Activity Report 2018

Project-Team EPIONE

E-Patient: Images, Data & MOdels for e-MediciNE

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Neuroscience and Medicine

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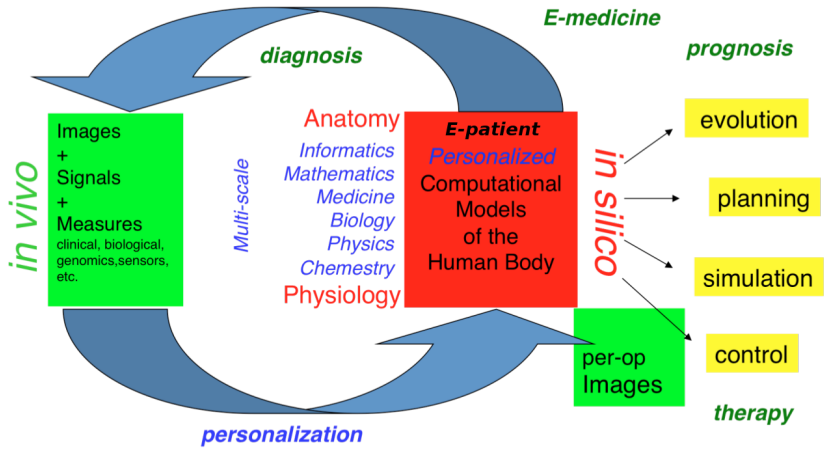

Figure 1. The e-patient for e-medicine

2. Overall Objectives

2.1. Description

Our long-term goal is to contribute to the development of what we call the e-patient (digital patient) for e-medicine (digital medicine).

- the e-patient (or digital patient) is a set of computational models of the human body able to describe and simulate the anatomy and the physiology of the patient's organs and tissues, at various scales, for an individual or a population. The e-patient can be seen as a framework to integrate and analyze in a coherent manner the heterogeneous information measured on the patient from disparate sources: imaging, biological, clinical, sensors, ...
- e-medicine (or digital medicine) is defined as the computational tools applied to the e-patient to assist the physician and the surgeon in their medical practice, to assess the diagnosis/prognosis, and to plan, control and evaluate the therapy.

The models that govern the algorithms designed for e-patients and e-medicine come from various disciplines: computer science, mathematics, medicine, statistics, physics, biology, chemistry, etc. The parameters of those models must be adjusted to an individual or a population based on the available images, signals and data. This adjustment is called personalization and usually requires solving difficult inverse problems. The overall picture of the construction of the personalized e-patient for e-medicine was presented at the College de France through an inaugural lecture and a series of courses and seminars (fr), concluded by an international workshop.

2.1.1. Organisation

The research organization in our field is often built on a virtuous triangle. On one vertex, academic research requires multidisciplinary collaborations associating informatics and mathematics to other disciplines: medicine, biology, physics, chemistry... On a second vertex, a clinical partnership is required to help defining pertinent questions, to get access to clinical data, and to clinically evaluate any proposed solution. On the third vertex, an industrial partnership can be introduced for the research activity itself, and also to transform any proposed solution into a validated product that can ultimately be transferred to the clinical sites for an effective use on the patients.

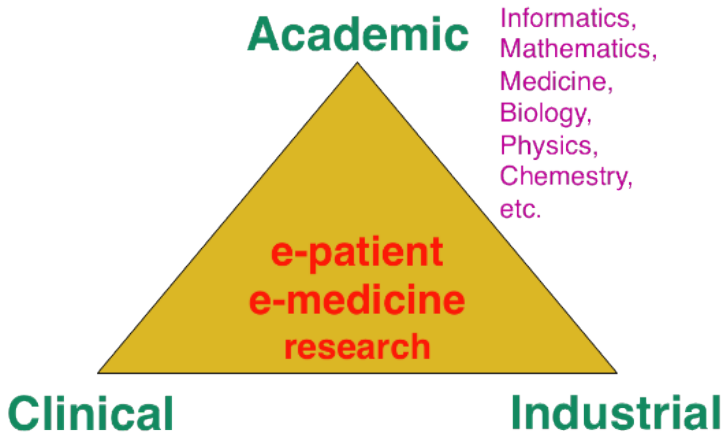

Figure 2. A pluridisciplinary research triangle

Keeping this triangle in mind, we choose our research directions within a virtuous circle: we look at difficult problems raised by our clinical or industrial partners, and then try to identify some classes of generic fundamental/theoretical problems associated to their resolution. We also study some fundamental/theoretical problems per se in order to produce fundamental scientific advances that can help in turn to promote new applications.

3. Research Program

3.1. Introduction

Our research objectives are organized along 5 scientific axes:

1. Biomedical Image Analysis & Machine Learning
2. Imaging & Phenomics, Biostatistics
3. Computational Anatomy, Geometric Statistics
4. Computational Physiology & Image-Guided Therapy
5. Computational Cardiology & Image-Based Cardiac Interventions

For each scientific axis, we introduce the context and the long term vision of our research.

3.2. Biomedical Image Analysis & Machine Learning

The long-term objective of biomedical image analysis is to extract, from biomedical images, pertinent information for the construction of the e-patient and for the development of e-medicine. This relates to the development of advanced segmentation and registration of images, the extraction of image biomarkers of pathologies, the detection and classification of image abnormalities, the construction of temporal models of motion or evolution from time-series of images, etc.

A good illustration of the current state of the art and of the remaining challenges can be found in these recent publications which address for instance the extraction of quantitative biomarkers on static or time varying images, as well as image registration and deformation analysis problems. This also applies to the analysis of microscopic and multi-scale images.

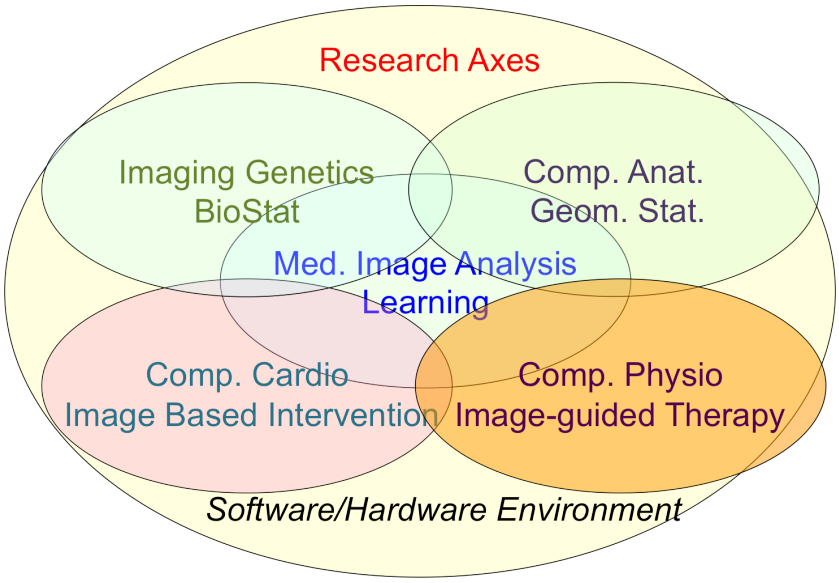

Figure 3. Epione's five main research axes

In addition, the growing availability of very large databases of biomedical images, the growing power of computers and the progress of machine learning (ML) approaches have opened up new opportunities for biomedical image analysis.

This is the reason why we decided to revisit a number of biomedical image analysis problems with ML approaches, including segmentation and registration problems, automatic detection of abnormalities, prediction of a missing imaging modality, etc. Not only those ML approaches often outperform the previous state-of-the-art solutions in terms of performances (accuracy of the results, computing times), but they also tend to offer a higher flexibility like the possibility to be transferred from one problem to another one with a similar framework. However, even when successful, ML approaches tend to suffer from a lack of explanatory power, which is particularly annoying for medical applications. We also plan to work on methods that can interpret the results of the ML algorithms that we develop.

- **Revisiting Segmentation problems with Machine Learning:** Through a partnership with Microsoft Research in Cambridge (UK), we are studying new segmentation methods based on deep learning with *weakly annotated* data. In effect, a complete segmentation ground truth is costly to collect in medical image analysis, as it requires the tedious task of contouring regions of interest and their validation by an expert. On the other hand, the label "presence" or "absence" of a lesion for instance (weak annotation) can be obtained at a much lower cost.

  We also plan to explore the application of deep learning methods to the fast segmentation of static or deformable organs. For instance we plan to use deep learning methods for the 3D consistent segmentation of the myocardium tissue of the 2 cardiac ventricles, an important preliminary step to mesh the cardiac muscle for computational anatomy, physiology and cardiology projects.
- **Revisiting Registration problems with Machine Learning:** We are studying, through a partnership with Siemens (Princeton), the possibility to apply robust non-rigid registration through agent-based action learning. We propose a decision process where the objective simplifies to iteratively finding the strategically next best step. An artificial agent is driven to solve the task of non-rigid registration through exploring the parametric space of a statistical deformation model built from training data.

Since it is difficult to extract trustworthy ground-truth deformation fields we propose a training scheme with synthetically deformed cases and few real inter-subject cases.

- **Prediction of an imaging modality from other imaging modalities with machine learning:** Through a partnership with the Brain and Stem Institute in Paris, we plan to develop deep learning approaches to quantify some brain alterations currently measured by an invasive nuclear medicine imaging modality (PET imaging with specific tracers), directly from a multi-sequence acquisition of a non-invasive imaging modality (MRI). This requires innovative approaches taking into account the relatively small size of the ground truth database (patients having undergone both PET and MR Image acquisitions) and exploiting the a priori knowledge on the brain anatomy. We believe that this approach could apply to other image prediction problems in the longer term.
- **Prediction of cardiac pathologies with machine learning and image simulation:** Following the important work on cardiac image simulation done during the ERC project MedYMA, we are currently able to simulate time-series of images of various cardiac pathologies for which we can vary the parameters of a generative electro-mechanical model. We plan to develop new deep learning methods exploiting both the *shape* and *motion* phenotypes present in the time-series of images to detect and characterize a number of cardiac pathologies, including subtle assynchronies, local ischemia or infarcts.
- **Measuring Brain, Cognition, Behaviour:** We developed a collaborative project MNC3 which is supported by the excellence initiative Idex UCA^{Jedi}. This project gathers partners from Inria, Nice Hospitals (physicians), Nice University, and IPMC (biologists). The goal is to provide a joint analysis of heterogenous data collected on patients with neurological and psychiatric diseases. Those data include medical imaging (mainly MRI), activity (measured by connected wrists or video or microphones), biology/genomics, and clinical information. We want to show the increase in the statistical power of a joint analysis of the data to classify a pathology and to quantify its evolution.

In addition to these mid-term goals, we have applied to two important projects with local clinicians. A project on "Lung cancer", headed by anatomopathologist P. Hofman, to better exploit the joint information coming from imaging and circulating tumoral cells (in collaboration with Median Tech company); and a project "Cluster headache", headed by neurosurgeon D. Fontaine, to better integrate and exploit information coming from imaging, genetics and clinic (in collaboration with Inria Team Athena).

3.3. Imaging & Phenomics, Biostatistics

The human phenotype is associated with a multitude of heterogeneous biomarkers quantified by imaging, clinical and biological measurements, reflecting the biological and patho-physiological processes governing the human body, and essentially linked to the underlying individual genotype.In order to deepen our understanding of these complex relationships and better identify pathological traits in individuals and clinical groups, a long-term objective of e-medicine is therefore to develop the tools for the joint analysis of this heterogeneous information, termed *Phenomics*, within the unified modeling setting of the e-patient.

