Activity Report 2016

Project-Team ASCLEPIOS

Analysis and Simulation of Biomedical Images

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Neuroscience and Medecine

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Creation of the Project-Team: 2005 November 01

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1. Members

Research Scientists

Nicholas Ayache [Team leader, Inria, Senior Researcher, HDR]
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Hervé Lombaert [Inria, Starting Research position, until Oct. 2016]
Marco Lorenzi [Inria, Researcher, from Dec. 2016]
Xavier Pennec [Inria, Senior Researcher, HDR]
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Engineers

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Loïc Cadour [Inria]
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PhD Students

Thomas Demarcy [Oticon Medical, Thesis CIFRE, until 2017]
Loïc Devilliers [Univ. Nice, ENS de Cachan, until 2018]
Sophie Giffard Roisin [Inria, VP2HF, until 2017]
Mehdi Hadj Hamou [Inria, ERC MedYMA , until Sep 2016]
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Matthieu Lê [Inria, ERC MedYMA, until June 2016]
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Loic Le Folgoc [Inria, until Jan. 2016]
Chloé Audigier [Inria, granted by Siemens Corp. Technologies until March 2016]

Visiting Scientists

Alan Garny [University of Auckland]
Clair Vandersteen [CHU Nice, Eyes Nose Throat Surgeon, until Sep 2016]

Administrative Assistant

Isabelle Strobant [Inria, AI]

2. Overall Objectives

2.1. Overall Objectives

There is an irreversible evolution of medical practice toward more quantitative and personalized decision processes for prevention, diagnosis and therapy.

This evolution is supported by a constantly increasing number of biomedical devices providing *in vivo* measurements of structures and processes inside the human body, at scales varying from the organ to the cellular and even molecular level. Among all these measurements, biomedical images of various forms play an even more central role everyday, along with the exploitation of the genetic information attached to each patient.

Facing the need for a more quantitative and personalized medicine based on larger and more complex sets of measurements, there is a crucial need for developing:

1. advanced image analysis tools capable of extracting the pertinent information from biomedical images and signals;
2. advanced models of the human body to correctly interpret this information; and
3. large distributed databases to calibrate and validate the models.

3. Research Program

3.1. Introduction

Tremendous progress has been made in the automated analysis of biomedical images during the past two decades [72]. Readers who are neophytes to the field of medical imaging will find an interesting presentation of acquisition techniques of the main medical imaging modalities in [64], [62]. Regarding target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [60], in N. Ayache's article [67] and in recent review articles [68], [72]. The scientific journals *Medical Image Analysis* [55], *Transactions on Medical Imaging* [61], and *Computer Assisted Surgery* [63] are also good reference material. One can have a good vision of the state of the art from the proceedings of the MICCAI'2010 (Medical Image Computing and Computer Assisted Intervention [58], [59]) and ISBI'2010 (Int. Symp. on Biomedical Imaging [57]) conferences.

For instance, for rigid parts of the body like the head, it is now possible to fuse in a completely automated manner images of the same patient taken from different imaging modalities (e.g. anatomical and functional), or to track the evolution of a pathology through the automated registration and comparison of a series of images taken at distant time instants [73], [83]. It is also possible to obtain from a Magnetic Resonance Image (MRI) of the head a reasonable segmentation of skull tissues, white matter, grey matter, and cerebro-spinal fluid [86], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [66], Ultrasound or Nuclear Medicine images [74].

Despite these advances and successes, statistical models of anatomy are still very crude, resulting in poor registration results in deformable regions of the body, or between different subjects. If some algorithms exploit the physical modeling of the image acquisition process, only a few actually model the physical or even the physiological properties of the human body itself. Coupling biomedical image analysis with anatomical and physiological models of the human body could not only provide a better understanding of observed images and signals, but also more efficient tools for detecting anomalies, predicting evolutions, simulating and assessing therapies.

3.2. Medical Image Analysis

The quality of biomedical images tends to improve constantly (better spatial and temporal resolution, better signal to noise ratio). Not only are the images multidimensional (3 spatial coordinates and possibly one temporal dimension), but medical protocols tend to include multisequence (or multiparametric) [1] and multi-modal images [2] for each single patient.

[1] Multisequence (or multiparametric) imaging consists in acquiring several images of a given patient with the same imaging modality (e.g. MRI, CT, US, SPECT, etc.) but with varying acquisition parameters. For instance, using MRI, patients followed for multiple sclerosis may undergo every six months a 3D multisequence MR acquisition protocol with different pulse sequences (called T1, T2, PD, Flair, etc.): by varying some parameters of the pulse sequences (e.g Echo Time and Repetition Time), images of the same regions are produced with quite different contrasts depending on the nature and function of the observed structures. In addition, one of the acquisitions (T1) can be combined with the injection of a contrast product (typically Gadolinium) to reveal vessels and some pathologies. Diffusion Tensor Images (DTI) can be acquired to measure the self diffusion of protons in every voxel, allowing the measurement for instance of the direction of white matter fibers in the brain (the same principle can be used to measure the direction of muscular fibers in the heart). Functional MRI of the brain can be acquired by exploiting the so-called Bold Effect (Blood Oxygen Level Dependency): slightly higher blood flow in active regions creates a subtle higher T2* signal which can be detected with sophisticated image processing techniques.

[2] Multimodal acquisition consists in acquiring from the same patient images of different modalities, in order to exploit their complementary nature. For instance, CT and MR may provide information on the anatomy (CT providing contrast between bones and soft tissues while MR within soft tissues of different nature) while SPECT and PET images may provide functional information by measuring a local level of metabolic activity.

Despite remarkable efforts and advances during the past twenty years, the central problems of segmentation and registration have not been solved in the general case. It is our objective in the short term to work on specific versions of these problems, taking into account as much *a priori* information as possible on the underlying anatomy and pathology at hand. It is also our objective to include more knowledge of the physics of image acquisition and observed tissues, as well as of the biological processes involved. Therefore the research activities mentioned in this section will incorporate the advances made in Computational Anatomy and Computational Physiology, as described in sections 3.3 and 3.4.

We plan to pursue our efforts on the following problems:

- multi-dimensional, multi-sequence and multi-modal image segmentation; and
- image Registration/Fusion.

3.3. Computational Anatomy

The aim of Computational Anatomy (CA) is to model and analyse the biological variability of the human anatomy. Typical applications cover the simulation of average anatomies and normal variations, the discovery of structural differences between healthy and diseased populations, and the detection and classification of pathologies from structural anomalies. [3]

Studying the variability of biological shapes is an old problem (cf. the book "On Shape and Growth" by D'Arcy Thompson [85]). Significant efforts have since been made to develop a theory for statistical shape analysis (one can refer to [71] for a good summary, and to the special issue of Neuroimage [84] for recent developments). Despite all these efforts, there are a number of challenging mathematical issues that remain largely unsolved. A particular issue is the computation of statistics on manifolds that can be of infinite dimension (e.g the group of diffeomorphisms).

There is a classical stratification of the problems into the following 3 levels [80]:

1. construction from medical images of anatomical manifolds of points, curves, surfaces and volumes;
2. assignment of a point to point correspondence between these manifolds using a specified class of transformations (e.g. rigid, affine, diffeomorphism);
3. generation of probability laws of anatomical variation from these correspondences.

We plan to focus our efforts on the following problems:

1. statistics on anatomical manifolds;
2. propagation of variability from anatomical manifolds;
3. linking anatomical variability to image analysis algorithms; and
4. grid-computing strategies to exploit large databases.

3.4. Computational Physiology

The objective of Computational Physiology (CP) is to provide models of the major functions of the human body and numerical methods to simulate them. The main applications are in medicine where CP can for instance be used to better understand the basic processes leading to the appearance of a pathology, to model its probable evolution and to plan, simulate, and monitor its therapy.

[3] The NIH has launched in 2005 the Alzheimer's Disease Neuroimaging Initiative (60 million USD), a multi-center MRI study of 800 patients who will be followed during several years. The aim is to establish new surrogate end-points from the automated analysis of temporal sequences, which is a challenging goal for researchers in Computational Anatomy. The data is to made available to qualified research groups involved or not in the study.

Quite advanced models have already been proposed to study at the molecular, cellular and organ level a number of physiological systems (see for instance [81], [78], [69], [82], [75]). While these models and new ones need to be developed, refined or validated, a grand challenge that we want to address in this project is the automatic adaptation of the model to a given patient by comparing the model with the available biomedical images and signals and possibly also some additional information (e.g. genetic). Building such *patient-specific models* is an ambitious goal, which requires the choice or construction of models with a complexity adapted to the resolution of the accessible measurements and the development of new data assimilation methods coping with massive numbers of measurements and unknowns.

There is a hierarchy of modeling levels for CP models of the human body [70]:

- the first level is mainly geometrical, and addresses the construction of a digital description of the anatomy [65], essentially acquired from medical imagery;
- the second level is physical, involving mainly the biomechanical modeling of various tissues, organs, vessels, muscles and bone structures [76];
- the third level is physiological, involving the modeling of the functions of the major organ systems [77] (e.g. cardiovascular, respiratory, digestive, central or peripheral nervous, muscular, reproductive, hormonal) or some pathological metabolism (e.g. evolution of cancerous or inflammatory lesions, formation of vessel stenoses, etc.); and
- a fourth level is cognitive, modeling the higher functions of the human brain [56].

These different levels of modeling are closely related to each other, and several physiological systems may interact with each other (e.g. the cardiopulmonary interaction [79]). The choice of the resolution at which each level is described is important, and may vary from microscopic to macroscopic, ideally through multiscale descriptions.

Building this complete hierarchy of models is necessary to evolve from a *Visible Human project* (essentially the first level of modeling) to a much more ambitious *Physiological Human project* (see [77], [78]). We will not address all the issues raised by this ambitious project, but instead focus on the topics detailed below. Among them, our objective is to identify some common methods for the resolution of the large inverse problem raised by the coupling of physiological models and medical images for the construction of patient-specific models (e.g. specific variational or sequential methods (EKF), dedicated particle filters). We also plan to develop specific expertise in the extraction of geometrical meshes from medical images for their further use in simulation procedures. Finally, computational models can be used for specific image analysis problems studied in section 3.2 (e.g. segmentation, registration, tracking). Application domains include

1. surgery simulation;
2. cardiac Imaging;
3. brain tumors, neo-angiogenesis, wound healing processes, ovocyte regulation, etc.

3.5. Clinical Validation

If the objective of many of the research activities of the project is the discovery of original methods and algorithms with a proof of its feasibility in a limited number of representative cases (i.e. proofs of concept) and publications in high quality scientific journals, we believe that it is important that a reasonable number of studies include a much more significant validation effort. As the BioMedical Image Analysis discipline becomes more mature, validation is necessary for the transformation of new ideas into clinical tools and/or industrial products. It also helps to get access to larger databases of images and signals, which in turn help to stimulate new ideas and concepts.

4. Highlights of the Year

4.1. Highlights of the Year

Marco Lorenzi has been recruited as Chargé de Recherche in the Asclepios team from December 2016.

4.1.1. Awards

- Nina Miolane received the l'Oréal-UNESCO Fellowship for Women In Science. She counts among the 30 awardees who have been selected by an independent jury to stress the excellence and originality of their scientific research and their dedication to share their knowledge in the broader society.
- Shuman Jia received the Best Challenge Paper Award during the 7th international workshop on Statistical Atlases and Computational Modeling of the Heart (STACOM), held in Conjunction with MICCAI 2016 in Athens, Greece.

BEST PAPER AWARD:

[39]
S. JIA, L. CADOUR, H. COCHET, M. SERMESANT. *STACOM-SLAWT Challenge: Left Atrial Wall Segmentation and Thickness Measurement Using Region Growing and Marker-Controlled Geodesic Active Contour*, in "7th International Statistical Atlases and Computational Modeling of the Heart (STACOM) Workshop, Held in Conjunction with MICCAI 2016", Athens, Greece, Lecture Notes in Computer Science, October 2016, In press, https://hal.inria.fr/hal-01373238

5. New Software and Platforms

5.1. LSVF

KEYWORDS: Health - Brain - Medical Image Processing - Medical Imaging

FUNCTIONAL DESCRIPTION:

The Longitudinal Stationary Velocity Fields Framework is a set of tools based on the SVF parameterization of diffeomorphic deformations that allows a new type of longitudinal deformation-based morphometric analyses. The framework comprises tools to compute the deformation encoded by the exponential of an SVF, the log-demons registration software and the Pole ladder, an algorithm to parallel transport deformation trajectories. These tools can be organized in a Longitudinal Log-Demons Pipeline (LLDP), to estimate the longitudinal brain deformations from image data series, transport them in a common space and perform statistical groupwise analyses.

Sources are available under custom licence.

