concerne les développements méthodologiques pour la personnalisation de modèles à partir de données cliniques, et plusieurs études applicatives. Le chapitre 3 concerne le suivi de mouvement, en se concentrant sur la régularisation mécanique et plusieurs études applicatives. Dans le dernier chapitre, je donne quelques perspectives sur mes recherches en cours et futures.

Title: Some contributions to cardiac and pulmonary biomechanical modeling, simulation & estimation

Keywords: Biomechanics, Modeling & Simulation, Heart, Lung, Growth & remodeling, Motion tracking

Abstract: In this document, I present a summary of my research activities of the past nine years. My work belongs to the general field of biomedical engineering science, whose objectives are (i) to better understand the phenomenon of life in health and disease, and (ii) to develop and analyze novel concepts and methods for biomedical engineering, *i.e.*, which will be the foundation of objective and quantitative tools for medicine, *i.e.*, for the diagnosis and treatment of patients. More precisely, my research focuses on the development of (i) models of the mechanics of living tissues and organs (exclusively the heart until 2017, then the lungs as well), (ii) methods and tools for the simulation of such models (which can be used as a prediction tool, *i.e.*, prognosis, but also to investigate competing hypothesis), and (iii) methods and tools for the estimation of model parameters based

on clinical data (which can be used to estimate quantities that cannot be measured *in vivo*, *i.e.*, augmented diagnosis, and to build personalized models that can be used to design patient-specific therapies, *i.e.*, optimized treatment).

In the manuscript, the presentation of the various works is split into three chapters, based on the main scientific problematic. Chapter 1 concerns biomechanical modeling, at various spatial (microstructural, tissue, organ) and temporal (function, remodeling) scales. Chapter 2 concerns methodological developments for model personalization based on clinical data, and multiple applications studies. Chapter 3 concerns motion tracking, focusing on mechanical regularization and multiple application studies. In the final chapter, I give some perspectives on ongoing and future research.