Ongoing research efforts aim at investigating optimal approaches at the crossroad between biomedical imaging and bioinformatics to exploit this diverse information. This is an exciting and promising research avenue, fostered by the recent availability of large amounts of data from joint imaging and biological studies (such as the UK biobank [1], ENIGMA [2], ADNI [3],...). However, we currently face important methodological challenges, which limit the ability in detecting and understanding meaningful associations between phenotype and biological information.

[1] http://www.ukbiobank.ac.uk/
[2] http://enigma.ini.usc.edu/.
[3] http://adni.loni.usc.edu/

To date the most common approach to the analysis of the joint variation between the structure and function of organs represented in medical images, and the classical -omics modalities from biology, such as genomics or lipidomics, is essentially based on the massive univariate statistical testing of single candidate features out of the many available. This is for example the case of genome-wide association studies (GWAS) aimed at identifying statistically significant effects in pools consisting of up to millions of genetics variants. Such approaches have known limitations such as multiple comparison problems, leading to underpowered discoveries of significant associations, and usually explain a rather limited amount of data variance. Although more sophisticated machine learning approaches have been proposed, the reliability and generalization of multivariate methods is currently hampered by the low sample size relatively to the usually large dimension of the parameters space.

To address these issues this research axis investigates novel methods for the integration of this heterogeneous information within a parsimonious and unified multivariate modeling framework. The cornerstone of the project consists in achieving an optimal trade-off between modeling flexibility and ability to generalize on unseen data by developing statistical learning methods informed by prior information, either inspired by "mechanistic" biological processes, or accounting for specific signal properties (such as the structured information from spatio-temporal image time series). Finally, particular attention will be paid to the effective exploitation of the methods in the growing Big Data scenario, either in the meta-analysis context, or for the application in large datasets and biobanks.

- **Modeling associations between imaging, clinical, and biological data.** The essential aspect of this research axis concerns the study of data regularization strategies encoding prior knowledge, for the identification of meaningful associations between biological information and imaging phenotype data. This knowledge can be represented by specific biological mechanisms, such as the complex non-local correlation patterns of the -omics encoded in genes pathways, or by known spatio-temporal relationship of the data (such as time series of biological measurements or images). This axis is based on the interaction with research partners in clinics and biology, such as IPMC (CNRS, France), the Lenval Children's Hospital (France), and University College London (UK). This kind of prior information can be used for defining scalable and parsimonious probabilistic regression models. For example, it can provide relational graphs of data interactions that can be modelled by means of Bayesian priors, or can motivate dimensionality reduction techniques and sparse frameworks to limit the effective size of the parameter space. Concerning the clinical application, an important avenue of research will come from the study of the *reduced* representations of the -omics data currently available in clinics, by focusing on the modeling of the disease variants reported in previous genetic findings. The combination of this kind of data with the information routinely available to clinicians, such as medical images and memory tests, has a great potential for leading to improved diagnostic instruments. The translation of this research into clinical practice is carried out thanks to the ongoing collaboration with primary clinical partners such as the University Hospital of Nice (MNC3 partner, France), the Dementia Research Centre of UCL (UK), and the Geneva University Hospital (CH).
- **Learning from collections of biomedical databases.** The current research scenario is characterised by medium/small scale (typically from 50 to 1000 patients) heterogeneous datasets distributed across centres and countries. The straightforward extension of learning algorithms successfully applied to big data problems is therefore difficult, and specific strategies need to be envisioned in order to optimally exploit the available information. To address this problem, we focus on learning approaches to jointly model clinical data localized in different centres. This is an important issue emerging from recent large-scale multi-centric imaging-genetics studies in which partners can only share model parameters (e.g. regression coefficients between specific genes and imaging features), as represented for example by the ENIGMA imaging-genetics study, led by the collaborators at University of Southern California. This problem requires the development of statistical methods for *online* model estimation, in order to access data hosted in different clinical institutions by simply transmitting the model parameters, that will be in turn updated by using the local available data. This approach is extended to the definition of stochastic optimization strategies in which model parameters are optimized on local datasets, and then summarized in a meta-analysis context.

Finally, this project studies strategies for aggregating the information from heterogeneous datasets, accounting for missing modalities due to different study design and protocols. The developed methodology finds important applications within the context of Big Data, for the development of effective learning strategies for massive datasets in the context of medical imaging (such as with the UK biobank), and beyond (ongoing collaboration with the Data Science team of EURECOM (France)).

3.4. Computational Anatomy, Geometric Statistics

Computational anatomy is an emerging discipline at the interface of geometry, statistics and image analysis which aims at developing algorithms to model and analyze the biological shape of tissues and organs. The goal is not only to establish generative models of organ anatomies across diseases, populations, species or ages but also to model the organ development across time (growth or aging) and to estimate their variability and link to other functional, genetic or structural information. Computational anatomy is a key component to support computational physiology and is evidently crucial for building the e-patient and to support e-medicine. Pivotal applications include the spatial normalization of subjects in neuroscience (mapping all the anatomies into a common reference system) and atlas to patient registration to map generic knowledge to patient-specific data. Our objectives will be to develop new efficient algorithmic methods to address the emerging challenges described below and to generate precise specific anatomical model in particular for the brain and the heart, but also other organs and structures (e.g. auditory system, lungs, breasts, etc.).

The objects of computational anatomy are often shapes extracted from images or images of labels (segmentation). The observed organ images can also be modeled using registration as the random diffeomorphic deformation of an unknown template (i.e. an orbit).In these cases as in many other applications, invariance properties lead us to consider that these objects belong to non-linear spaces that have a geometric structure. Thus, the mathematical foundations of computational anatomy rely on statistics on non-linear spaces.

- **Geometric Statistics** aim at studying this abstracted problem at the theoretical level. Our goal is to advance the fundamental knowledge in this area, with potential applications to new areas outside of medical imaging. Several challenges which constitute shorter term objectives in this direction are described below.
- **Large databases and longitudinal evolution:** The emergence of larger databases of anatomical images (ADNI, UK biobank) and the increasing availability of temporal evolution drives the need for efficient and scalable statistical techniques. A key issue is to understand how to construct hierarchical models in a non-linear setting.
- **Non-parametric models of variability:** Despite important successes, anatomical data also tend to exhibit a larger variability than what can be modeled with a standard multivariate unimodal Gaussian model. This raises the need for new statistical models to describe the anatomical variability like Bayesian statistics or sample-based statistical model like multi-atlas and archetypal techniques. A second objective is thus to develop efficient algorithmic methods for encoding the statistical variability into models.
- **Intelligible reduced-order models:** Last but not least, these statistical models should live in low dimensional spaces with parameters that can be interpreted by clinicians. This requires of course dimension reduction and variable selection techniques. In this process, it is also fundamental to align the selected variable to a dictionary of clinically meaningful terms (an ontology), so that the statistical model can not only be used to predict but also to explain.

3.4.1. Geometric Statistics

- **Foundations of statistical estimation on geometric spaces:** Beyond the now classical Riemannian spaces, this axis will develop the foundations of statistical estimation on affine connection spaces (e.g. Lie groups), quotient and stratified metric spaces (e.g. orbifolds and tree spaces). In addition to the curvature, one of the key problem is the introduction of singularities at the boundary of the regular strata (non-smooth and non-convex analysis).

- **Parametric and non-parametric dimension reduction methods in non-linear spaces:** The goal is to extend what is currently done with the Fréchet mean (i.e. a 0-dimensional approximation space) to higher dimensional subspaces and finally to a complete hierarchy of embedded subspaces (flags) that iteratively model the data with more and more precision. The Barycentric Subspace Analysis (BSA) generalization of principal component analysis which was recently proposed in the team will of course be a tool of choice for that. In this process, a key issue is to estimate efficiently not only the model parameters (mean point, subspace, flag) but also their uncertainty. Here, we want to quantify the influence of curvature and singularities on non-asymptotic estimation theory since we always have a finite (and often too limited) number of samples. As the mean is generally not unique in curved spaces, this also leads to consider that the results of estimation procedures should be changed from points to singular distributions. A key challenge in developing such a geometrization of statistics will not only be to unify the theory for the different geometric structures, but also to provide efficient practical algorithms to implement them.
- **Learning the geometry from the data:** Data can be efficiently approximated with locally Euclidean spaces when they are very finely sampled with respect to the curvature (big data setting). In the high dimensional low sample size (small data) setting, we believe that invariance properties are essential to reasonably interpolate and approximate. New apparently antagonistic notions like approximate invariance could be the key to this interaction between geometry and learning.

  Beyond the traditional statistical survey of the anatomical shapes that is developed in computational anatomy above, we intend to explore other application fields exhibiting geometric but non-medical data. For instance, applications can be found in Brain-Computer Interfaces (BCI), tree-spaces in phylogenetics, Quantum Physics, etc.

3.5. Computational Physiology & Image-Guided Therapy

Computational Physiology aims at developing computational models of human organ *functions*, an important component of the e-patient, with applications in e-medicine and more specifically in computer-aided prevention, diagnosis, therapy planning and therapy guidance. The focus of our research is on *descriptive* (allowing to reproduce available observations), *discriminative* (allowing to separate two populations), and above all *predictive models* which can be personalized from patient data including medical images, biosignals, biological information and other available metadata. A key aspect of this scientific axis is therefore the coupling of biophysical models with patient data which implies that we are mostly considering models with relatively few and identifiable parameters. To this end, *data assimilation* methods aiming at estimating biophysical model parameters in order to reproduce available patient data are preferably developed as they potentially lead to predictive models suitable for therapy planning.

Previous research projects in computational physiology have led us to develop biomechanical models representing quasi-static small or large soft tissue deformations (e.g. liver or breast deformation after surgery), mechanical growth or atrophy models (e.g. simulating brain atrophy related to neurodegenerative diseases), heat transfer models (e.g. simulating radiofrequency ablation of tumors), and tumor growth models (e.g. brain or lung tumor growth).

To improve the data assimilation of biophysical models from patient data, a long term objective of our research will be to develop *joint imaging and biophysical generative models in a probabilistic framework* which simultaneously describe the appearance and function of an organ (or its pathologies) in medical images. Indeed, current approaches for the personalization of biophysical models often proceed in two separate steps. In a first stage, geometric, kinematic or functional features are first extracted from medical images. In a second stage, they are used by personalization methods to optimize model parameters in order to match the extracted features. In this process, subtle information present in the image which could be informative for biophysical models is often lost which may lead to limited personalization results. Instead, we propose to develop more integrative approaches where the extraction of image features would be performed jointly with the model parameter fitting. Those imaging and biophysical generative models should lead to a *better understanding*

of the content of images, to a *better personalization* of model parameters and also *better estimates of their uncertainty*.

This improved coupling between images and model should *help solving various practical problems* driven by clinical applications. Depending on available resources, datasets, and clinical problems, we wish to develop a new expertise for the simulation of *tissue perfusion* (e.g. to capture the uptake of contrast agent or radioactive tracers), or *blood flow in medium / small vessels* (e.g. to capture the transport of drugs or radioactive materials in interventional radiology).