- Participants: Mehdi Hadj-Hamou, Marco Lorenzi and Xavier Pennec
- Contact: Xavier Pennec
- URL: http://team.inria.fr/asclepios/software/stationary-velocity-field-tools/
- URL: http://team.inria.fr/asclepios/software/lcclogdemons/

5.2. medInria

KEYWORDS: Segmentation - Health - DWI - Visualization - Medical Imaging

SCIENTIFIC DESCRIPTION

It aims at creating an easily extensible platform for the distribution of research algorithms developed at Inria for medical image processing. This project has been funded by the D2T (ADT MedInria-NT) in 2010 and renewed in 2012. The Visages team leads this Inria national project and participates in the development of the common core architecture and features of the software as well as in the development of specific plugins for the team's algorithm.

FUNCTIONAL DESCRIPTION

MedInria is a free software platform dedicated to medical data visualization and processing.

- Participants: Jaime Garcia Guevara, Theodore Papadopoulo, Olivier Commowick, Rene-Paul Debroize, Guillaume Pasquier, Laurence Catanese, Olivier Commowick, Alexandre Abadie, Benoit Bleuze, Clement Philipot, Fatih Arslan, Florian Vichot, John Stark, Julien Wintz, Loïc Cadour, Maxime Sermesant, Michael Knopke, Nicolas Toussaint, Olivier Clatz, Pierre Fillard, Sergio Medina, Stephan Schmitt and Hakim Fadil
- Partners: HARVARD Medical School - IHU LIRYC - King's College London - UPF Barcelona - NIH
- Contact: Olivier Commowick
- URL: http://med.inria.fr

5.3. MUSIC

Multi-modality Platform for Specific Imaging in Cardiology

KEYWORDS: Health - Cardiac - Computer-assisted interventions - Cardiac Electrophysiology - Medical imaging

FUNCTIONAL DESCRIPTION

MUSIC is a software developed by the Asclepios research project in close collaboration with the IHU LIRYC in order to propose functionalities dedicated to cardiac interventional planning and guidance. This includes specific tools (algorithms of segmentation, registration, etc.) as well as pipelines. The software is based on the MedInria platform.

- Participants: Loïc Cadour, Maxime Sermesant, Florian Vichot, Hakim Fadil, Florent Collot and Mathilde Merle
- Contact: Maxime Sermesant
- URL: https://team.inria.fr/asclepios/software/music/

5.4. SOFA

Simulation Open Framework Architecture

KEYWORDS: Physical simulation - Health - Biomechanics - GPU - Computer-assisted surgery

FUNCTIONAL DESCRIPTION

SOFA is an Open Source framework primarily targeted at real-time simulation, with an emphasis on medical simulation. It is mostly intended for the research community to help develop new algorithms, but can also be used as an efficient prototyping tool. Based on an advanced software architecture, it allows : the creation of complex and evolving simulations by combining new algorithms with algorithms already included in SOFA, the modification of most parameters of the simulation (deformable behavior, surface representation, solver, constraints, collision algorithm, etc.) by simply editing an XML file, the building of complex models from simpler ones using a scene-graph description, the efficient simulation of the dynamics of interacting objects using abstract equation solvers, the reuse and easy comparison of a variety of available methods.

A software consortium around SOFA is currently being set up to strengthen the perenial developement of the plateform https://www.sofa-framework.org/consortium/. The software is available under the LGPL licence.

- Participants: Chloé Audigier, Sophie Giffard-Roisin, Qiao Zheng, Roch-Philippe Molléro and Hervé Delingette
- Contact: Hervé Delingette
- URL: http://www.sofa-framework.org

5.5. VP2HF

Virtual Physiological Human for Heart Failure Platform

KEYWORDS: Health - Cardiac - Medical - Image - Processing - Medical imaging

FUNCTIONAL DESCRIPTION

The VP2HF software is developed by the Asclepios team and brings together all the research produced by the VP2HF's partners. It contains MedInria plugins implemented by teams such as UPF Barcelona, KCL, and specific tools provided by Philips (algorithms of segmentation, scar segmentation, ...). It aims at integrating in a single clinical workflow, tools to improve the therapy selection and treatment optimisation for patients suffering from heart failure.

- Participants: Maxime Sermesant, Hakim Fadil and Loïc Cadour
- Contact: Maxime Sermesant
- URL: http://www.vp2hf.eu

6. New Results

6.1. Medical Image Analysis

6.1.1. Segmentation and Anatomical Variability of the Cochlea from Medical Images

Participants: Thomas Demarcy [Correspondant], Hervé Delingette, Clair Vandersteen [IUFC, Nice], Dan Gnansia [Oticon Medical], Nicholas Ayache.

This work is supported by the National Association for Research in Technology (ANRT) through the CIFRE Grant 2013-1165 and Oticon Medical (Vallauris). Part of this work is also funded by the European Research Council through the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images). This work is a collaboration with the Department of Ear Nose Throat Surgery (IUFC, Nice) and the Nice University Hospital (CHU).

Image segmentation, Surgery planning, Shape modeling, Anatomical variability, Cochlear implant, Temporal bone.

- We evaluated the optimal electrode diameter in relation to the cochlear shape [20].
- We proposed a novel framework for estimating the insertion depth and its uncertainty from segmented CT images based on a new parametric shape model [37].
- We provided a proof of concept for the estimation of postoperative cochlear implant electrode-array position from clinical CT [44] (Fig. 1).

6.1.2. Infarct Localization and Uncertainty Quantification from Myocardial Deformation

Participants: Nicolas Duchateau [Correspondant], Maxime Sermesant.

This work received the partial support from the European Union 7th Framework Programme (VP2HF FP7-2013-611823) and the European Research Council (MedYMA ERC-AdG-2011-291080).

Myocardial infarct, Computer-aided diagnosis, Dimensionality reduction, Biomechanical modeling.

- We build upon preliminary work for the automatic localization of myocardial infarct from local wall deformation, which has potential for risk stratification from routine examination such as 3D echocardiography. Non-linear dimensionality reduction serves to estimate the Euclidean space of coordinates encoding deformation patterns (training phase), and is combined with multi-scale kernel regressions to link the deformation patterns, the low-dimensional coordinates and the infarct location for new cases (testing phase).
- We extend this approach by considering the different components of myocardial strain considered in clinical practice, and by taking advantage of the space of low-dimensional coordinates to model uncertainty in the infarct localization [18].

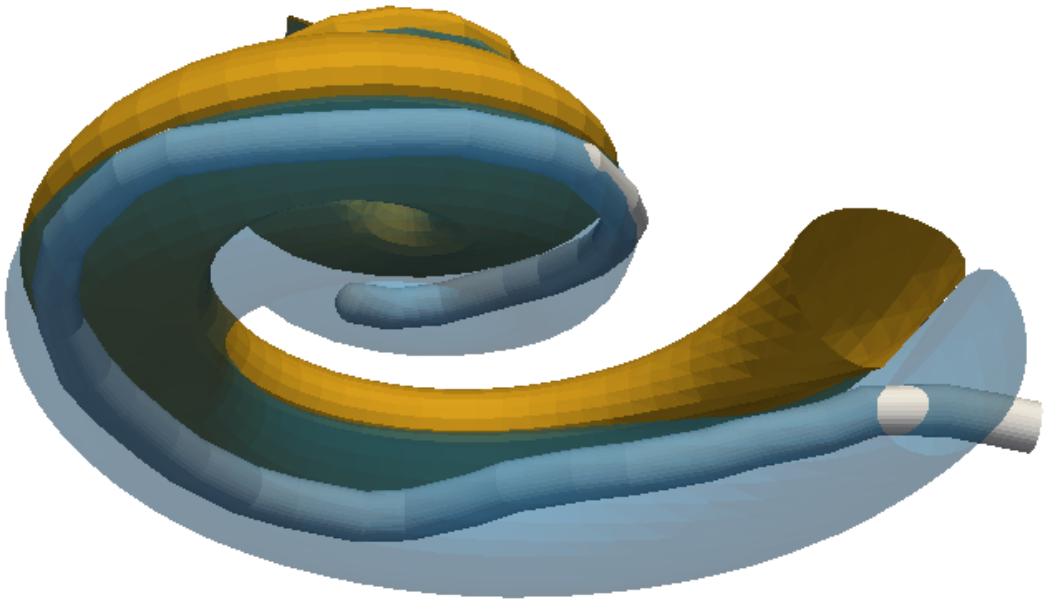

Figure 1. Cochlear implant electrode-array position (white) with respect to scala tympani (blue) and scala vestibuli (orange).

- These concepts were tested on 500 synthetic cases with infarcts of random extent, shape, and location, generated from a realistic electromechanical model, and 108 pairs of 3D echocardiographic sequences and delayed-enhancement magnetic resonance images from real cases. Infarct prediction is made at a spatial resolution more than 10 times smaller than the current diagnosis, made regionally. Our method is accurate, and significantly outperforms the clinically-used thresholding of the deformation patterns. Uncertainty adds value to refine the diagnosis and eventually re-examine suspicious cases.

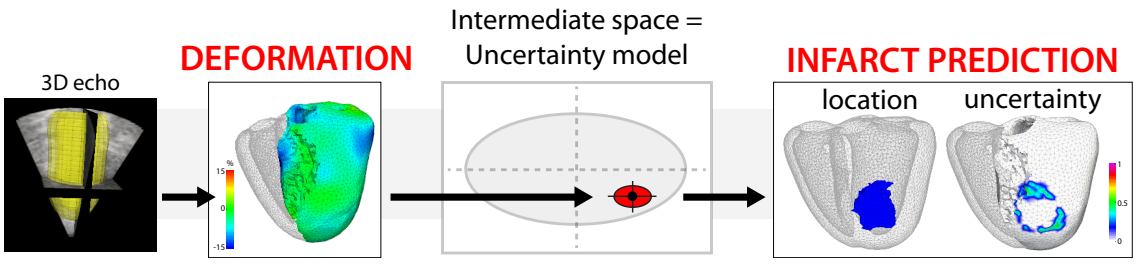

Figure 2. Overview of the proposed localization of myocardial infarct and uncertainty quantification from local wall deformation, extracted from 3D echocardiographic sequences.

6.1.3. Longitudinal Analysis and Modeling of Brain Development

Participants: Mehdi Hadj-Hamou [Correspondant], Xavier Pennec, Nicholas Ayache, Hervé Lemaitre [Inserm U1000], Jean-Luc Martinot [Inserm U1000].

This work is partly funded through the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Processing pipeline, Brain development, Adolescence, Longitudinal analysis, Non-rigid registration algorithm, Extrapolation.

1. We propose and detail a deformation-based morphometry computational framework, called Longitudinal Log-Demons Framework (LLDF), to estimate the longitudinal brain deformations from image data series, transport them in a common space and perform statistical group-wise analyses. It is based on freely available software and tools, and consists of three main steps (cf. Fig. 3):
   - Pre-processing;
   - Position correction; and
   - Non-linear deformation analysis.

   It is based on the LCC log-Demons non-linear symmetric diffeomorphic registration algorithm with an additional modulation of the similarity term using a confidence mask to increase the robustness with respect to brain boundary intensity artifacts.
2. This work led to a published journal publication [23].
3. The LLDF pipeline is exemplified on the longitudinal Open Access Series of Imaging Studies (OASIS) database and is applied to the study of longitudinal trajectories during adolescence, for which little is known. The aim of this project is to provide models of brain development during adolescence based on diffeomorphic registration parametrised by SVFs. We particularly focused our study on the link between sexual dimorphism and the longitudinal evolution of the brain. This work was done in collaboration with J.L. Martinot et H. Lemaître (Inserm U1000).