- **Reduced Computational Biophysical Models**. Clinical constraint and uncertainty estimation inevitably lead to the requirement of relatively fast computation of biophysical models. In addition to hardware acceleration (GPU, multithreading) we will explore various ways to accelerate the computation of models through intrusive (e.g. proper orthogonal decomposition, computation of condensed stiffness matrices in non-linear mechanics) or non intrusive methods (e.g. polynomial chaos expansion, Gaussian processes).
- **Uncertainty estimation of Biophysical Models**. We will pursue our research on this topic by developing Bayesian methods to estimate the posterior probability of model parameters, initial and boundary conditions from image features or image voxels. Such approaches rely on the definition of relevant likelihood terms relating the model state variables to the observable quantities in images. When possible joint imaging and biophysical generative models will be developed to avoid to rely on intermediate image features. Approximate inference of uncertainty will be estimated through Variational Bayes approaches whose accuracy will be evaluated through a comparison with stochastic sampling methods (e.g. MCMC). Through this uncertainty estimation, we also aim at developing a reliable framework to select the most sensitive and discriminative parameters of a given model but also to select the biophysical model best suited to solve a given problem (e.g. prediction of therapy outcome).
- **High Order Finite Element Modeling**. Soft tissue biomechanical models have until now been formulated as linear elastic or hyperelastic materials discretized as linear tetrahedra finite elements. While being very generic, those elements are known to suffer from numerical locking for nearly incompressible materials and lead to poor estimate of stress field. We will develop efficient implementation and assembly methods using high order tetrahedral (and possibly hexahedral) elements. To maintain the number of nodes relatively low while keeping a good accuracy, we intend to develop elements of adaptive degree (p-refinement) driven by local error indices. Solution for meshing surfaces or volumes with curved high order elements will be developed in collaboration with the Titane and Aromath Inria teams.
- **Clinical Applications**. We plan to develop new applications of therapy planning and therapy guidance through existing or emerging collaborations related to the following problems : breast reconstruction following insertion of breast implants (with Anatoscope), planning of cochlear electrodes implantation (with CHU Nice and Oticon Medical), lung deformation following COPD or pulmonary fibrosis (with CHU Nice), echography based elastometry (with CHU Nice).

3.6. Computational Cardiology & Image-Based Cardiac Interventions

Computational Cardiology has been an active research topic within the Computational Anatomy and Computational Physiology axes of the previous Asclepios project, leading to the development of personalized computational models of the heart designed to help characterizing the cardiac function and predict the effect of some device therapies like cardiac resynchronisation or tissue ablation. This axis of research has now gained a lot of maturity and a critical mass of involved scientists to justify an individualized research axis of the new project Epione, while maintaining many constructive interactions with the 4 other research axes of the project. This will develop all the cardiovascular aspects of the e-patient for cardiac e-medicine.

The new challenges we want to address in computational cardiology are related to the introduction of new levels of modeling and to new clinical and biological applications. They also integrate the presence of new sources of measurements and the potential access to very large multimodal databases of images and measurements at various spatial and temporal scales.

Our goal will be to combine two complementary computational approaches: *machine learning* and *biophysical modelling*. This research axis will leverage on the added value of such a combination. Also we will refine our biophysical modeling by the introduction of a pharmacokinetics/pharmacodynamics (PK/PD) component able to describe the effect of a drug on the cardiac function. This will come in complement to the current geometric, electrical, mechanical and hemodynamic components of our biophysical model of the heart. We will also carefully model the uncertainty in our modeling, and try to provide algorithms fast enough to allow future clinical translation.

- Physics of Ultrasound Images for Probe Design: we will design a digital phantom of the human torso in order to help the design of echocardiographic probes. This will be done in collaboration with GE Healthcare whose excellence centre for cardiac ultrasound probes is located in Sophia Antipolis.
- Cardiac Pharmacodynamics for Drug Personalisation: we will add to our biophysical cardiac model a pharmacodynamics model, coupled with a pharmacokinetics model and a personalisation framework in order to help the adjustment of drug therapy to a given patient. This will be done in collaboration with ExactCure, a start up company specialised on this topic.
- New Imaging Modality Coupling MRI and Electrodes: we will use our fast models in order to regularize the ill-posed inverse problem of cardiac electrocardiography in order to estimate cardiac electrical activity from body surface potentials. This will be done within the ERC Starting Grant ECSTATIC coordinated by Hubert Cochet from the IHU Liryc, Bordeaux.
- Cardiac Imaging during Exercise: a particular aspect of the cardiac function is its constant adaptation to satisfy the needs of the human body. This dynamic aspect provides important information on the cardiac function but is challenging to measure. We will set up exercise protocols with Nice University Hospital and STAPS in order to model and quantify such an adaptation of the cardiac function.
- Sudden Cardiac Death is the cause of important mortality (300 000 per year in Europe, same in US) and it is difficult to identify people at risk. Based on a large multi-centric database of images, we will learn the image features correlated with a high risk of arrhythmia, with the IHU Liryc.
- Personalising models from connected objects: with the Internet of Things and the pletora of sensors available today, the cardiac function can be monitored almost continuously. Such new data open up possibilities for novel methods and tools for diagnosis, prognosis and therapy.

4. Highlights of the Year

4.1. Highlights of the Year

4.1.1. Awards

- Xavier Pennec received an ERC advanced grant on geometric statistics for life sciences.
- Shuman Jia ranked 2nd in the AI Data Challenge organized by the French Society of Radiology.
- Shuman Jia earned 2nd prize at the Pierre Lafitte PhD competition.
- Fanny Orlhac was awarded for the L'Oréal-UNESCO grant for women in science 2018.
- Wen Wei received a travel award at the MICCAI conference.
- Wen Wei received a travel award from the SFRMBM (french society of magnetic resonance in biology and medicine) for the Joint Annual Meeting ISMRM-ESMRMB 2018.
- Nina Miolane received the second prize (special mention) for the AFRIF (french association for shape interpretation and recognition) PhD prize for her PhD entitled "Geometric Statistics for Computational Anatomy" realized in the context of the associated team GeomStats under the direction of Xavier Pennec (Inria Sophia Antipolis) and Susan Holmes (Stanford University).

5. New Software and Platforms

5.1. CardiacSegmentationPropagation

KEYWORDS: 3D - Segmentation - Cardiac - MRI - Deep learning

FUNCTIONAL DESCRIPTION: Training of a deep learning model which is used for cardiac segmentation in short-axis MRI image stacks.

- Authors: Qiao Zheng, Hervé Delingette, Nicolas Duchateau and Nicholas Ayache
- Contact: Qiao Zheng
- Publication: hal-01753086, version 1

5.2. CardiacMotionFlow

KEYWORDS: 3D - Deep learning - Cardiac - Classification
FUNCTIONAL DESCRIPTION: Creation of a deep learning model for the motion tracking of the heart, extraction of characteristic quantities of the movement and shape of the heart to classify a sequence of cine-MRI cardiac images in terms of the types of pathologies (infarcted heart, dilated , hypertrophied, abnormality of the right ventricle).

- Contact: Qiao Zheng

5.3. MedInria

KEYWORDS: Visualization - DWI - Health - Segmentation - Medical imaging
SCIENTIFIC DESCRIPTION: medInria 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, renewed in 2012. A fast-track ADT was awarded in 2017 to transition the software core to more recent dependencies and study the possibility of a consortium creation.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: Maxime Sermesant, Olivier Commowick and Théodore Papadopoulo
- Partners: HARVARD Medical School - IHU - LIRYC - NIH
- Contact: Olivier Commowick
- URL: http://med.inria.fr

5.4. GP-ProgressionModel

GP progression model
KEYWORDS: Data modeling - Data visualization - Data integration - Machine learning - Biostatistics - Statistical modeling - Medical applications - Evolution - Brain - Uncertainly - Uncertainty quantification - Alzheimer's disease - Probability - Stochastic models - Stochastic process - Trajectory Modeling - Marker selection - Health - Statistic analysis - Statistics - Bayesian estimation
FUNCTIONAL DESCRIPTION: Disease progression modeling (DPM) of Alzheimer's disease (AD) aims at revealing long term pathological trajectories from short term clinical data. Along with the ability of providing a data-driven description of the natural evolution of the pathology, DPM has the potential of representing a valuable clinical instrument for automatic diagnosis, by explicitly describing the biomarker transition from normal to pathological stages along the disease time axis.

In this software we reformulate DPM within a probabilistic setting to quantify the diagnostic uncertainty of individual disease severity in an hypothetical clinical scenario, with respect to missing measurements, biomarkers, and follow-up information. The proposed formulation of DPM provides a statistical reference for the accurate probabilistic assessment of the pathological stage of de-novo individuals, and represents a valuable instrument for quantifying the variability and the diagnostic value of biomarkers across disease stages.

This software is based on the publication:

Probabilistic disease progression modeling to characterize diagnostic uncertainty: Application to staging and prediction in Alzheimer's disease. Marco Lorenzi, Maurizio Filippone, Daniel C. Alexander, Sebastien Ourselin Neuroimage. 2017 Oct 24. pii: S1053-8119(17)30706-1. doi: 10.1016/j.neuroimage.2017.08.059. HAL Id : hal-01617750 https://hal.archives-ouvertes.fr/hal-01617750/

- Authors: Marco Lorenzi and Maurizio Filippone
- Contact: Marco Lorenzi
- URL: http://gpprogressionmodel.inria.fr

5.5. Music

Multi-modality Platform for Specific Imaging in Cardiology
KEYWORDS: Medical imaging - Cardiac Electrophysiology - Computer-assisted surgery - Cardiac - Health
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: Florent Collot, Mathilde Merle and Maxime Sermesant
- Partner: IHU- Bordeau
- Contact: Maxime Sermesant
- URL: https://team.inria.fr/asclepios/software/music/

5.6. SOFA

Simulation Open Framework Architecture
KEYWORDS: Real time - Multi-physics simulation - Medical applications
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.

- Participants: Christian Duriez, François Faure, Hervé Delingette and Stéphane Cotin
- Partner: IGG
- Contact: Stéphane Cotin
- URL: http://www.sofa-framework.org

5.7. geomstats

Computations and statistics on manifolds with geometric structures
KEYWORD: Geometry

FUNCTIONAL DESCRIPTION: Geomstats is a python package that performs computations on manifolds such as hyperspheres, hyperbolic spaces, spaces of symmetric positive definite matrices and Lie groups of transformations. It provides efficient and extensively unit-tested implementations of these manifolds, together with useful Riemannian metrics and associated Exponential and Logarithm maps. The corresponding geodesic distances provide a range of intuitive choices of Machine Learning loss functions. We also give the corresponding Riemannian gradients. The operations implemented in geomstats are available with different computing backends such as numpy, tensorflow and keras. Geomstats manifold computations have are integrated into keras deep learning framework thanks to GPU-enabled implementations.

- Partner: Stanford Department of Statistics
- Contact: Nina Miolane
- URL: https://github.com/geomstats/

6. New Results

6.1. Medical Image Analysis

6.1.1. Learning a Probabilistic Model for Diffeomorphic Registration

Participants: Julian Krebs [Correspondant], Hervé Delingette, Tommaso Mansi [Siemens Healthineers, Princeton, NJ, USA], Nicholas Ayache.

This work is funded by Siemens Healthineers, Princeton, NJ, USA

deformable registration, probabilistic modeling, deep learning, latent variable model, deformation transport, disease clustering

We developed a probabilistic approach for deformable image registration in 3-D using deep learning methods [30]. This method includes:

- A probabilistic formulation of the registration problem through unsupervised learning of an encoded deformation model (Fig. 4).
- A differentiable exponentiation layer and an user-adjustable smoothness layer that ensure the outputs of neural networks to be regular and diffeomorphic.
- An analysis of size and structure of a latent variable space for registration.
- Experiments on deformation transport and disease clustering.

6.1.2. Learning Myelin Content in Multiple Sclerosis from Multimodal MRI

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

This work is done in collaboration with the Aramis-Project team of Inria in Paris and the researchers at the Brain and Spinal Cord Institute (ICM) located in Paris.

Multiple Sclerosis, MRI, PET, GANs

- We predict myelin content from multiparametric MRI [36].
- We design an adaptive loss and a sketch-refinement process for GANs, decomposing the problem into anatomy/physiology and myelin content prediction (Fig. 5).
- We show similar results to the PET-derived gold standard.