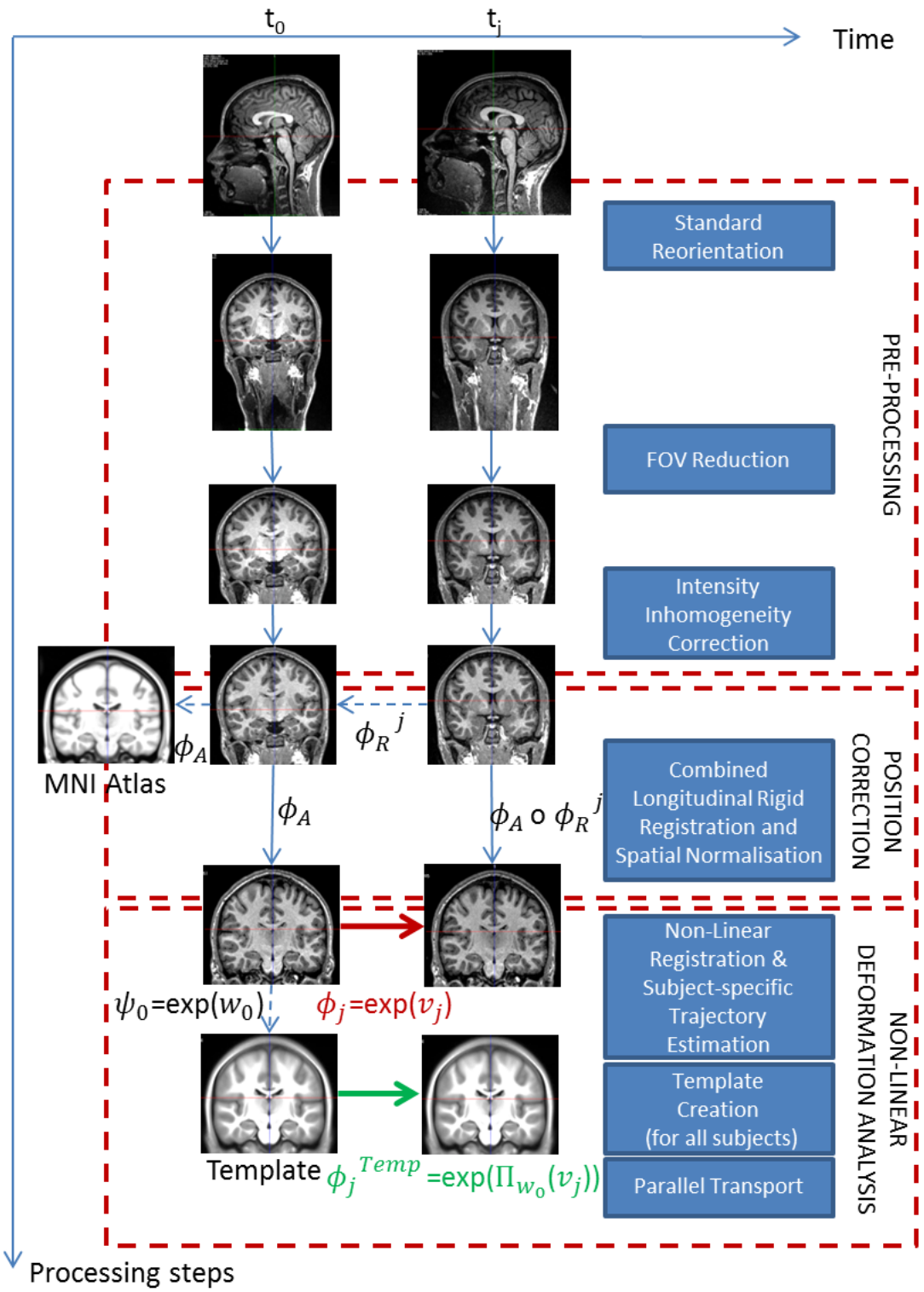

Figure 3. Processing pipeline for longitudinal analysis.

6.1.4. Left Atrial Wall Segmentation and Thickness Measurement using Region Growing and Marker-Controlled Geodesic Active Contour

Participants: Shuman Jia [Correspondant], Loïc Cadour, Hubert Cochet [IHU Liryc, Bordeaux], Maxime Sermesant.

The authors acknowledge the partial funding by the Agence Nationale de la Recherche (ANR)/ERA CoSysMed SysAFib and ANR MIGAT projects.

Atrial fibrillation, Left atrial wall thickness, Image segmentation, Cardiac computed tomography (CT), Region growing, Geodesic active contour.

We proposed a method to segment the left atrial (LA) wall and measure the wall thickness from cardiac computed tomography images, making use of patient-specific intensity value information and surrounding environment (see Fig. 4).

We partially implemented the method in the MUSIC software and tested our pipeline on 10 datasets. The results achieved a good match of wall thickness with manual segmentation. We received a Best Paper Award for this work [39] at the 2016 STACOM Workshop in Athens, Greece.

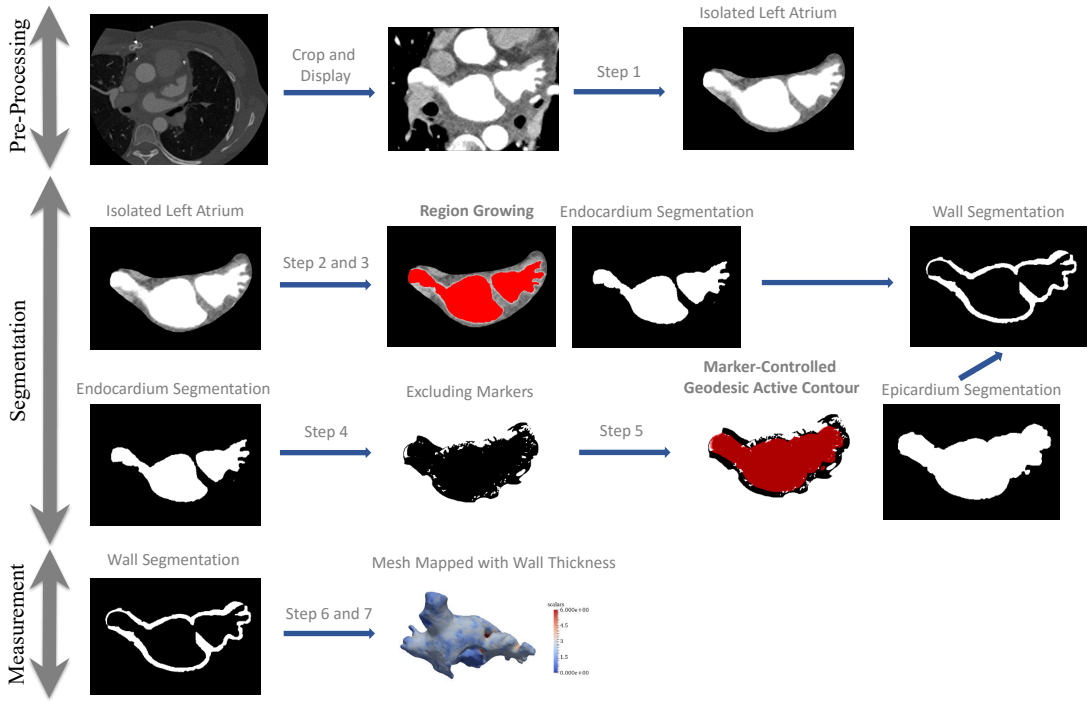

Figure 4. Flowchart of the method.

6.1.5. Weakly Supervised Learning for Tumor Segmentation

Participants: Pawel Mlynarski [Correspondant], Nicholas Ayache, Hervé Delingette, Antonio Criminisi [MSR].

This work is funded by the Inria-Microsoft joint center and is done in cooperation with Microsoft Research in Cambridge.

Deep Learning, Segmentation, Classification, Tumor.

- The goal of this work is to develop new machine learning methods for the localization and segmentation of tumors, without relying on the ground truth provided by experts. In particular, we study Deep Learning methods for classification and weakly supervised localization (Figure 5).
- We proposed two methods of synthesis of brain 3D MR images, in order to use them during the training of Neural Nets. The proposed methods showed to improve our performance in localization of brain tumors.

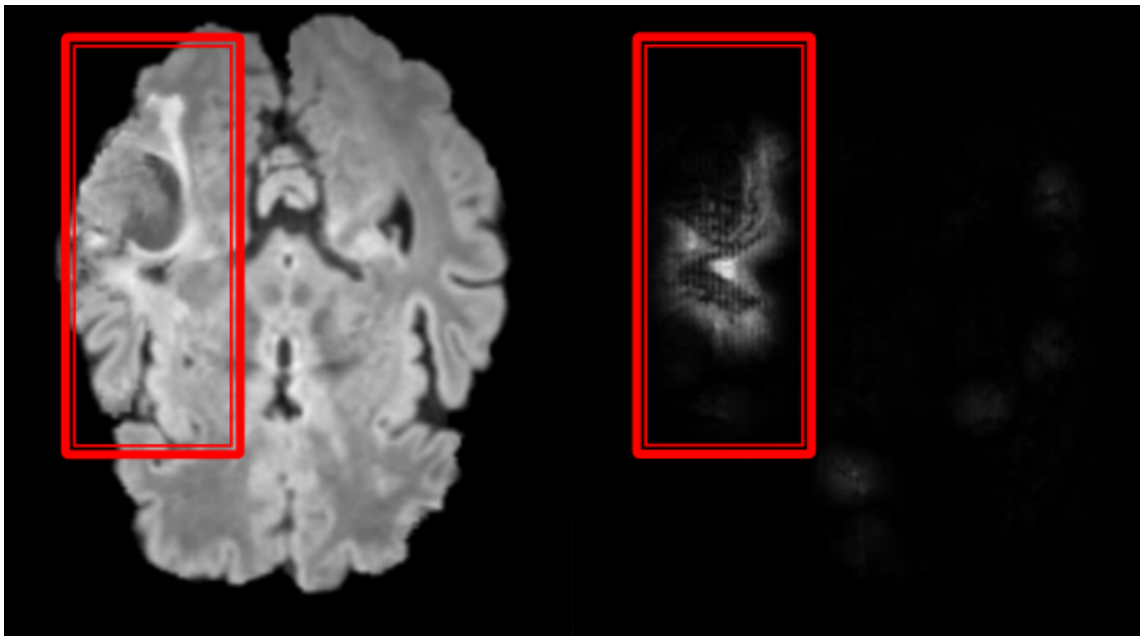

Figure 5. Left: axial slice of a brain MR image containing a tumor. Right: test of a weakly supervised (no ground truth provided during the training) Deep Learning method for an approximate localization of the tumor.

6.1.6. Inter-Operative Relocalization in Flexible Endoscopy

Participants: Anant Vemuri [Correspondant], Stéphane Nicolau, Luc Soler, Nicholas Ayache.

This work has been performed in collaboration with IHU Strasbourg and IRCAD, France.

Computer-assisted intervention, Barrett's esophagus, Biopsy relocalization, Electromagnetic tracking.

Oesophageal adenocarcinoma arises from Barrett's oesophagus, which is the most serious complication of gastro-oesophageal reflux disease. Strategies for screening involve periodic surveillance and tissue biopsies. A major challenge in such regular examinations is to record and track the disease evolution and relocalization of biopsied sites to provide targeted treatments.

In support of this work, the thesis [6] was defended before a committee of medical experts and scientific reviewers, on April 26th 2016.

References:

- Vemuri, Nicolau, Sportes, Marescaux, Soler, Ayache. Inter-Operative Biopsy Site Relocalization in Endoluminal Surgery [35].
- Nicolau, Vemuri, Soler, Marescaux. Anatomical site relocalisation using dual data synchronisation (patent) [49].

6.1.7. *Learning Brain Alterations in Multiple Sclerosis from Multimodal Neuroimaging Data*

Participants: Wen Wei, Nicholas Ayache, Stanley Durrleman [ARAMIS], Olivier Colliot [ARAMIS].

Multiple sclerosis, Neuroimageing.

The goal of this topic is to develop a machine learning approach that can predict different types of PET-derived brain alterations using multiple local and regional MRI measures.

6.1.8. *Deep Learning for Cardiac Image Analysis*

Participants: Qiao Zheng [Correspondant], Hervé Delingette, Nicholas Ayache.

Deep learning, Artificial neural network, Cardiac image.

Deep learning has proven to be very successful in computer vision and image understanding. However, its potential for medical image analysis has yet to be explored. We apply deep learning on cardiac images in order to learn cardiac image processing and anomaly detection. Our work includes data collection and preprocessing, software engineering, learning process design, etc.

6.2. Computational Anatomy

6.2.1. *Inconsistency of the Estimation of the Template in Quotient Spaces*

Participants: Loïc Devilliers [Correspondant], Stéphanie Allassonnière [Ecole Polytechnique], Alain Trouvé [ENS Cachan], Xavier Pennec.

Atlas computation, Template estimation, Fréchet mean, Quotient spaces, Inconsistency.

One issue in computational anatomy is to compute a template (a prototype of our data) in presence of two effects: an unknown deformation on data and the noise due to error in measurement in the ambient space considered here as an infinite dimensional linear space. The template computation can be done by minimizing an energy function (or variance) in the quotient space. In [50], we show that this method can lead to inconsistency that we quantify (see Fig. 6). This paves the way to a better understanding of the geometric and statistic foundation of the template estimation.

6.2.2. *Geometric Statistics for Computational Anatomy*

Participants: Nina Miolane [Correspondent], Xavier Pennec.

This work is conducted jointly with the Department of Statistics of Stanford, in the context of the associated team GeomStats of the program Inria@SiliconValley.

Statistics, Computational anatomy, Differential geometry, Template shape, Asymptotic bias.

- First, we have shown in [52] that the usual algorithm of template organ shape estimation is biased (see Fig. 7). We proposed two bootstrap procedures that quantify the bias and correct it.
- In [53], we unified the template estimation problem with a manifold learning problem. We showed how the Bayesian framework enables correction in cases that are pathological if only the Maximum Likelihood estimator is used.

6.2.3. *Barycentric Subspace Analysis: a new Symmetric Group-Wise Paradigm for Cardiac Motion Tracking*

Participants: Marc-Michel Rohé [Correspondant], Maxime Sermesant, Xavier Pennec.

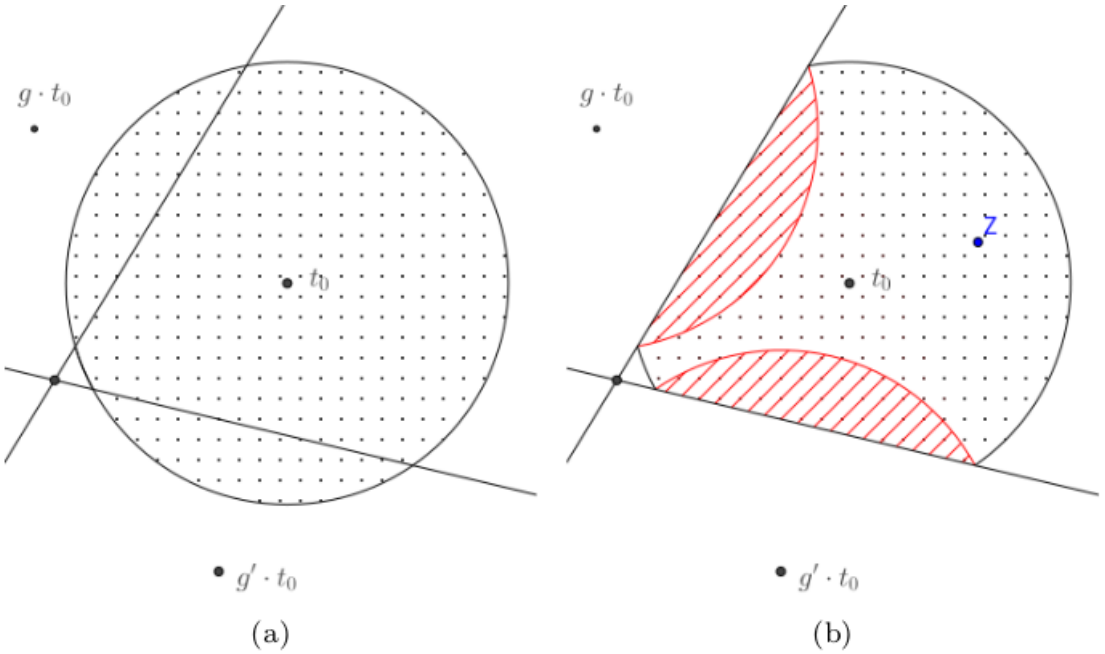

Figure 6. Geometric origin of the inconsistency: the distribution in the ambient space (panel (a)) is folded by the quotient (symmetries around the two lines, panel (b)), which biases the distribution in the quotient space.

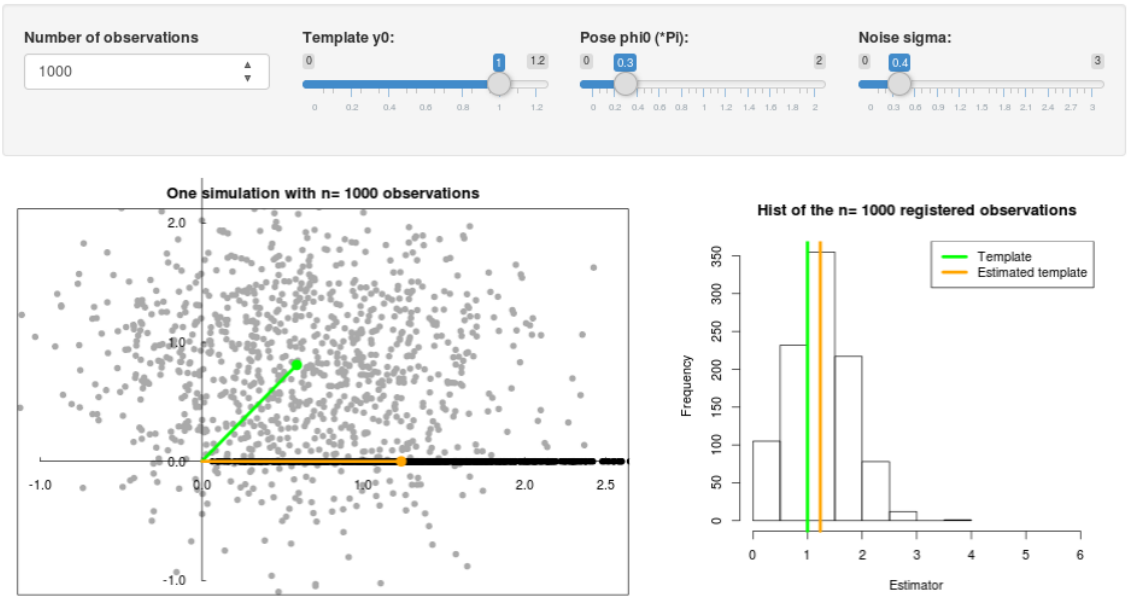

Figure 7. In this toy example, the template estimate (in orange) is biased with respect to the parameter (in green).

The authors acknowledge the partial funding by the EU FP7-funded project MD-Paedigree (Grant Agreement 600932).

Low-dimensional analysis, Cardiac motion, Registration, Image synthesis.

We propose a novel approach to study cardiac motion in 4D image sequences using low-dimensional subspace analysis [43]. Instead of building subspaces relying on a mean value we use a novel type of subspaces called Barycentric Subspaces, which are are implicitly defined based on $k+1$ reference images instead of being defined with respect to one reference image. This allows:

- First: to build low-dimensional representation of the cardiac motion signature which actually separates perfectly two different populations.
- Second: to build a better prior for the cardiac motion tracking, which improves the registration accuracy at end-systole by 30%.
- Third: to reconstruct the sequence of images with better accuracy than traditional single reference methods.

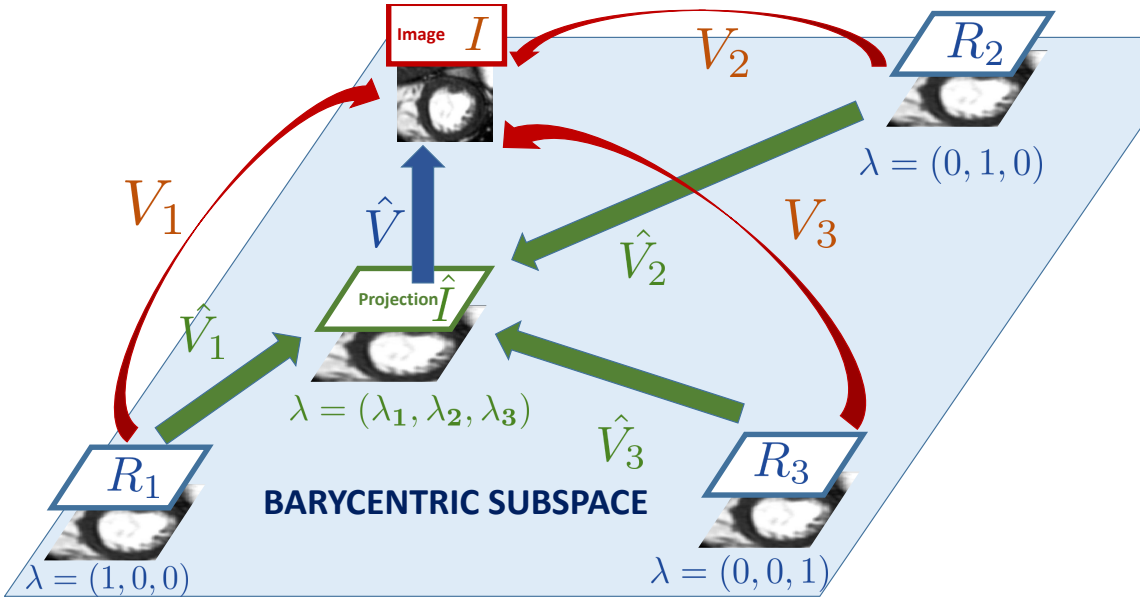

Figure 8.

6.2.4. Compact Representation of Longitudinal Deformations

Participants: Raphaël Sivera [Correspondant], Hervé Delingette, Xavier Pennec, Nicholas Ayache.

Longitudinal modeling, Learning in manifolds, Structured sparsity.

The use of a comprehensive and meaningful decomposition of a set of structural transformations would be useful to describe evolutions and to enhance diagnosis. In this context, we aim to model the brain anatomical evolution which goes along the Alzheimer's neurodegenerative disease. Based on the Stationary Velocity Fields representation of diffeomorphisms, we proposed a description of deformations in both space and time. The objective is to go beyond simple discriminative approaches (see Fig. 9) to propose a synthetic description of the disease evolution, population and subject-wise.

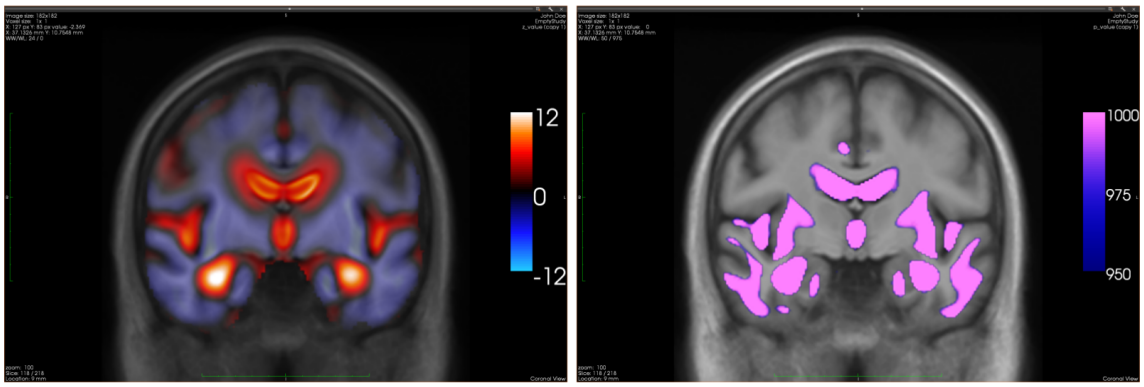

Figure 9. Left: z-values associated with group-wise differences between controls and Alzheimer-diagnosed subjects. Right: Areas of statistically significant differences.

6.3. Computational Physiology

6.3.1. Computational Modeling of Radiofrequency Ablation for the Planning and Guidance of Abdominal Tumor Treatment

Participants: Chloé Audigier [Correspondant], Hervé Delingette, Tommaso Mansi, Nicholas Ayache.

This work is carried out between the Asclepios research group, Inria Sophia Antipolis, France and the Medical Imaging Technologies, Healthcare Technology Center, Siemens Medical Solutions USA, Princeton, NJ.

Radio frequency ablation modeling, Patient-specific simulation, Lattice Boltzmann method, Computer model, Computational fluid dynamics, Heat transfer, Cellular necrosis, Parameter estimation, Therapy planning, Liver, Pre-clinical study, Medical imaging.

RFA is a minimally invasive therapy appropriated for liver tumor ablation. However, a patient-specific predictive tool to plan and guide the treatment is needed. We developed a computational framework for patient-specific planning of RFA with the following contributions:

- A detailed computational model of the biophysical mechanisms (heat transfer, cellular necrosis, hepatic blood flow) involved in RFA of abdominal tumors based on patient images.
- A new implementation of the bio-heat equations coupled with a cellular necrosis model using the Lattice Boltzmann Method (LBM) on Graphics Processing Units (GPU), which allows near real-time computation.
- A CFD and porous media solver using LBM algorithm to compute the patient-specific blood flow in the hepatic circulatory system and the blood flow distribution inside the parenchyma.
- A complete patient-specific geometry including hepatic venous and arterial circulation system.
- The automatic estimation of the main parameters of the model. Two personalization strategies tested and evaluated on clinical and pre-clinical data.
- The evaluation of the proposed model on a clinical dataset of ten patients.
- The evaluation on a preclinical dataset of five swines from a comprehensive experimental set-up specially designed for RFA model validation.

6.3.2. Cardiac Electrophysiology Simulation for Arrhythmia Treatment Guidance

Participants: Rocio Cabrera Lozoya [Correspondant], Maxime Sermesant, Nicholas Ayache.