6.1.3. Consistent and Robust Segmentation of Cardiac Images with Propagation

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

This project is funded by European Research Council (MedYMA ERC-AdG-2011-291080).

Cardiac segmentation, deep learning, neural network, 3D consistency, spatial propagation

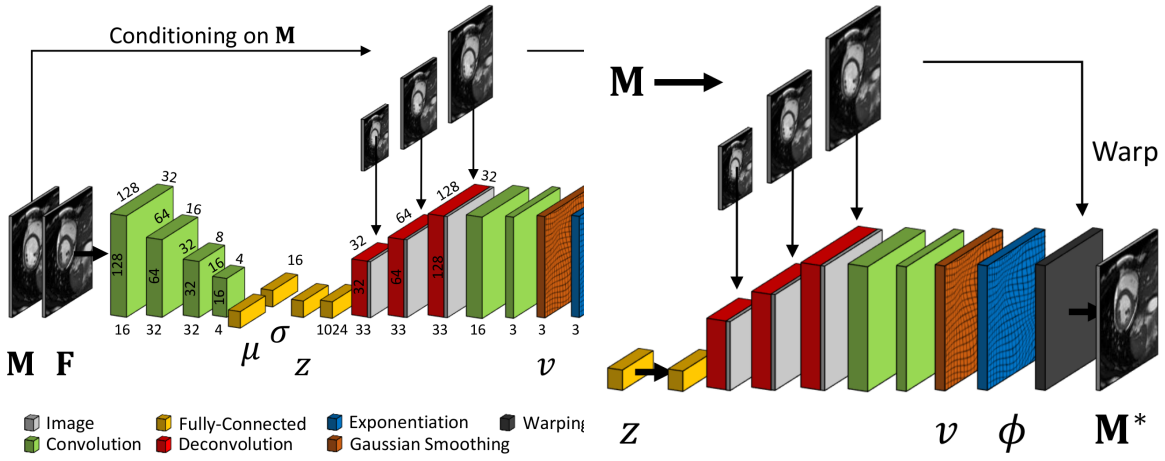

Figure 4. (Left) Probabilistic registration network including a diffeomorphic layer (exponentiation). Deformations are encoded in z from which velocities are decoded while being conditioned on the moving image. (Right) Decoder network for sampling and deformation transport: Apply z-code conditioned on any new image M.

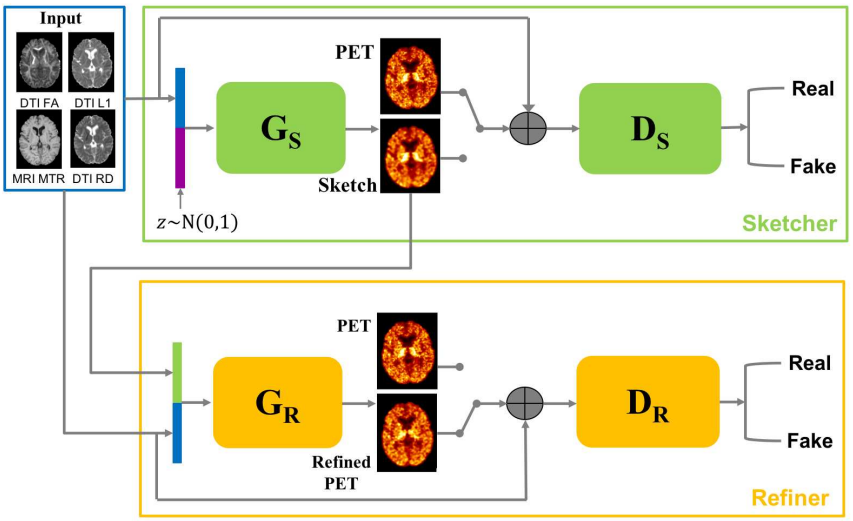

Figure 5. The sketcher receives MR images and generates the preliminary anatomy and physiology information. The refiner receives MR images IM and the sketch IS. Then it refines and generates PET images.

We propose a method based on deep learning to perform cardiac segmentation on short axis MRI image stacks iteratively from the top slice (around the base) to the bottom slice (around the apex) [26][62]. At each iteration, a novel variant of U-net is applied to propagate the segmentation of a slice to the adjacent slice below it (Fig. 6).

- 3D-consistency is hence explicitly enforced.
- Robustness and generalization ability to unseen cases are demonstrated.
- Results comparable or even better than the state-of-the-art are achieved.

The corresponding open source software, CardiacSegmentationPropagation, is available in https://team.inria.fr/epione/en/software/.

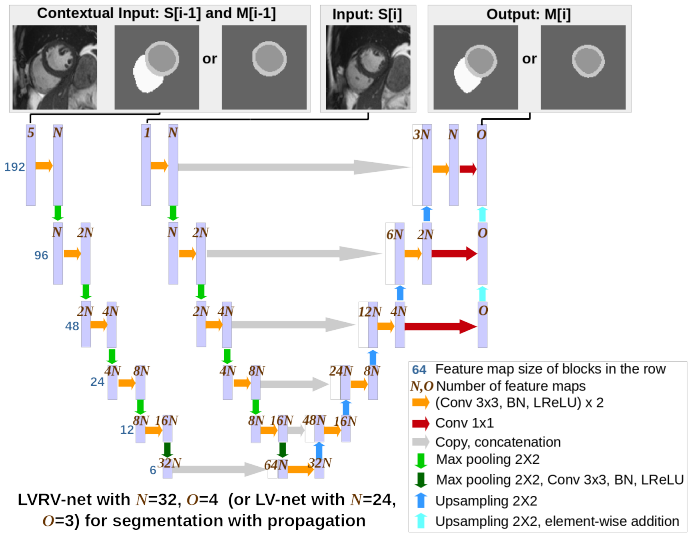

Figure 6. Propagation of cardiac segmentation by a neural network.

6.1.4. Deep Learning for Tumor Segmentation

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

This work is funded by Inria-Microsoft Joint Center and is done in cooperation with Microsoft Research in Cambridge.

deep learning, semi-supervised learning, segmentation, MRI, tumors

- We proposed a model for tumor segmentation which is able to analyze a very large spatial context by combining 2D and 3D CNNs [56] (Fig. 7). Top-3 performance was obtained on BRATS 2017 challenge.
- We proposed an approach to train CNNs for tumor segmentation with a mixed level of supervision [55]. Our approach significantly improves segmentation accuracy compared to standard supervised learning.
- We designed a system for segmentation of organs at risk for protontherapy. Promising preliminary results were obtained.

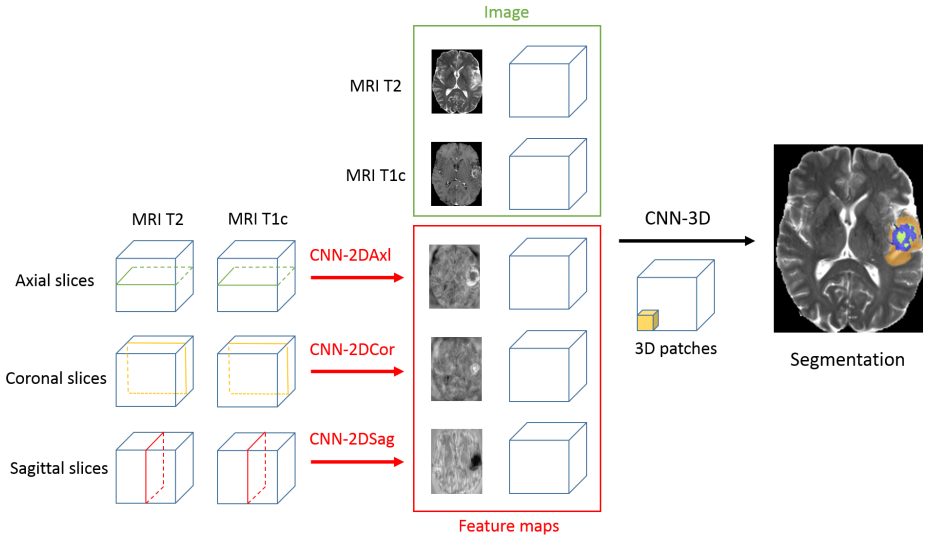

Figure 7. Illustration of our 2D-3D model for brain tumor segmentation.

6.2. Imaging & Phenomics, Biostatistics

6.2.1. Radiomic analysis to improve diagnosis and therapy in oncology

Participants: Fanny Orlhac [Correspondant], Nicholas Ayache, Charles Bouveyron, Jacques Darcourt [CAL], Hervé Delingette, Olivier Humbert [CAL], Pierre-Alexandre Mattei [Copenhague University], Thierry Pourcher [CEA], Fanny Vandenbos [CHU Nice].

Inria postdoctoral fellowship for 16 months

Radiomics, Statistical learning, Metabolomics

- We proposed a modeling which extends the High-Dimensional Discriminant Analysis (HDDA) model by incorporating a sparsity pattern for each class, called sparse HDDA (sHDDA) [21].
- We demonstrated its efficacy in identifying lung lesions based on CT radiomic features (see Figure 8) [21] or triple-negative breast lesions from PET radiomic features and metabolomic data [34], [32], [33]. Thanks to the class-specific variable selection, the final model can be easily interpreted by physicians.
- We also demonstrated the capacity of the ComBat method to harmonize radiomic features extracted from PET images acquired with different imaging protocols [40], [39].

6.2.2. Statistical learning on large databases of heterogeneous imaging, cognitive and behavioral data

Participants: Luigi Antelmi [Correspondent], Marco Lorenzi, Valeria Manera, Philippe Robert, Nicholas Ayache.

Supported by the French government, through the UCA^{JEDI} Investments in the Future project managed by the National Research Agency (ANR) ref. num. ANR-15-IDEX-01, our research is within the MNC3 initiative (Médecine Numérique: Cerveau, Cognition, Comportement), in collaboration with the Institut Claude Pompidou (CHU of Nice). Computational facilities are funded by the grant AAP Santé 06 2017-260 DGA-DSH, and by the Inria Sophia Antipolis - Méditerranée, "NEF" computation cluster.

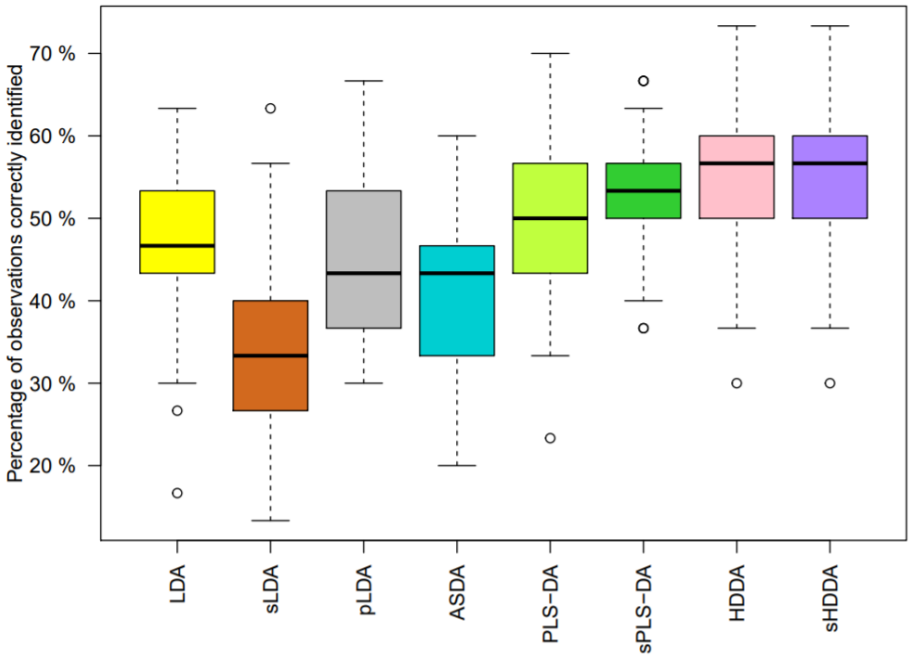

Figure 8. Classification accuracy of the eight statistical methods, including HDDA in pink and sHDDA in purple, to identifying lung lesions based on radiomic features extracted from CT images.

statistical learning, joint analysis, neuroimaging

The aim of our work is to build scalable learning models for the joint analysis of heterogeneous biomedical data, to be applied to the investigation of neurological and neuropsychiatric disorders from collections of brain imaging, body sensors, biological and clinical data available in current large-scale databases such as ADNI[4] and local clinical cohorts.

We developed a computationally efficient formulation of probabilistic latent variable models [37]. This approach is capable to highlight meaningful relationships among biomarkers in the context of Alzheimer's disease (Figure 9) that can be used to develop optimal strategies for disease quantification and prediction.

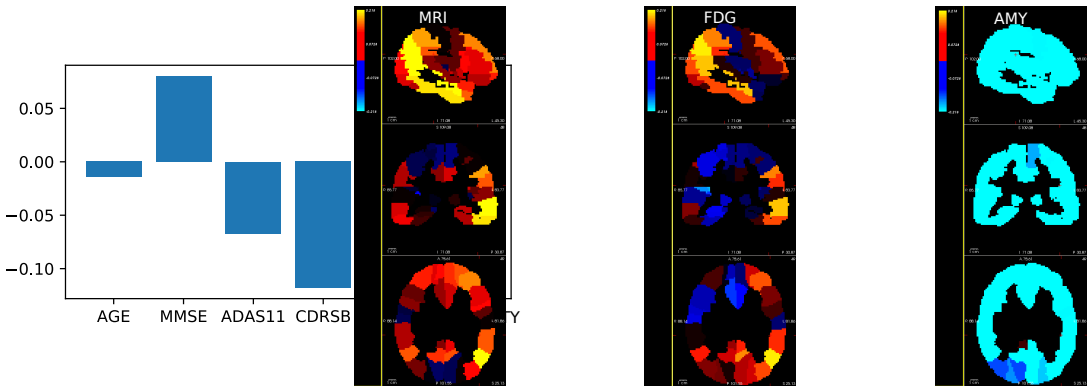

Figure 9. Joint relationships among Alzheimer's disease biomarkers discovered by our multi-channel model in the ADNI dataset. Relationships in line with the current literature discoveries. Clinical biomarkers on the left; brain imaging biomarkers on the right: gray matter density (MRI), glucose uptake (FDG), amyloid uptake (AMY).

6.2.3. Joint Biological & Imaging markers for the Diagnosis of severe lung diseases

Participants: Benoît Audelan [Correspondant], Hervé Delingette, Nicholas Ayache.

Lung cancer, Early detection, Sparse Bayesian Learning

Lung cancer is among the most common cancer and is considered to be one of the most important public health problem. The aim of this work is to improve the detection of lung cancer by combining imaging and biological markers. Exploratory analysis have been conducted to discriminate cancer patients versus controls from circulating miRNAs data using sparse Bayesian learning and to automatically pre-process lung CT images (Fig. 10).

6.2.4. A data-driven model of mechanistic brain atrophy propagation in dementia

Participants: Sara Garbarino [Correspondant], Marco Lorenzi.

Sara Garbarino acknowledges financial support from the French government managed by L'Agence Nationale de la Recherche under Investissements d'Avenir UCA JEDI (ANR-15-IDEX-01) through the project "AtroPro-Dem: A data-driven model of mechanistic brain Atrophy Propagation in Dementia".

Gaussian Processes, Bayesian non–parametric modelling, neuroimaging data, protein dynamics, brain network

[4] http://adni.loni.usc.edu/

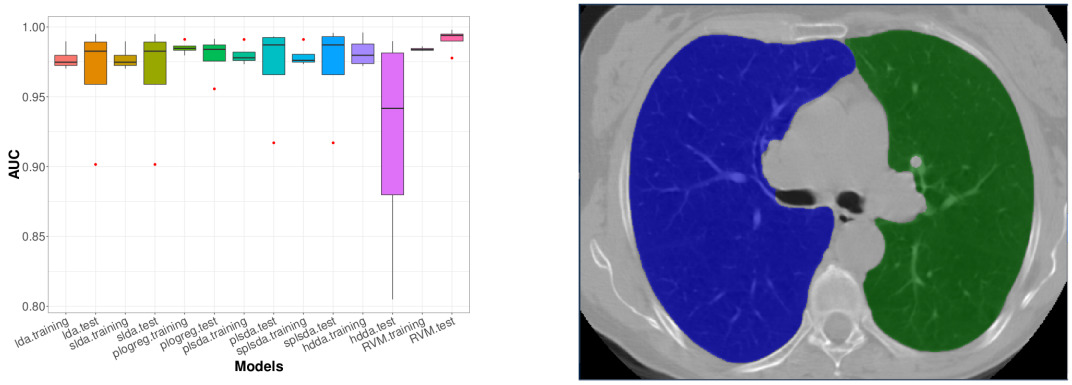

Figure 10. Comparison of statistical methods for classifying lung cancer patient from miRNAs data and lung segmentation

Models of misfolded proteins aim at discovering the bio-mechanical properties of neurological diseases by identifying plausible associated dynamical systems. Solving these systems along the full disease trajectory is usually challenging, due to the lack of a well defined time axis for the pathology. This issue is solved by disease progression models where long-term progression trajectories are estimated via time reparametrization of individual observations. However, due to their loose assumptions on the dynamics, they do not provide insights on the bio-mechanical properties of protein propagation.

In this project we propose a unified model of spatio-temporal protein dynamics based on the joint estimation of long-term protein dynamics and time reparameterization of individuals observations (Figure 11). The model is expressed within a Gaussian Process regression setting, where constraints on the dynamics are imposed through non–linear dynamical systems.

6.2.5. Federated Learning in Distributed Medical Databases: Meta-Analysis of Large-Scale Subcortical Brain Data

Participants: Santiago Silva [Correspondant], Marco Lorenzi, Boris Gutman, Andre Altman, Eduardo Romero, Paul M. Thompson.

This work was supported by the French government, through the UCAJEDI Investments in the Future project managed by the National Research Agency (ANR) with the reference number ANR-15-IDEX-01 (project Meta-ImaGen).

Federated learning, distributed databases, PCA, SVD, meta-analysis, brain disease.

We proposed a federated learning framework for securely accessing and meta-analyzing any biomedical data without sharing individual information.

- A frontend pipeline for preprocessing and analyzing data was proposed, including: standardization, confounders correction, and variability analysis via federated PCA.
- Tested on multi-centric and multi-diagnosis databases (ADNI, PPMI and UK-Biobank) showed a clear differentiation between control and Alzheimer's subjects (Figure 12).
- Further developments of this study will extend the proposed analysis to large-scale imaging genetics data, such as in the context of the ENIGMA meta-study.

6.3. Computational Anatomy

6.3.1. Statistical Learning of Heterogeneous Data in Large-Scale Clinical Databases

Participants: Clement Abi Nader [Correspondant], Nicholas Ayache, Philippe Robert, Marco Lorenzi.

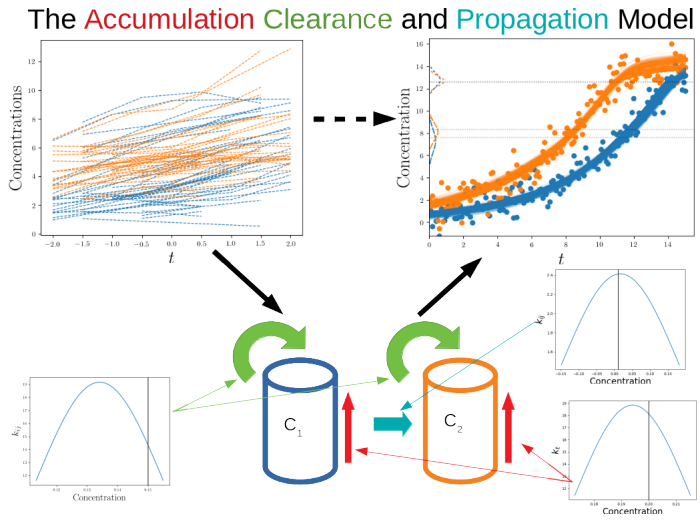

Figure 11. Schematic representation of our framework. Here we have two brain regions whose concentrations are collected for many subjects over a short term time span. The dynamics of such concentrations is described in terms of accumulation, clearance and propagation parameters. The proposed Bayesian framework estimates the distribution of such parameters and the long term trajectories with respect to the estimated disease time axis.

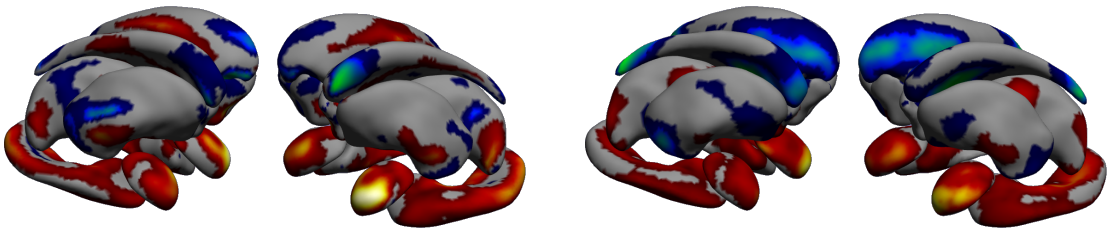

Figure 12. First principal component estimated with the proposed federated framework. The component maps prevalently hippocampi and amigdalae. ***Left:*** *Thickness.* ***Right:*** *Log-Jacobians.*

Gaussian Process, Alzheimer's Disease, Disease Progression Modelling

The aim of this project is to develop a spatio-temporal model of Alzheimer's Disease (AD) progession [47]. We assume that the brain progression is characterized by independent spatio-temporal sources that we want to separate. We estimate brain structures involved in the disease progression at different resolutions thus dealing with the non-stationarity of medical images, while assigning to each of them a monotonic temporal progression using monotonic Gaussian processes (Figure 13, left-middle panel). We also compute an individual time-shift parameter to assess the disease stage of each subject (Figure 13, right panel).

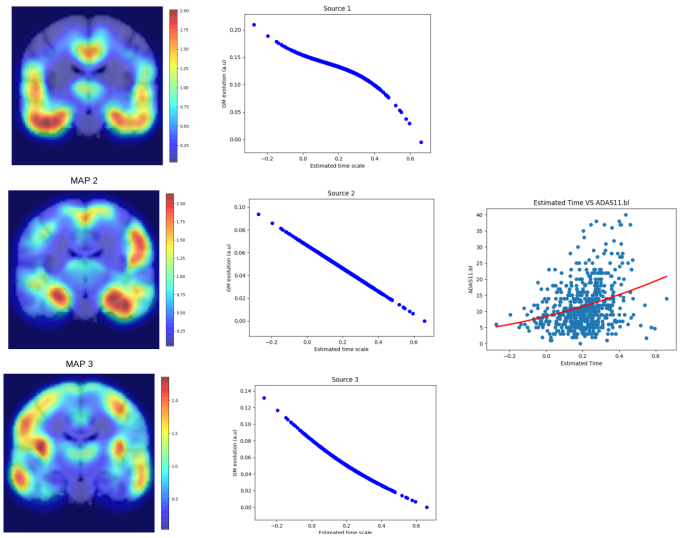

Figure 13. Left-Middle: Brain structures involved in AD along with their temporal evolution. Right: Correlation between ADAS11 cognitive score and the individual time-shift.