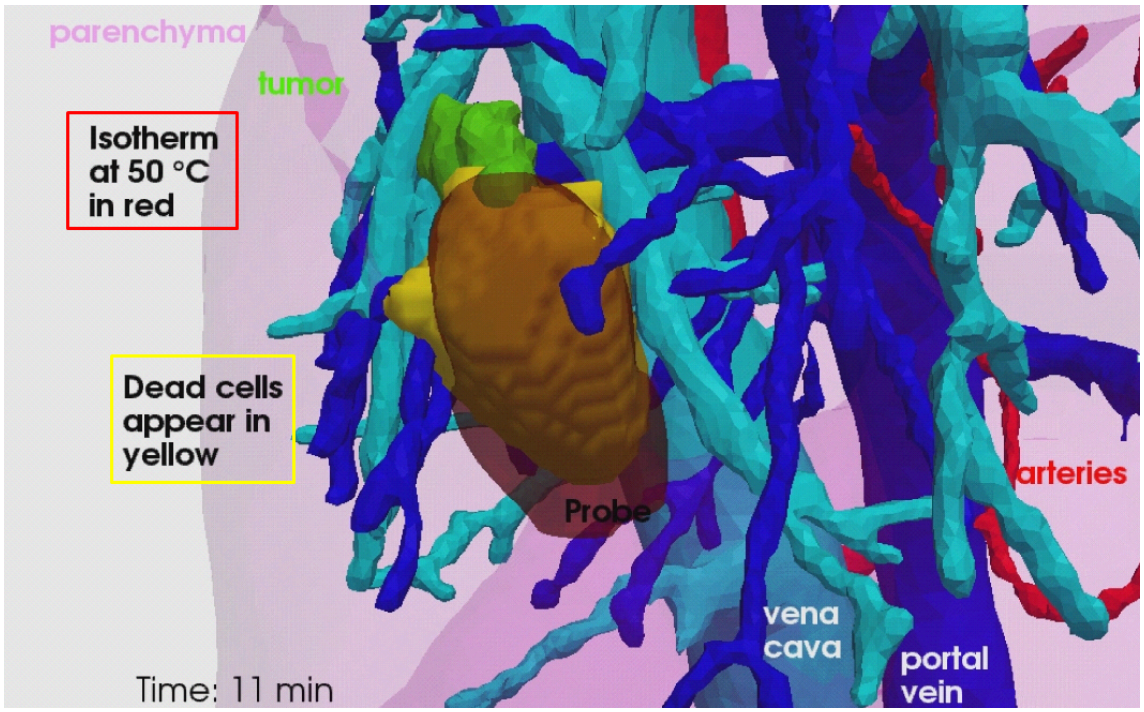

Figure 10. Computed isotherm at 50°C and computed necrosis appears in a subject-specific geometry.

Part of this work was funded by the European Research Council through the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Cardiac electrophysiology modeling, Intracardiac electrogram modeling, Radiofrequency ablation planning, Electroanatomical mapping.

1. We developed silico patient-specific models constructed from 3D delayed-enhanced MRI to simulate intracardiac electrograms (EGM), including abnormal EGM as they are potential radiofrequency ablation targets (see Fig. 11) [14].
2. We derived a cardiac model using personalized electro-anatomical parameters and imaging data to define the underlying ventricular tachycardia (VT) substrate and predict re-entrant VT circuits [16].

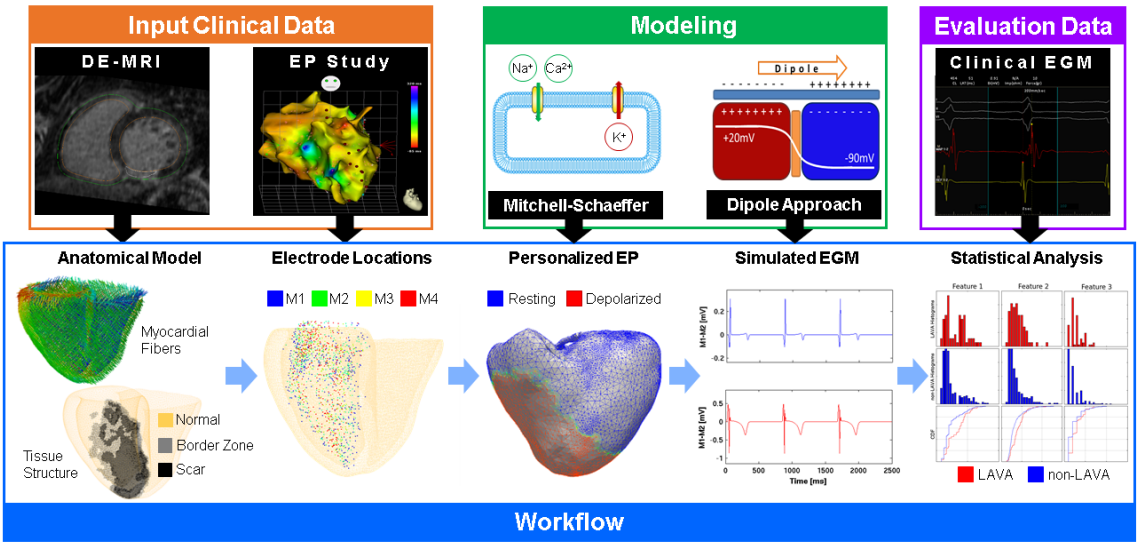

Figure 11. Pipeline developed to simulate intracardiac electrogram using patient-specific models.

6.3.3. Non-Invasive Personalisation of a Cardiac Electrophysiology Model from Body Surface Potential Mapping

Participants: Sophie Giffard Roisin [Correspondant], Maxime Sermesant, Nicholas Ayache, Hervé Delingette.

This work has been supported by the European Project FP7 under grant agreement VP2HF (no 611823) and the ERC Advanced Grant MedYMA (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Cardiac modeling, Personalised simulation, Inverse problem of ECG, Electrical simulation.

Within the VP2HF project, non-invasive cardiac electrical data has been acquired at the St Thomas' Hospital, London. It consists of Body Surface Potential Mapping (BSPM), which are recordings of the electrical potential on several locations on the surface of the torso. In [19], we use non-invasive data (BSPM) to personalise the main parameters of a cardiac electrophysiological (EP) model for predicting different pacing conditions (see Fig. 12). This is an encouraging first step towards a pre-operative prediction of different pacing conditions to assist clinicians for CRT decision and procedure. We have also worked on ECG data that are more commonly used in practice. In [38], we estimated the purkinje activation from 12-lead ECG using an intermittent left bundle brand block patient dataset.

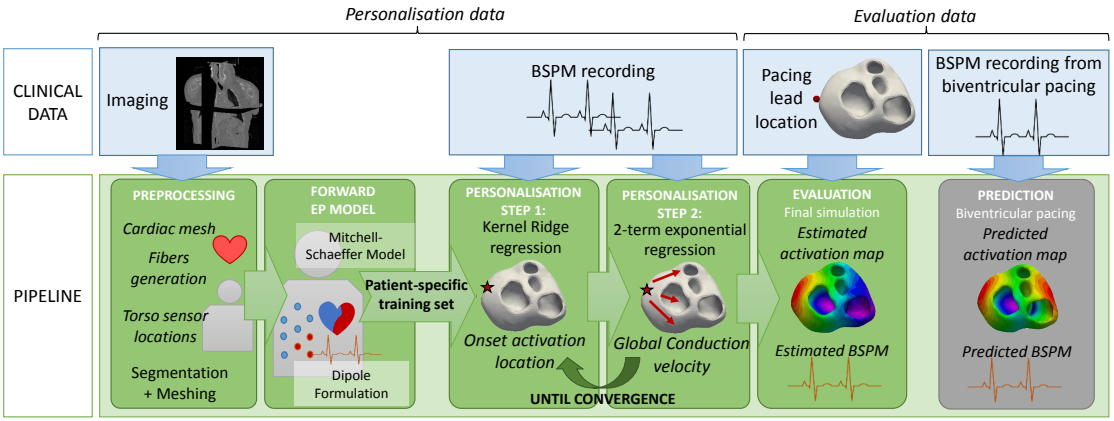

Figure 12. Personalisation framework.

6.3.4. Biophysical Modeling and Simulation of Longitudinal Brain MRIs with Atrophy in Alzheimer's Disease

Participants: Bishesh Khanal [Correspondant], Nicholas Ayache, Xavier Pennec.

This work has been partly supported by the European Research Council through the ERC Advanced Grant MedYMA (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Alzheimer's Disease (AD), Modeling brain deformation, Biophysical model, Simulation.

- We completed a simulation tool that can simulate large databases of virtual realistic longitudinal MRIs with known volume changes[51]. This was based on our biophysical model of brain deformation due to atrophy in Alzheimer's Disease (AD)[25].
- We have released our simulation software, named simul@trophy, as an open source software https://inria-asclepios.github.io/simul-atrophy/.

6.3.5. Brain Tumor Growth Personalization and Segmentation Uncertainty

Participants: Matthieu Lê [Correspondant], Hervé Delingette, Jan Unkelbach, Nicholas Ayache.

This work is carried out between the Ascelpios research group, Inria Sophia Antipolis, France and the Department of Radiation Oncology of the Massachusetts General Hospital, Boston, USA.

Tumor growth, Radiotherapy, Modeling, Personalization, Segmentation, Uncertainty, Bayesian.

- We elaborated a method for the synthesis of magnetic resonance images (MRIs) presenting glioblastoma [17].
- We elaborated a method for the sampling of several plausible segmentations, based on a single clinical one. This allows the uncertainty quantification of the radiotherapy plan based on several sample clinical target volumes [30].
- We elaborated a method for the Bayesian personalization of a brain tumor growth model based on clinical MRIs [28].
- We combined the segmentation sampling method with the tumor growth model personalization to personalize radiotherapy planning (see Fig. 14).

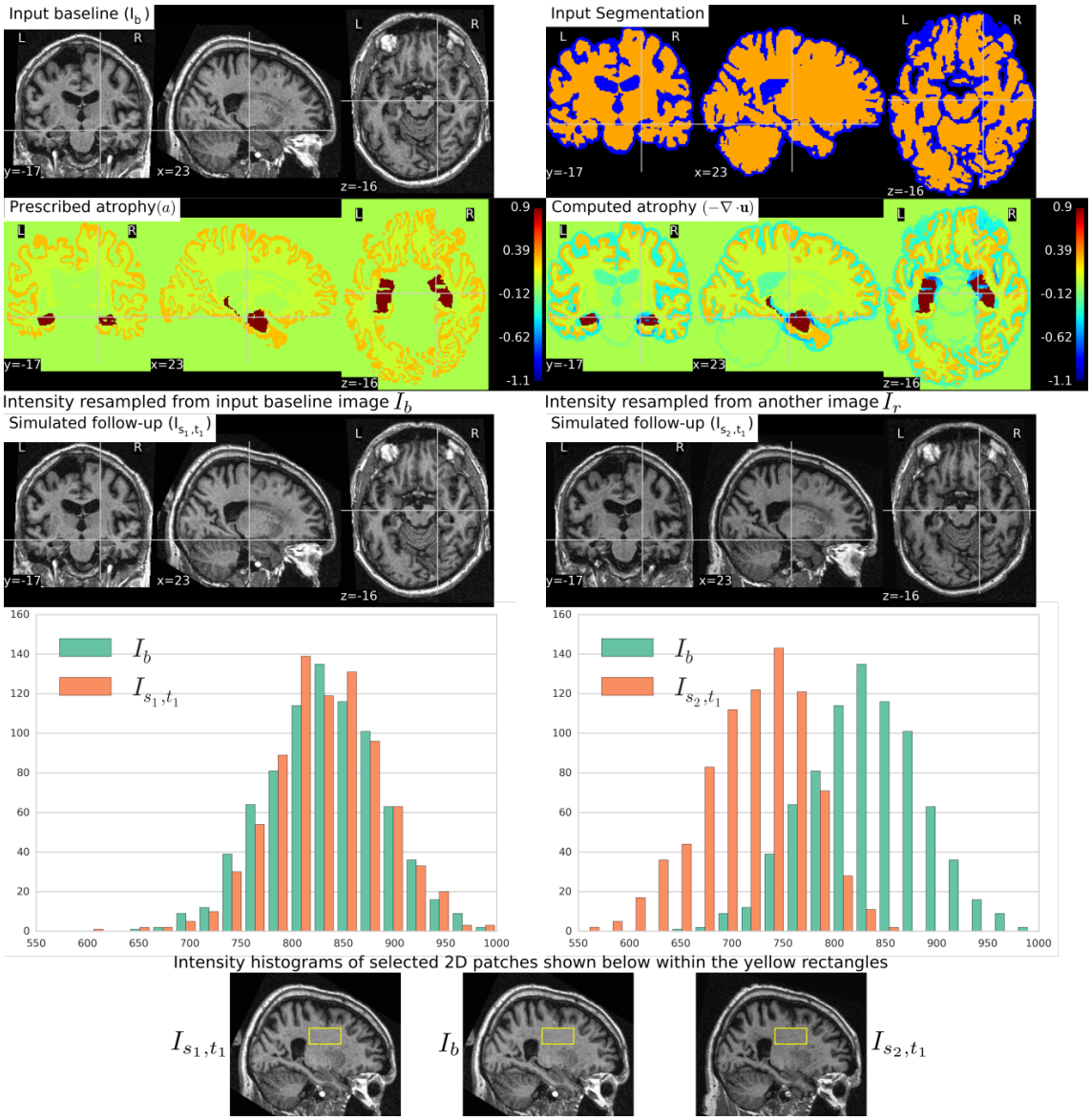

Figure 13. ***1st row:*** *(left) input baseline image I_b; (right) its input segmentation image.* ***2nd row:*** *(left) prescribed atrophy; (right) the atrophy computed from the simulated deformation.* ***3rd row:*** *(left) first time-point simulated follow-up image I_{s_1,t_1} where the intensity is resampled from the input baseline image I_b; (right) first time-point simulated follow-up image I_{s_2,t_2} where the intensity is resampled from a MRI taken at a different time-point than I_b, but of the same patient.* ***4th row:*** *intensity histogram comparison of the two simulated images in the third row.* ***5th row:*** *a relatively uniform region of which the histogram is shown.*