6.3.2. A model of brain morphological evolution

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

Longitudinal modeling, Deformation framework, Brain morphology, Alzheimer's disease, Aging.

We proposed a deformation-based generative model of the brain morphological evolution that can jointly describes the effect of aging and Alzheimer's disease. It relies on longitudinal description of the aging and disease consequences and can be use to compute image-based cross-sectional progression markers. This approach is able to propose a description of the disease evolution, population and subject-wise(see Figure 14) and open the way to a better modeling of the disease progression.

6.3.3. Geometric statistics

Participant: Xavier Pennec [Correspondant].

This work is partially funded by the ERC-Adv G-Statistics.

Statistics on manifolds, Differential geometry,

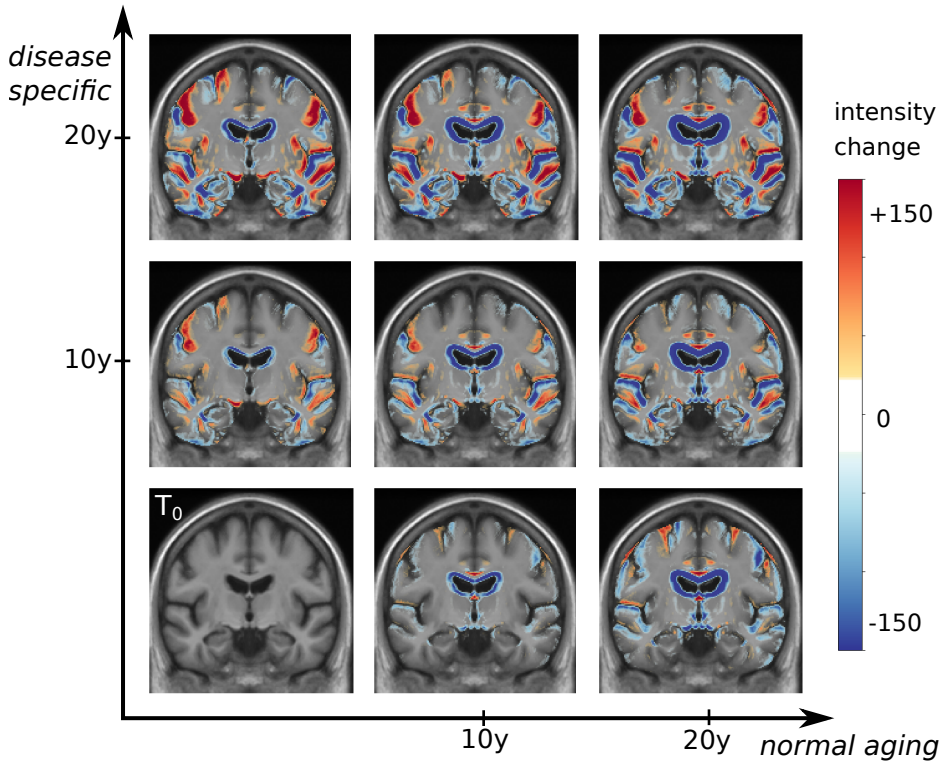

Figure 14. Representation of the 2D parametric template subspace generated by the model. In these images, the bottom row correspond to a healthy evolution, and the diagonal (from bottom left to top right) to a typical pathological evolution. The colors represent the voxel-wise intensity differences between the images and the reference T_0 to highlight the boundary shifts between tissues and CSF.

Beyond the mean value, Principal Component Analysis (PCA) is often used to describe the main modes of variability and to create low dimensional models of the data. Generalizing these tools to manifolds is a difficult problem. In order to define low dimensional parametric subspaces in manifolds, we proposed in [22] to use the locus of points that are weighted means of a number of reference points. These barycentric subspaces locally define submanifolds which can naturally be nested to provide a hierarchy of properly embedded subspaces of increasing dimension (a flag) approximating the data better and better. This defines a generalization of PCA to manifolds called Barycentric Subspace Analysis (BSA) which provides a new perspective for dimension reduction. It appears to be well suited for implicit manifolds such as the ones defined by multiple registrations in longitudinal or cross-section image analysis. An example of such an application was provided in [23] for 4D cardiac image sequences.

In classical estimation problems, the number of samples is always finite. The variability that this induces on the estimated empirical mean is a classical result of the law of large numbers in the asymptotic regime. In manifolds, it is not clear how the curvature influences the estimation of the empirical Fréchet mean with a finite number of samples. Preliminary results showed that there is an unexpected bias inversely proportional to the number of samples induced by the gradient of the curvature and a correction term of the same order on the covariance matrix slowering or accelerating the effective convergence rate towards the Fréchet mean of the underlying distribution. These preliminary results were derived using a new simple methodology that is also extending the validity from Riemannian manifolds to affine connection spaces [45].

6.3.4. *Brain template as a Fréchet mean in quotient spaces*

Participants: Nina Miolane [Correspondant], Xavier Pennec.

Computational anatomy, Morphological brain template, Hierarchical modeling.

Geometrically, the procedure used to construct the reference anatomy for normalizing the measurements of individual subject in neuroimaging studies can be summarized as the Fréchet mean of the images projected in a quotient space. We have previously shown that this procedure is asymptotically biased, therefore inconsistent. In [15], we presented a methodology that quantifies spatially the brain template's asymptotic bias. We identify the main variables controlling the inconsistency. This leads us to investigate the topology of the template's intensity levels sets, represented by its Morse-Smale complex. We have proposed a topologically constrained adaptation of the template computation that constructs a hierarchical template with bounded bias. We apply our method to the analysis of a brain template of 136 T1 weighted MR images from the Open Access Series of Imaging Studies (OASIS) database.

6.3.5. *Cardiac Motion Evolution Modeling from Cross-Sectional Data using Tensor Decomposition*

Participants: Kristin Mcleod [Simula Research Laboratory], Maxime Sermesant, Xavier Pennec.

Cardiac motion tracking, modeling cardiac motion evolution over time

Cardiac disease can reduce the ability of the ventricles to function well enough to sustain long-term pumping efficiency. We proposed in [14] a cardiac motion tracking method to study and model cohort effects related to age with respect to cardiac function. The proposed approach makes use of a Polyaffine model for describing cardiac motion of a given subject, which gives a compact parameterisation that reliably and accurately describes the cardiac motion across populations. Using this method, a data tensor of motion parameters is extracted for a given population. The partial least squares method for higher-order arrays is used to build a model to describe the motion parameters with respect to age, from which a model of motion given age is derived. Based on cross-sectional statistical analysis with the data tensor of each subject treated as an observation along time, the left ventricular motion over time of Tetralogy of Fallot patients is analysed to understand the temporal evolution of functional abnormalities in this population compared to healthy motion dynamics (see Figure 15).

6.3.6. *Challenging cardiac shape and motion statistics*

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

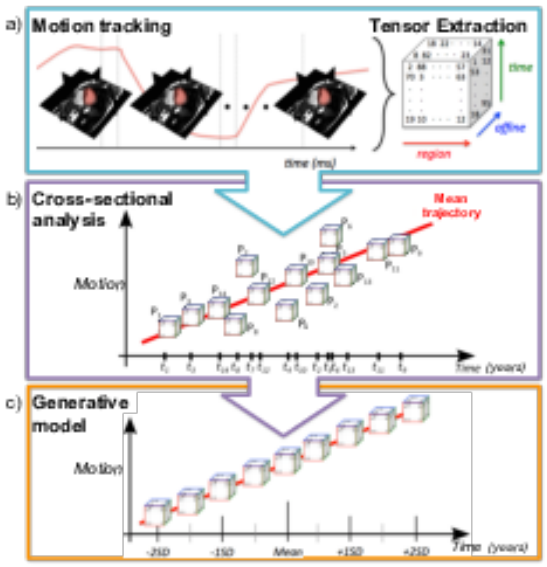

Figure 15. Building a generative model of the long-term motion changes in a population (c) by a) building a data tensor of polyaffine motion parameters that represent the motion over the cardiac cycle for each subject in the population using cross-sectional statistical analysis of polyaffine tensors and b) performing cross-sectional statistical analysis of the data tensors.

Shape statistics, Non-rigid registration, Deep learning, Cardiac shape and motion

Two of the methods previously developed by Marc-Michel Rohé in his PhD were benchmarked against other state of the art methods in two successive MICCAI challenges. First, the SVF-net developed to perform a very-fast inter-subject heart registration based on convolutional neural networks was embedded into a multi-atlas segmentation pipeline and tested against other deep learning techniques for the automatic MRI cardiac multi-structures segmentation [2]. Second, a combination of polyaffine cardiac motion tracking and supervised learning was used to predict myocardial infarction [25]. Both challenges demonstrate the good performances of the tested methods.

6.4. Computational Physiology

6.4.1. CIMPLE : Cochlear Implantation Modeling, PLanning & Evaluation

Participants: Zihao Wang [Correspondant], Hervé Delingette, Thomas Demarcy [Oticon Medical], Clair Vandersteen [IUFC], Nicolas Guevara [IUFC], Charles Raffaelli [CHU], Dan Gnansia [Oticon Medical], Nicholas Ayache.

This work is funded by the Provence-Alpes-Côte-d'Azur region, the Université Côte d'Azur and Oticon Medical.

Statistic Learning, Image segmentation, Cochlea Implantation

The work aims to establish an effective, quantitative and rapid assessment method for human cochlear implantation planning and adjustment.

During last one year, our team explored a cost-effectively and practically algorithm to achieve the goal.

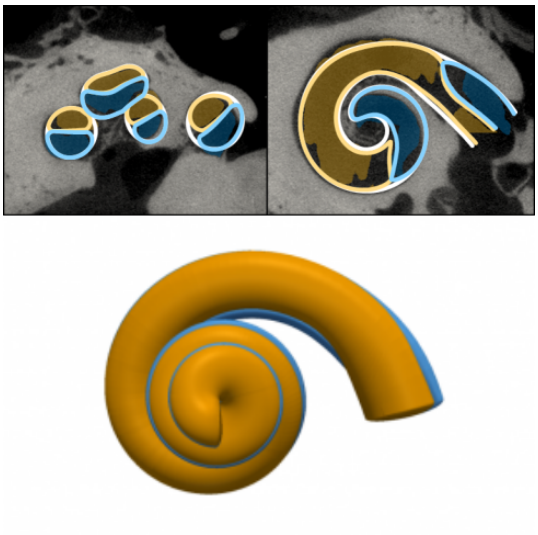

Figure 16. The figure shown a example segmentation on micro-CT image. Lower is the parametric model that quantitative mesure the cochea shape.

6.5. Computational Cardiology & Image-Based Cardiac Interventions

6.5.1. Population-based priors for group-wise Personalisation

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

The authors acknowledge the partial funding by the MD-Paedigree EU Project.

Personalised cardiac model, Parameter observability, Statistical modeling, Dimensionality reduction, Heterogeneous clinical data, Imputation

Personalised cardiac models have a large number of parameters while the available data for a given patient is typically limited to a small set of measurements, thus the parameters cannot be estimated uniquely. This is a practical obstacle for clinical applications, where accurate parameter values can be important. Here we explore an original approach based on an algorithm called Iteratively Updated Priors (IUP), in which we perform successive personalisations of a full database through Maximum A Posteriori (MAP) estimation, where the prior probability at an iteration is set from the distribution of personalised parameters in the database at the previous iteration (Figure 17). At the convergence of the algorithm, estimated parameters of the population lie on a linear subspace of reduced (and possibly sufficient) dimension in which for each case of the database, there is a (possibly unique) parameter value for which the simulation fits the measurements. We first show how this property can help the modeler select a relevant parameter subspace for personalisation. In addition, since the resulting priors in this subspace represent the population statistics in this subspace, they can be used to perform consistent parameter estimation for cases where measurements are possibly different or missing in the database, which we illustrate with the personalisation of a heterogeneous database of 811 cases [18].