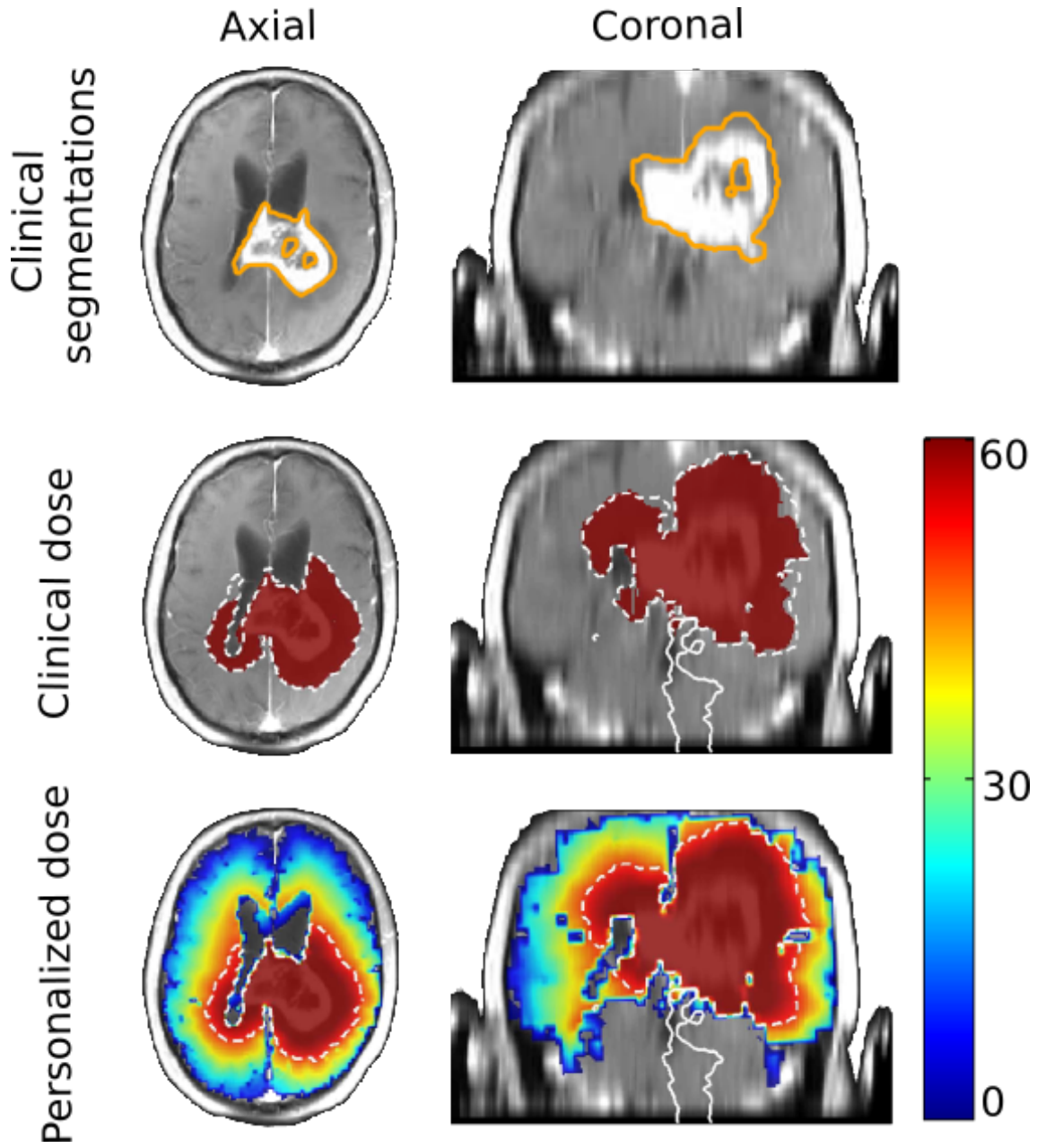

Figure 14. The clinical segmentation of the T1Gd abnormality (top, orange line) is used to define the clinical target volume (CTV, white dashed line) as a 2 cm expansion of the segmentation. In clinical settings, 60 Gy is prescribed to the CTV. We propose to personalize the prescription dose (bottom) to account for tumor infiltration and segmentation uncertainty.

6.3.6. A Multiscale Cardiac Model for Fast Personalisation and Exploitation

Participants: Roch Philippe Molléro [Correspondant], Xavier Pennec, Hervé Delingette, Nicholas Ayache, Maxime Sermesant.

This work has been partially funded by the EU FP7-funded project MD-Paedigree (Grant Agreement 600932) and contributes to the objectives of the ERC advanced grant MedYMA (2011-291080).

Cardiac modeling, Reduced model, Multi-fidelity modeling, Parameter estimation, Finite element mechanical modeling.

We developped a multi-fidelity 0D/3D cardiac model that allows us to get reliable (and extremely fast) approximations of the global behaviour of the 3D model with 0D simulations.

By making geometrical assumptions of symmetry, we first built a reduced 0D model of the heart which is very fast (15 beats/seconds). Then, we developped an original coupling method between the parameters of the 3D model and those of the 0D model. We used this multi-fidelity of the heart (in 0D and 3D) to speed-up an efficient optimization algorithm (the genetic algorithm CMA-ES) for the 3D model. As a result, we now have a fast personalisation method for the 3D model (see 15).

This methodology lead to a publication and poster presentation at the MICCAI Conference 2016 [41].

We applied this methodology in particuar to the cohort of 34 different heart geometries and data from the project MD-PAEDIGREE.

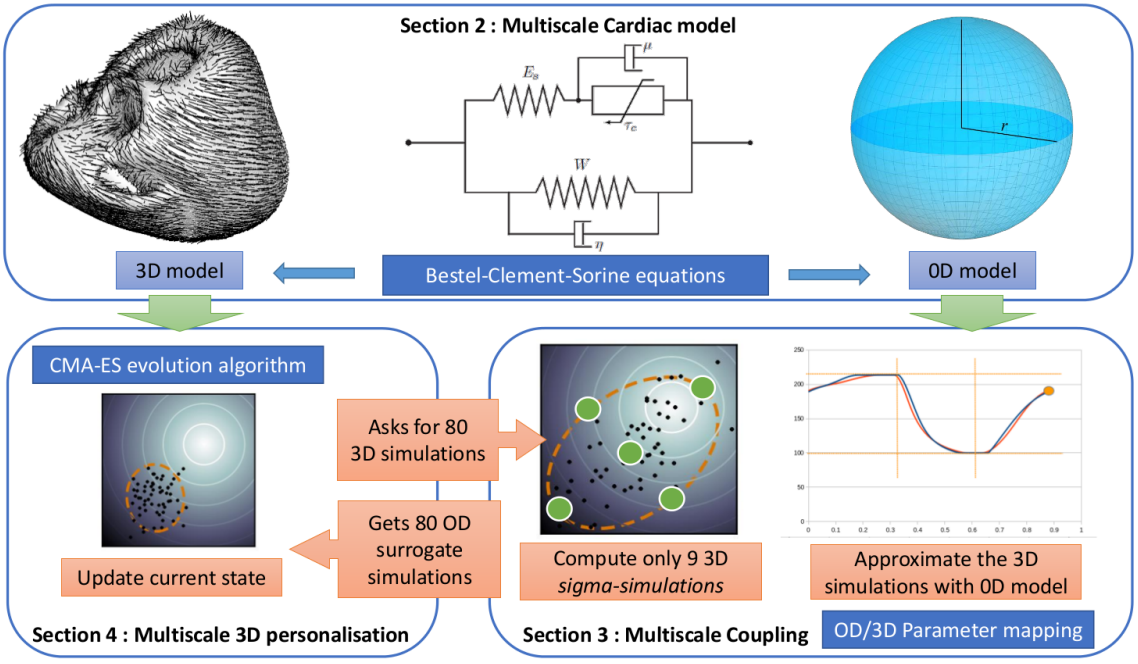

Figure 15. Multi-fidelity model and personalisation pipeline.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

7.1.1. CIFRE PhD Fellowships

7.1.1.1. Neurelec/Oticon Medical

Participants: Thomas Demarcy [correspondent], Hervé Delingette, Nicholas Ayache, Dan Gnansia [Oticon Medical].

The work of Thomas Demarcy, *Segmentation and anatomic variability of the cochlea and other temporal bone structures from medical images*, is supported by a PhD fellowship from the Neurelec/Oticon Medical company.

7.1.2. Inria - Mauna Kea Technologies I-Lab SIWA

Participants: Nicholas Ayache [correspondent], Xavier Pennec, Marzieh Kohandani Tafreshi, Rémi Cuingnet.

This I-lab involves the Mauna Kea Technologies company.

The first focus of this I-lab is to develop efficient and friendly content-based image retrieval (CBIR) tools to help users make a diagnosis. The second focus is on image registration to provide near real-time and robust image registration tools built on GPU implementations for image stabilization and super-resolution since it is a critical method for the smart atlas.

For more information, see this link [4]. The I-lab SIWA ended in March 2016.

7.1.3. Microsoft Research

Microsoft Research is funding through the Inria-Microsoft joint lab the projects "4D Cardiac MR Images" [5] and "Medilearn" [6] which aim at analyzing large databases of cardiac images to help the diagnosis of cardiac diseases and planning of therapy. This project involves A. Crimisi from MSR and partially funds the PhDs of Loic Le Folgoc, Pawel Mlynarski as well as the post doctoral stay of Hervé Lombaert.

7.1.4. Spin-off company Therapixel

Therapixel[7] is a spin-off of the Asclepios (Inria Sophia Antipolis) and Parietal (Inria Saclay) project teams founded in 2013. Therapixel makes surgical information systems. It relies on depth sensing, advanced software processing and innovative user interfaces to provide touchless control of the computer. This technology allows for a direct control of the computer, which sterility constraints made impractical in the past. In 2015, Therapixel obtained the CE marking of its product on touchless visualization of medical images.

7.1.5. Siemens HealthCare

Siemens Healthcare, Medical Imaging Technologies, Princeton, NJ (U.S.A). is funding the Phd work of Julian Krebs which aims at developping robust medical image registration methods

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. Consulting for Industry

Nicholas Ayache is a scientific consultant for the company Mauna Kea Technologies (Paris).

[4] https://lisa.sophia.inria.fr/siwa-loasis-numerique-dinria-et-de-mauna-kea-706.html
[5] http://www.msr-inria.fr/projects/4d-cardiac-mr-images
[6] http://www.msr-inria.fr/projects/medilearn
[7] http://www.therapixel.com/

8.1.2. Collaboration with national hospitals

The Asclepios-project team collaborates with the following 3 French IHU (University Hospital Institute): the IHU-Strasbourg (Pr J. Marescaux and L. Soler) on image-guided surgery, the IHU-Bordeaux (Pr M. Haïssaguere and Pr P. Jaïs) on cardiac imaging and modeling and the IHU-Pitié Salpétrière (Dr. O. Colliot and S. Durrleman) on neuroimaging.

We also have long term collaborations with the CHU Nice and Centre Antoine Lacassagne in Nice.

The Asclepios-project team is part of the EQUIPEX MUSIC consortium with Bordeaux University Hospital, which aim is to exploit an XMR interventional room equipped with a MUSIC workstation.

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

8.2.1.1. MD PAEDIGREE

Title: Model-Driven European Paediatric Digital Repository

Programme: FP7

Period: March 2013 - February 2017

Coordinator: Ospedale Pediatrico Bambini Gesù, Rome.

Partners:

Athena Research and Innovation Center in Information Communication & Knowledge Technologies (Greece)

Biomolecular Research Genomics (Italy)

Deutsches Herzzentrum Berlin (Germany)

Empirica Gesellschaft für Kommunikations- und Technologie Forschung Mbh (Germany)

Fraunhofer-Gesellschaft Zur Foerderung Der Angewandten Forschung E.V (Germany)

Haute Ecole Specialisée de Suisse Occidentale (Switzerland)

Istituto Giannina Gaslini (Italy)

Katholieke Universiteit Leuven (Belgium)

Lynkeus (Italy)

Motek Medical B.V. (Netherlands)

Ospedale Pediatrico Bambino Gesu (Italy)

Siemens Aktiengesellschaft (Germany)

Siemens Corporation (United States)

Technische Universiteit Delft (Netherlands)

University College London (United Kingdom)

Universitair Medisch Centrum Utrecht (Netherlands)

Universita Degli Studi di Roma Lapienza (Italy)

The University of Sheffield (United Kingdom)

Universitatea Transilvania Din Brasov (Romania)

Stichting Vu-Vumc (Netherlands)

Maat Francerl (France)

Inria contact: Xavier Pennec

MD-Paedigree is a clinically-led VPH project that addresses both the first and the second actions of part B of Objective ICT-2011.5.2:

1. it enhances existing disease models stemming from former EC-funded research projects (Health-e-Child and Sim-e-Child) and from industry and academia, by developing robust and reusable multi-scale models for more predictive, individualised, effective and safer healthcare in several disease areas;
2. it builds on the eHealth platform already developed for Health-e-Child and Sim-e-Child to establish a worldwide advanced paediatric digital repository.

Integrating the point of care through state-of-the-art and fast response interfaces, MD-Paedigree services a broad range of off-the-shelf models and simulations to support physicians and clinical researchers in their daily work. MD-Paedigree vertically integrates data, information and knowledge of incoming patients, in participating hospitals from across Europe and the USA, and provides innovative tools to define new workflows of models towards personalised predictive medicine. Conceived as a part of the 'VPH Infostructure' described in the ARGOS, MD-Paedigree encompasses a set of services for storage, sharing, similarity search, outcome analysis, risk stratification, and personalised decision support in paediatrics within its innovative model-driven data and workflow-based digital repository. As a specific implementation of the VPH-Share project, MD-Paedigree fully interoperates with it. It has the ambition to be the dominant tool within its purview. MD-Paedigree integrates methodological approaches from the targeted specialties and consequently analyzes biomedical data derived from a multitude of heterogeneous sources (from clinical, genetic and metagenomic analysis, to MRI and US image analytics, to haemodynamics, to real-time processing of musculoskeletal parameters and fibres biomechanical data, etc.), as well as specialised biomechanical and imaging VPH simulation models.

8.2.1.2. VP2HF

Title: Computer model derived indices for optimal patient-specific treatment selection and planning in Heart Failure

Programme: FP7

Period: October 2013 - September 2016

Coordinator: King's College, London.

Partners:

Centron Diagnostics Ltd (United Kingdom)

CHU Côte de Nacre, Caen (France)

King's College London (United Kingdom)

Philips Technologie (Germany)

Philips France (France)

Simula Research Laboratory As (Norway)

Université Catholique de Louvain (Belgium)

Universitat Pompeu Fabra (Spain)

Inria contact: Dominique Chapelle / Maxime Sermesant

Heart failure (HF) is one of the major health issues in Europe affecting 6 million patients and growing substantially because of the ageing population and improving survival following myocardial infarction. The poor short to medium term prognosis of these patients means that treatments, such as cardiac re-synchronisation therapy and mitral valve repair, can have substantial impact. However, these therapies, are ineffective in up to 50% of treated patients and involve significant morbidity and substantial cost. The primary aim of VP2HF is to bring together image and data processing tools with statistical and integrated biophysical models mainly developed in previous VPH projects, into a single clinical workflow to improve therapy selection and treatment optimisation in HF. The tools will be tested and validated on 200 patients (including 50 historical datasets) across 3 clinical sites, including a prospective clinical study on 50 patients in the last year of the project. The key innovations in VP2HF, which make it likely that the project results will be commercially exploited and have major clinical impact, are:

1. all tools to process images and signals, and to obtain the statistical and biophysical models will be integrated into one clinical software platform that can be easily and intuitively used by clinicians and tried out in the prospective clinical study;
2. to select only the appropriate parts of the tool chain, we use a decision tree stratification approach, which will add maximum value to the predictions that will be used in individual patients, so that the more resource intensive parts will be used when they will add real value.

We expect that the study will result in substantially improved efficacy of the decision making process compared with current guidelines, and that an integrated package that is used as part of clinical workflow will ensure the industrial project partners, in particular Philips, will develop project outputs into dedicated products that will have significant clinical impact.

8.2.1.3. MedYMA

Title: Biophysical Modeling and Analysis of Dynamic Medical Images

Programme: FP7

Type: ERC

Period: April 2012 - March 2017

Coordinator: Inria

Inria contact: Nicholas Ayache

During the past decades, exceptional progress was made with in vivo medical imaging technologies to capture the anatomical, structural and physiological properties of tissues and organs in patients, with an ever increasing spatial and temporal resolution. Physicians are now faced with a formidable overflow of information, especially when a time dimension is added to the already hard to integrate 3-D spatial, multimodal and multiscale dimensions of modern medical images. This increasingly hampers the early detection and understanding of subtle image modifications, which can have a vital impact on the patient's health. To change this situation, a new generation of computational models for the simulation and analysis of dynamic medical images is introduced. Thanks to their generative nature, they will allow the construction of databases of synthetic and realistic medical image sequences simulating various evolving diseases, producing an invaluable new resource for training and benchmarking. Leveraging on their principled biophysical and statistical foundations, these new models will bring an added clinical value once they have been personalized with innovative methods to fit the medical images of any specific patient. By explicitly revealing the underlying evolving biophysical processes observable in the images, this approach will yield new groundbreaking image processing tools to correctly interpret the patient's condition (computer aided diagnosis), to accurately predict the future evolution (computer aided prognosis), and to precisely simulate and monitor an optimal and personalized therapeutic strategy (computer aided therapy). First applications concern high impact diseases including brain tumors, Alzheimer's disease, heart failure and cardiac arrhythmia and will open new horizons in computational medical imaging.

8.3. International Initiatives

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

8.3.1.1. GeomStats

Title: Geometric Statistics in Computational Anatomy: Non-linear Subspace Learning Beyond the Riemannian Structure

International Partner (Institution - Laboratory - Researcher):

Stanford (United States) - Department of Statistics - Susan Holmes

Start year: 2015

See also: http://www-sop.inria.fr/asclepios/projects/GeomStats/

The scientific goal of the associated team is to develop the field of geometric statistics with key applications in computational anatomy.

Computational anatomy is an emerging discipline at the interface of geometry, statistics, image analysis and medicine that aims at analyzing and modeling the biological variability of the organs shapes at the population level. An important application in neuroimaging is the spatial normalization of subjects which is necessary to compare anatomies and functions through images in populations with different clinical conditions.

The research directions have been broken into three axes, the first two being methodologically driven and the last one being application driven. The first axis aims at generalizing the statistical framework from Riemannian to more general geometric structures and even non-manifold spaces (e.g. stratified spaces). The goal is to understand what is gained or lost using each geometric structure. The second axis aims at developing subspace learning methods in non-linear manifolds. This objective contrasts with most manifold learning methods which assumes that subspaces are embedded in a large enough Euclidean space. The third scientific direction is application driven with cross-sectional and longitudinal brain neuroimaging studies. The goal will be to extract reduced models of the brain anatomy that best describe and discriminate the populations under study. One intend for instance to show where is impact of a treatment for traumatic brain injuries.

8.3.2. Inria International Partners

8.3.2.1. Informal International Partners

8.3.2.1.1. St Thomas' Hospital, King's College London, United Kingdom

Maxime Sermesant is a visiting lecturer in the Division of Imaging Sciences and Biomedical Engineering, St Thomas' Hospital, King's College London lead by Pr Reza Razavi. The XMR facility within this hospital is a unique opportunity to validate and exploit the cardiovascular modelling work.

8.3.2.1.2. Massachusetts General Hospital, Boston

A collaboration with Dr Jan Unklebach, Assistant Professor of Radiation Oncology and Dr Jayashree Kalpathy-Cramer, radiology instructor was initiated in 2013 around the topics of tumor growth modeling, radiotherapy planning and edema characterization from MRI.

8.3.2.1.3. University College London (UCL), London, UK

Marco Lorenzi holds an honorary position with the Translational Imaging Group of UCL, led by Prof. Sebastien Ourselin. His collaboration is around the topic of spatio-temporal analysis of medical images, with special focus on brain imaging analysis and biomarker development in Alzheim disease. He is also collaborating with the "Progression Over Neurodegenerative Disorders" (POND) group (Prof. Daniel Alexander) for developing new computational models and techniques for learning characteristic patterns of disease progression using large longitudinal clinical data sets, with special focus on dementias.

8.3.2.1.4. Imaging Genetics Center (IGC), University of Southern California (USC), CA, USA

Marco Lorenzi is currently collaborator with the IGC for the investigation of the very complex relationship between brain atrophy and genetics in Alzheimer's disease, in particular for demonstrating the effectiveness of multivariate statistical models in providing a meaningful description of the relationship between genotype and brain phenotype.

8.3.2.1.5. Other International Hospitals

Collaborations with several other European hospitals have been established through the European projects VP2HF and MD PAEDIGREE.

8.4. International Research Visitors

8.4.1. Visits of International Scientists

8.4.1.1. Research Stays Abroad

In the context of the Associated team GeomStats, part of the Inria International Lab Inria@SiliconValley, Nina Miolane spent 3 months (April to June 2016) at the Stanford Statistics Department:

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Organisation

9.1.1.1. General Chair, Scientific Chair

- **X. Pennec** organized a workshop on the Geometry of shapes Workshop (Math in the Mine) from June 26 to July 2, 2016, at la Minière de Vallauria, Alpes Maritimes, FR.

9.1.1.2. Member of the Organizing Committees

- **M. Sermesant** was a co-chair of the MICCAI 2016 Workshop Statistical Atlases and Computational Models of the Heart (STACOM 2016), which was held in Athens, Greece, on October 17, 2016. He also co-organised the Cardiac Imaging Research Day at the French Radiologists Conference.

9.1.2. Scientific Events Selection

9.1.2.1. Member of the Conference Program Committees

- **X. Pennec** was a member of the program committee of RFIA RFP 2016 (Reconnaissance de Formes et Perception) (Clermont-Ferrand, FR), the 2nd Int. W. on Differential Geometry in Computer Vision Diff-CVML'16, Las Vegas, USA), and of the Workshop on Biomedical Image Registration (WBIR 2016, Las-Vegas, USA).
- **H. Delingette** was program committee member of the conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2016), the MICCAI 2016 workshop on Simulation and Synthesis of Medical Imaging (SASHIMI'16), and the Eurographics conference on Visual Computing for Biology and Medicine (VCBM'16).

9.1.2.2. Reviewer

- **H. Delingette** was a reviewer for the International Symposium on Biomedical Imaging (ISBI'16), the international conference on computer-aided interventions (IPCAI'16), the conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2016), the European Conference on Computer Vision (ECCV 2016), the International Conference on Computer Vision and Pattern Recognition (CVPR 2016).
- **M. Sermesant** was a reviewer for the MICCAI 2016 conference.
- **X. Pennec** was a reviewer for the conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2016), the European Conference on Computer Vision (ECCV 2016) and the int. Workshop on Representation, analysis and recognition of shape and motion FroM Imaging data (RFMI 2016).

9.1.3. Journal

9.1.3.1. Member of the Editorial Boards

- **N. Ayache** is the co-founder and the Co-Editor in Chief with J. Duncan (Professor at Yale) of *Medical Image Analysis* [8]. This scientific journal was created in 1996 and is published by Elsevier.
- **N. Ayache** is a member of the editorial board of the following journals: *Medical Image Technology* (Japanese journal) and *Journal of Computer Assisted Surgery* (Wiley).
- **H. Delingette** is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier).
- **I. Strobant** is editorial coordinator for *Medical Image Analysis*, Elsevier (since october 2001).
- **X. Pennec** is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier), of the *International Journal of Computer Vision* (Springer), of the SIAM *Journal on Imaging Sciences (SIIMS)*, and of the *Journal of Mathematical Imaging and Vision (JMIV)*.

[8] http://www.elsevier.com/wps/find/journaleditorialboard.cws_home/620983/editorialboard

9.1.3.2. Reviewer - Reviewing Activities

- **H. Delingette** was a reviewer for the following journals: *Medical Image Analysis* (Elsevier), IEEE Transactions in Medical Imaging, IEEE Transactions in Biomedical Engineering, Computer Vision and Image Understanding, Biomedical Engineering, Computers in Biology and Medicine and Journal of Fluids and Structures.
- **X. Pennec** was a reviewer for the following journals: Biometrika, Chaos, Proceedings on the London Mathematical Society (PLMS), SIAM journal on Imaging Sciences (SIIMS), Medical Image Analysis (MedIA), IEEE Transactions on Pattern Analysis (PAMI), NeuroImage (NIMG).
- **M. Sermesant** was a reviewer for the following journals: Journal of the American College of Cardiology, IEEE Transactions on Medical Imaging, IEEE Transactions on Biomedical Engineering, Medical Image Analysis and Computers in Biology and Medecine.