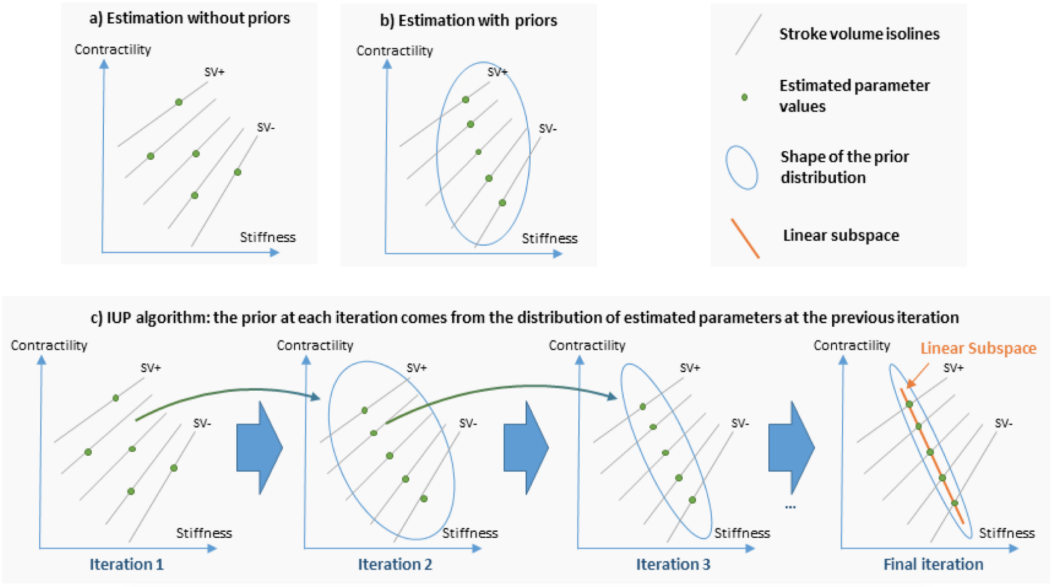

Figure 17. Schematic representation of parameter estimation problem: both contractility and stiffness are estimated from the stroke volume (SV). Both have an influence on the stroke volume (SV) so there are isolines of stroke volume (in grey) for varying parameters. (a) estimation without priors, the estimated values (green) for each case can be anywhere on an isoline (grey). (b) estimation performed with a prior (Gaussian covariance in blue), estimated values are grouped closer to prior mean. (c) Iteratively Updated Priors (IUP) algorithm performs successive estimations where the prior is set from the distribution of estimated parameters at the previous iteration. This leads the parameters to lie on a reduced linear subspace (orange).

6.5.2. Fast Personalized Computer Simulation of Electrical Activation from CT Imaging in Post-infarction Ventricular Tachycardia

Participants: Nicolas Cedilnik [Correspondant], Hubert Cochet [IHU Liryc, Bordeaux], Maxime Sermesant.

This work is funded by the IHU Liryc, in Bordeaux.

Cardiac modeling, Personalised simulation, ablation, intervention guidance.

In the vast majority of post-MI VT ablation procedures, VT is either non inducible or non mappable. We introduce a fast and robust model of cardiac electrophysiology that can be directly parameterized from CT images to predict activation maps (Figure 18). The model is based on the Eikonal equation for wave propagation, where local conduction velocities are estimated from CT. A fully automated method is used to segment the LV wall and assign local conduction velocity according to local LV thickness. Then, a "channelness" filter automatically detects potential VT isthmuses as channels of preserved thickness within severely thinned scar. The model can then be paced within each channel to produce simulated activation maps within seconds. A neural network for automated LV wall segmentation was trained on 450 CTs segmented by experts. Validation, performed on another 50 cases, showed excellent accuracy (Dice score vs. expert 0.95). In 11 patients undergoing post-MI VT ablation (age 58±13, 9 men), simulated activation maps were validated vs. 25 high density maps acquired in Rhythmia (16 paced, 9 VT). Quantitative differences between predicted and measured local activation times remained substantial, particularly in dense scar (> 50ms). Nonetheless, activation patterns were well predicted in most cases (22/25), the 3 poor correlations being observed in patients with fewer scar. Personalized simulation of activation maps from CT scan is feasible and reliably reproduces activation patterns in post-MI VT. The method is fast enough to be used clinically in an interactive fashion for procedural planning [4].

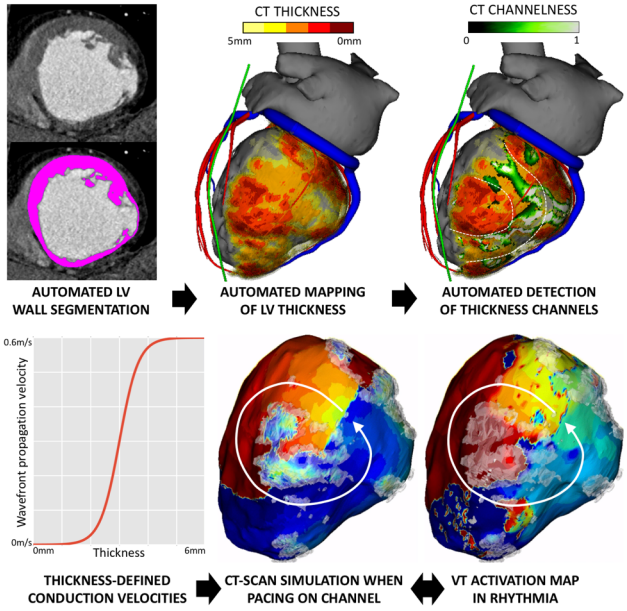

Figure 18. Our image-based model personalization pipeline

6.5.3. Cardiac Modeling, Medical Imaging and Machine Learning for Electrostructural Tomography

Participants: Tania Marina Bacoyannis [Correspondant], Hubert Cochet [IHU Liryc, Bordeaux], Maxime Sermesant.

This work is funded within the ERC Project ECSTATIC with the IHU Liryc, in Bordeaux.

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

Electrocardiographic imaging (ECGI) aims at reconstructing cardiac activity from torso measurements.To achieve this one has to solve the ill-posed inverse problem of the torso propagation. We propose a novel application for Deep Learning Networks to learn spatio-temporal correlations on ECGI (Figure 19). We developped a conditional variational auto-encoder (CVAE).The input are activation maps and the model takes two conditions: on one hand the cardiac shape(cardiac segmentation) and the other one the ECG signals.

The model currently involves simulated data: 120 activations maps were simulated from one cardiac geometry along with simulated body surface potential maps.80% of the data was used for training and the remaining 20% for testing. As a result we were able to observe a good prediction of the activation pattern.

Next, we will test the model with real data provided by the IHU Liryc.

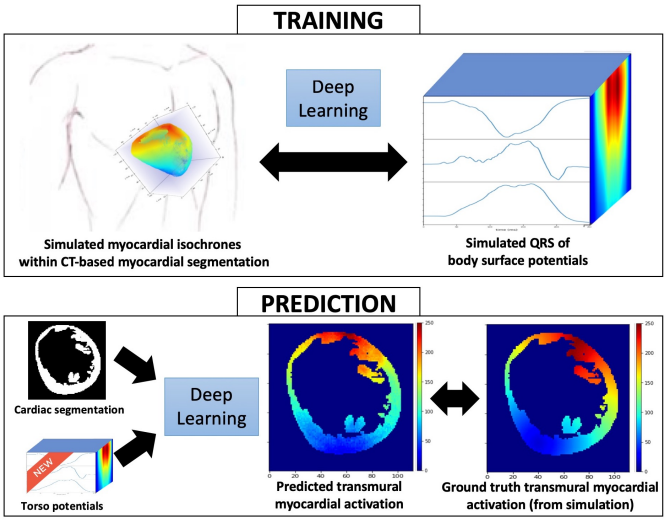

Figure 19. Setup of the conditional variational auto-encoder based on synthetic data

6.5.4. Discovering the link between cardiovascular pathologies and neurodegeneration through biophysical and statistical models of cardiac and brain images

Participants: Jaume Banus Cobo [Correspondant], Maxime Sermesant, Marco Lorenzi.

Université Côte d'Azur (UCA)

Lumped models - Biophysical simulation - Statistical learning

The project aims at developing a computational model of the relationship between cardiac function and brain damage from large-scale clinical databases of multi-modal and multi-organ medical images. The model is based on advanced statistical learning tools for discovering relevant imaging features related to cardiac dysfunction and brain damage; these features are combined within a unified mechanistic framework to providing a novel understanding of the relationship between cardiac function, vascular pathology and brain damage (Fig. 20). We are also testing data-driven statistical learning models for the discovery of associations between cardiac function and brain damage. For example, by applying CCA we identified a first component that shows a positive correlation between the volume of white matter hyper intensities (WMHs), the number of WMHs lesions, the brain ventricles volume and high blood pressure values. On the other side we observed a second component, inversely associated to the first one, in which we observe a strong correlation between ejection fraction (EF) and total brain volume (white matter plus grey matter).

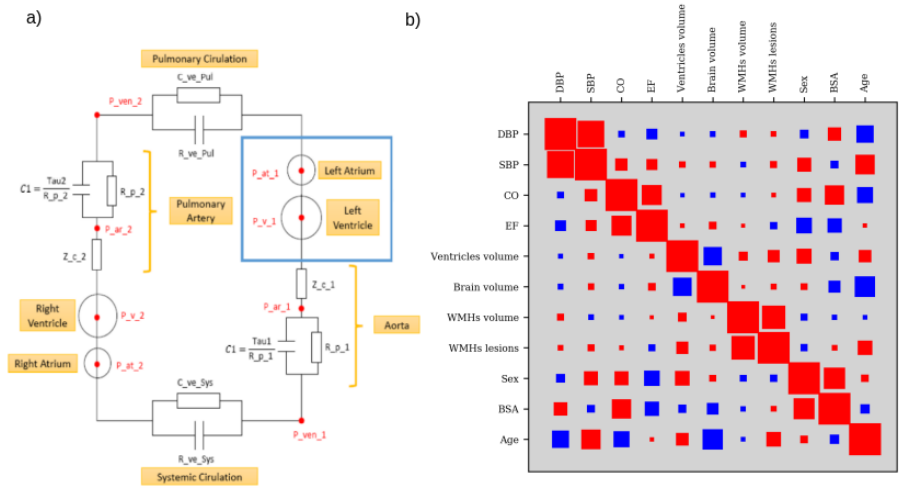

Figure 20. a) Schematic representation of the 0D model used to simulate the whole body circulation, its parameters are optimized to fit the available clinical measurements b) Partial correlations between cardiovascular, brain and demographic variables. Red represents positive correlation and blue negative correlation.

6.5.5. Automatic Image Segmentation of cardiac structures with Adapted U-Net

Participants: Shuman Jia [Correspondant], Antoine Despinasse, Zihao Wang, Hervé Delingette, Xavier Pennec, Hubert Cochet, Maxime Sermesant.

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

We proposed automated, two-stage, three-dimensional U-Nets with a contour loss, to segment the left atrium, as explained in [28], which obtained state-of-the-art results in the STACOM international challenge (Figure 21). Using similar method, we participated in Data Challenge organised at Journées Francophones de Radiologie and obtained a second place for renal cortex segmentation.