9.1.4. Invited Talks

- **Nicholas Ayache** gave the following invited lectures:
  - To honor Michel Lazdunski, Nice Hospital, January 2016
  - Science and Society event, Toulouse, May 2016
  - Institut Universitaire de France, Annual Event, Rennes, June 2016
  - Connected Health, Monaco, June 2016
  - SSIMA Summer School, Bucharest, July 2016
  - MISS Summer School, Favigna, August 2016
  - Academy of Sciences , Sept 2016
  - IHU Liryc, Bordeaux, Sept 2016
- **Hervé Delingette** gave the following invited lectures at the:
  - MICCAI 2016 Programme Committee Workshop on May 27th in London.
  - Biomedical Image Analysis Seminar at University of Basel on November 22nd.
- **Xavier Pennec** gave invited lectures at the following events:
  - Colloquium of the Dieudonné Lab (LJAD), Nice University, October 10, 2016.
  - VIth Int. W. on Representation, analysis and recognition of shape and motion FroM Imaging data (RFMI 2016), Sidi Bou Said village, Tunisia, October 27-29 2016.
  - International Workshop on Geometry, PDE's and Lie Groups in Image Analysis, Eindhoven (NL) 24-26 August 2016.
  - Workshop on Geometry and Stochastics of Nonlinear, Functional and Graph Data, Bornholm (DK), 15-19 August 2016.
  - 12th IEEE IVMSP Workshop 2016, Bordeaux (FR), July 11-12, 2016.
  - Statistical Analysis of Manifold-Valued Data and Beyond: Nottingham workshop, 4-6 April 2016, UK.
  - Mathematical Imaging and Surface Processing, Mathematisches Forschungsinstitut Oberwolfach (DE), 24-30 January 2016.
- **Maxime Sermesant** gave an invited lecture at the Virtual Physiological Human Summer School, Barcelona.

9.1.5. Leadership within the Scientific Community

- **H. Delingette** is a member of the MICCAI Society Board of Directors from 2016 to 2019.
- **Nicholas Ayache** is a member of the French Academy of Sciences in the section of Mechanics and Informatics.

9.1.6. Scientific Expertise

- **Nicholas Ayache** was invited in Nagoya, Japan in February 2016 to evaluate a national program on the "Multidisciplinary Computational Anatomy Initiative" funded by the MEXT. He has been a member of the Research Council of the "Fondation pour la Recherche Médicale (FRM)" since January 2015.
- **Xavier Pennec** was an evaluator for the Fonds de la Recherche Scientifique-FNRS, Belgium, the Alpes Grenoble Innovation Recherche (AGIR) projects, and for the PhD fellowships of Ecole Normale cachan.
- **H. Delingette** was an evaluator for the ECOS Sud France-Chili program, for the European Research Concil, for the Comet program in Austria (FWF), for the International Graduate School of Science and Engineering (IGSSE) of the Technical University of Munich.
- **M. Sermesant** is a member of the Medical Simulation Working Group of Aviesan.

9.1.7. Research Administration

- **Nicholas Ayache** is a member of the scientific council of the Ile de France region since 2016.
- **Xavier Pennec** is a member of the Doctoral follow-up Committee (CSD) at Inria Sophia Antipolis, of the the "Comité de la Recherche Biomédicale en Santé Publique (CRBSP)" of the Nice hospitals, in charge of the relationships of Inria-Sophia with the Nice University Hospital (CHU), of and the board of the Ecole doctorale STIC.
- **H. Delingette** is a member of the local committee in charge of the scientific selection of visiting scientists (Comité NICE) and the local committee on the immersive platform.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Master: H. Delingette and X. Pennec, Introduction to Medical Image Analysis, 21h course (28.5 ETD), Master 2 MVA, ENS Cachan, France.

Master: X. Pennec and H. Delingette, Advanced Medical Imaging, 21h course (28.5 ETD), Master 2 MVA and École Centrale de Paris, France.

Master: X. Pennec and H. Delingette, Computational Anatomy and Physiology, 21h course (28.5 ETD), Master CBB - Computational Biology and Biomedicine, Univ. Nice-Sophia Antipolis.

Master: M. Sermesant, Computational Anatomy and Physiology, 3h course (4.5 ETD), Master CBB - Computational Biology and Biomedicine, Univ. Nice-Sophia Antipolis.

Master: X. Pennec is co-responsible of the Master CBB - Computational Biology and Biomedicine, Univ. Nice-Sophia Antipolis.

9.2.2. Theses Defended

- Pietro Gori , *Statistics on the brain connectivity of patients with neurological diseases*, University of Paris. Started in 2012. Thesis in collaboration with the Aramis project-team, co-directed by O. Colliot, S. Durrleman and N. Ayache. Defended on January 8, 2016.
- Mehdi Hadj-Hamou, *Biophysical modeling of the anatomical evolution of the brain*, Nice Sophia Antipolis University. Co-directed by N. Ayache and X. Pennec. Defended on December 14, 2016.
- Bishesh Khanal, *Modeling the atrophy of the brain in Alzheimer's disease*, Nice Sophia Antipolis University. Co-directed by X. Pennec and N. Ayache. Defended on July 20, 2016.
- Nina Miolane, *Geometric Statistics in Computational Anatomy: Template Estimation and Subspace Learning in Manifolds, Lie groups and Stratified Spaces*, Nice-Sophia Antipolis University. Directed by X. Pennec. Defended on December 16, 2016.

- Anant Vemuri, *Inter-operative biopsy site relocalization in gastroscopy : application to oesophagus*, Nice Sophia Antipolis University. Co-directed by S. Nicolau and N. Ayache. Defended on April 26th 2016.
- Matthieu Lê, *Brain tumor growth modeling : application to radiotherapy imaging*, Nice Sophia Antipolis University. Co-directed by H. Delingette and N. Ayache. Defended on June 23rd 2016.
- HdR : Maxime Sermesant, When Cardiac Biophysics Meets Groupwise Statistics: Complementary Modelling Approaches for Patient-Specific Medicine, Universite Nice Sophia Antipolis, June 9.

9.2.3. PhD in progress

Marc-Michel Rohé, *Analyse statistique spatio-temporelle des formes, déformations, flots et propriétés physiologiques du cœur*, Nice Sophia Antipolis University. Started in 2014. Co-directed by X. Pennec and M. Sermesant.

Sophie Giffard-Roisin, *Non-invasive Estimation of Cardiac Electrophysiological Parameters*, Nice Sophia Antipolis University. Started in 2014. Co-directed by N. Ayache and M. Sermesant.

Roch Molléro, *Uncertainty quantification in personalized electromechanical models. Application to cardiomyopathies and obesity*, Nice Sophia Antipolis University. Started in 2014. Co-directed by N. Ayache and M. Sermesant.

Thomas Demarcy, *Segmentation and anatomic variability of the cochlea and other temporal bone structures from medical images*, Nice Sophia Antipolis University. Started in 2014. Directed by H. Delingette.

Loïc Devilliers, *Consistency of statistics on infinite dimensional orbifolds – Applications to computational anatomy*, Nice Sophia Antipolis University. Started in October 2015. Co-directed by X Pennec and St. Allassonière.

Raphaël Sivera, *Analyse statistique de l'évolution de structures morphologiques partir de séquences temporelles d'IRM*, Nice Sophia Antipolis University. Started in October 2015. Co-directed by N. Ayache and H. Delingette.

Pawel Mlynarski, *Tumor segmentation based on Random Forests and Convolutional Neural Networks trained on partially annotaded data*, Nice Sophia Antipolis University. Started in December 2015. Co-directed by N. Ayache and H. Delingette.

Qiao Zheng, *Deep learning for cardiac image analysis*, Nice Sophia Antipolis University. Started in January 2016. Co-directed by N. Ayache and H. Delingette.

Shuman Jia, *Population-based Model of Atrial Fibrillation: from Shape Statistics to Group-wise Physiology*, Nice Sophia Antipolis University. Started in 2016. Co-directed by M. Sermesant and X. Pennec.

Wen Wei, *Learning Brain Alterations in Multiple Sclerosis from Multimodal Neuroimaging Data*, Nice Sophia Antipolis University. Started in 2016. Co-directed by N.Ayache and O.Colliot.

Julian Krebs, *Robust image registration based on machine learning*, Nice Sophia Antipolis University. Started in 2016. Co-directed by H. Delingette and N. Ayache.

9.2.4. Juries

N. Ayache was co-supervisor of the PhD theses of Matthieu Lê (Univ. of Nice Sophia Antipolis), Anant Vemuri (Univ. of Nice Sophia Antipolis), Pietro Gori (University of Paris), Mehdi Hadj-Hamou (Univ. of Nice Sophia Antipolis), and Bishesh Khanal (Univ. of Nice Sophia Antipolis). He was a member of the PhD thesis committee of Nina Miolane (Univ. of Nice Sophia Antipolis).

Hervé Delingette was co-supervisor of the PhD thesis of Matthieu Lê (Univ. of Nice Sophia Antipolis). He was a reviewer in the PhD thesis committee of Vincent Jaouen (Univ. of Tours) and of Tom Haeck (University KUL Leuven, Belgium). He was a member of the PhD thesis committee of Bishesh Khanal (Univ. of Nice Sophia Antipolis).

Xavier Pennec was supervisor or co-supervisor of the PhD theses of Bishesh Khanal (Univ. of Nice Sophia Antipolis), Mehdi Hadj-Hamou (Univ. of Nice Sophia Antipolis) and Nina Miolane (Univ. of Nice Sophia Antipolis).
Maxime Sermesant was a reviewer and a member of the PhD jury of Andjela Davidovic, Bordeaux University (Dec 9).

9.3. Popularization

- Nina Miolane participated to the following popularization events:
  - Speaker at Unesco France's Ceremony for 70th Anniversary.
  - Speaker at the Women Forum Global Meeting 2016. How to bring more women in the sci-tech workforce?
  - Speaker at the L'Oreal-Unesco Prizes Ceremony 2016.
  - Journal regional de France 3 Azur (Oct. 31 2016)
  - Invited on "Le Club de la Tete au Carre". France Inter (National Radio), Oct. 14 2016.
- M. Sermesant gave general audience lectures in regional high schools, during the Science Festival in Juan-les-Pins Congress center (Oct 23), and during the Inria-Industry meeting (Dec 1).

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] M. HADJ-HAMOU. *Beyond Volumetry in Longitudinal Deformation-Based Morphometry: Application to Sexual Dimorphism during Adolescence*, Universite Nice Cote d'Azur, December 2016, https://hal.inria.fr/tel-01416569

[2] B. KHANAL. *Modeling and simulation of realistic longitudinal structural brain MRIs with atrophy in Alzheimer's disease*, Université Nice Sophia Antipolis, July 2016, https://tel.archives-ouvertes.fr/tel-01384678

[3] M. LEˆ. *Brain tumor growth modeling : application to radiotherapy*, Université Nice Sophia Antipolis, June 2016, https://tel.archives-ouvertes.fr/tel-01376688

[4] N. MIOLANE. *Geometric Statistics for Computational Anatomy*, Inria Sophia Antipolis, December 2016, https://hal.inria.fr/tel-01411886

[5] M. SERMESANT. *When Cardiac Biophysics Meets Groupwise Statistics: Complementary Modelling Approaches for Patient-Specific Medicine*, Université de Nice - Sophia Antipolis, June 2016, Habilitation à diriger des recherches, https://hal.inria.fr/tel-01337145

[6] A. S. VEMURI. *Inter-operative biopsy site relocalization in gastroscopy : application to oesophagus*, Université Nice Sophia Antipolis, April 2016, https://tel.archives-ouvertes.fr/tel-01310047

Articles in International Peer-Reviewed Journals

[7] M. ALESSANDRINI, B. HEYDE, S. QUEIRÓS, S. CYGAN, M. ZONTAK, O. SOMPHONE, O. BERNARD, M. SERMESANT, H. DELINGETTE, D. BARBOSA, M. DE CRAENE, M. O'DONNELL, J. D'HOOGE. *Detailed Evaluation of Five 3D Speckle Tracking Algorithms Using Synthetic Echocardiographic Recordings*, in "IEEE Transactions on Medical Imaging", 2016, vol. 35, n^{o} 8, pp. 1915-1926 [*DOI :* 10.1109/TMI.2016.2537848], https://hal.archives-ouvertes.fr/hal-01373083

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