6.5.6. Parallel Transport of Surface Deformation

Participants: Shuman Jia [Correspondant], Nicolas Duchateau, Pamela Moceri, Xavier Pennec, Maxime Sermesant.

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

We looked into normalization of temporal deformation and proposed a more symmetric mapping scheme for pole ladder, which relies on geodesic symmetries around mid-points, as illustrated in [29] (Figure 22)). This modified parallel transport method method was shown to be of order 4 on general manifolds and exact in symmetric spaces [58].

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

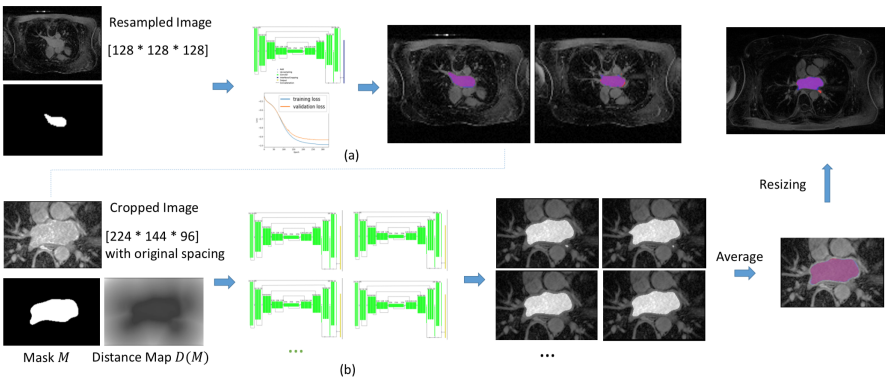

Figure 21. The framework of successive U-Nets training. (a) The fist U-Net - cropping; (b) the second U-Net - segmenting, with ensemble prediction models. We show here axial slices of MR images, overlapped with manual segmentation of the left atrium in blue, our segmentation in red, intersection of the two in purple.

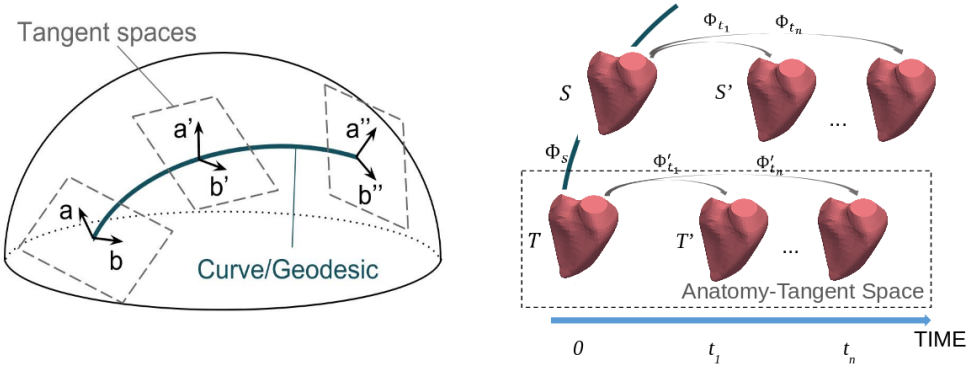

Figure 22. Illustration of parallel transport of vectors a and b along a curve (left) and its application to cardiac imaging (right) with a focus on surfaces.

7.1.1. 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 Pawel Mlynarski.

7.1.2. 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.

7.1.3. Spin-off company inHEART

inHEART[8] is a spin-off of the Asclepios team and IHU Liryc founded in 2017. inHEART provides a service to generate detailed anatomical and structural meshes from medical images, that can be used during ablation interventions. inHEART received 2 awards, one from Aquitaine region and one i-LAB from the BPI.

7.1.4. Siemens HealthCare

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

7.1.5. Median Technologies

Median technologies, Sophia Antipolis (FR) funded the 5 months gap year internship of Souhaiel Riahi and the 6 months Master 2 level internship of Nour Ediine al Orjany, co-advised by Xavier Pennec and Hervé Delingette on the characterization of hepatic lesions and fibrosis in CT image using machine learning methods

8. Partnerships and Cooperations

8.1. Regional Initiatives

- N. Ayache and P. Robert are principal investigators of the project MNC3 (Médecine Numérique, Cerveau, Cognition, Comportement) funded by Idex Jedi UCA (2017-2021, 450k€). M. Lorenzi (Inria) actively participates to the supervision of this project with the help of V. Manera (ICP).
- Hervé Delingette is the principal investigator of the LungMark project funded by Idex Jedi UCA (2018-2021).
- Hervé Delingette is the principal investigator of the CIMPLE project, funded by Idex Jedi UCA (2018-2021), the region PACA and Oticon Medical. The region PACA and Oticon Medical are co-funding the Phd of Zihao Wang.
- Marco Lorenzi is principal investigator of the project Big Data for Brain Research, funded during 2017-20 by the Département des Alpes Maritimes.
- Marco Lorenzi is principal investigator of the project MetaImaGen, funded by Idex Jedi UCA (2018-2020, 37k€).
- Maxime Sermesant is principal investigator of the project "The Digital Heart" and the innovation action "Digital Heart Phantom" with General Electrics, funded by Idex UCA Jedi. These projects gather the local cardiac research in academia, clinics and industry.

[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] http://www.inheart.fr/

8.2. National Initiatives

8.2.1. Consulting for Industry

- Nicholas Ayache is a scientific consultant for the company Mauna Kea Technologies (Paris).
- Marco Lorenzi is a scientific consultant for the company MyDataModels (Sophia Antipolis).
- Xavier Pennec is a scientific consultant for the company Median Technologies (Sophia Antipolis)
- Maxime Sermesant is a scientific consultant for the company inHEART (Bordeaux)

8.2.2. Collaboration with national hospitals

The Epione-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.

8.3. European Initiatives

8.3.1. FP7 & H2020 Projects

8.3.1.1. ERC ECSTATIC

Title: Electrostructural Tomography – Towards Multiparametric Imaging of Cardiac Electrical Disorders

Programm: H2020

Type: ERC

Duration: 2017 - 2022

Coordinator: U. Bordeaux

Inria contact: Maxime Sermesant

Cardiac electrical diseases are directly responsible for sudden cardiac death, heart failure and stroke. They result from a complex interplay between myocardial electrical activation and structural heterogeneity. Current diagnostic strategy based on separate electrocardiographic and imaging assessment is unable to grasp both these aspects. Improvements in personalized diagnostics are urgently needed as existing curative or preventive therapies (catheter ablation, multisite pacing, and implantable defibrillators) cannot be offered until patients are correctly recognized.

ECSTATIC aims at achieving a major advance in the way cardiac electrical diseases are characterized and thus diagnosed and treated, through the development of a novel non-invasive modality (Electrostructural Tomography), combining magnetic resonance imaging (MRI) and non-invasive cardiac mapping (NIM) technologies.

The approach will consist of: (1) hybridising NIM and MRI technologies to enable the joint acquisition of magnetic resonance images of the heart and torso and of a large array of body surface potentials within a single environment; (2) personalising the inverse problem of electrocardiography based on MRI characteristics within the heart and torso, to enable accurate reconstruction of cardiac electrophysiological maps from body surface potentials within the 3D cardiac tissue; and (3) developing a novel disease characterisation framework based on registered non-invasive imaging and electrophysiological data, and propose novel diagnostic and prognostic markers.

This project will dramatically impact the tailored management of cardiac electrical disorders, with applications for diagnosis, risk stratification/patient selection and guidance of pacing and catheter ablation therapies. It will bridge two medical fields (cardiac electrophysiology and imaging), thereby creating a new research area and a novel semiology with the potential to modify the existing classification of cardiac electrical diseases.

8.3.1.2. ERC G-statistics

Title: Biophysical Modeling and Analysis of Dynamic Medical Images
Programme: FP7
Type: ERC
Period: 2018-2023
Coordinator: Inria
Inria contact: Xavier Pennec

G-Statistics aims at exploring the foundations of statistics on non-linear spaces with applications in the Life Siences. Invariance under gauge transformation groups provides the natural structure explaining the laws of physics. In life sciences, new mathematical tools are needed to estimate approximate invariance and establish general but approximate laws. Rephrasing Poincaré: a geometry cannot be more true than another, it may just be more convenient, and statisticians must find the most convenient one for their data. At the crossing of geometry and statistics, G-Statistics aims at grounding the mathematical foundations of geometric statistics and to exemplify their impact on selected applications in the life sciences.

So far, mainly Riemannian manifolds and negatively curved metric spaces have been studied. Other geometric structures like quotient spaces, stratified spaces or affine connection spaces naturally arise in applications. G-Statistics will explore ways to unify statistical estimation theories, explaining how the statistical estimations diverges from the Euclidean case in the presence of curvature, singularities, stratification. Beyond classical manifolds, particular emphasis will be put on flags of subspaces in manifolds as they appear to be natural mathematical object to encode hierarchically embedded approximation spaces.

In order to establish geometric statistics as an effective discipline, G-Statistics will propose new mathematical structures and characterizations of their properties. It will also implement novel generic algorithms and illustrate the impact of some of their efficient specializations on selected applications in life sciences. Surveying the manifolds of anatomical shapes and forecasting their evolution from databases of medical images is a key problem in computational anatomy requiring dimension reduction in non-linear spaces and Lie groups. By inventing radically new principled estimations methods, we aim at illustrating the power of the methodology and strengthening the "unreasonable effectiveness of mathematics" for life sciences.

8.3.2. Collaborations in European Programs, Except FP7 & H2020

Program: ERA CoSysMed
Project acronym: SysAFib
Project title: Systems medicine for diagnosis and stratification of atrial fibrillation
Duration: Mai 2016 - Mai 2019
Coordinator: Simula, Norway
Inria contact: Maxime Sermesant
Other partners: Inria, Helmholtz Zentrum München, Oslo University Hospital, Maastricht University, CardioCentro Ticino/CCMC
Abstract: Atrial fibrillation (AF) sharply increases the risk of stroke and is associated with a number of other severe complications, including heart failure. The SysAFib project aims to combine advanced data analysis and computer simulations with classical clinical approaches to create a decision support tool for treating AF. Diverse data sources, such as the individual patient's medical history, clinical measurements and genetic data will be combined into a single tool for optimizing and personalizing AF therapy. SysAFib's ultimate goal is to deliver the right treatment to the right patient at the right time, stopping AF in its tracks and ending the need for repeat invasive procedures.

8.4. International Initiatives

8.4.1. Inria International Labs

Inria@SiliconValley

Associate Team involved in the International Lab:

8.4.1.1. 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: 2018

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

The scientific goal of the associated team led by X. Pennec 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 analysing and modelling the biological variability of the organs shapes at the population level. An important application in neuroimaging is the spatial normalization of subjects that is necessary to compare anatomies and functions through images in populations with different clinical conditions. Following the developments of the last 3 years of the associated team GeomStat, the new research directions have been broken into three axes. The first axis aims at continuing the progresses in theoretical and applied Geometric statistics, with a first theme studying the impact of curvature on the estimation with a finite sample, and a second axis extending the current work on Barycentric Subspace Analysis (BSA), notably with algorithms. The second axis aims at developing a hierarchical atlas of the brain anatomy based on the stratification of the space of image orbits under diffeomorphisms. The third axis explores three important applications of low-dimensional subspace learning in manifolds using BSA in neuroscience: the approximation of EEG signals for brain-computer interfaces (BCI); the acceleration and robustification of Tensor Distribution Functions (TDF) estimation in diffusion images; and the efficient inference in spaces of rank-deficient symmetric matrices for imaging-genetics from multi-centric databases.

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

8.4.2.1. PersoCardioLearn

Title: Personalization of Cardiac Models using Experimental Data and Machine Learning

International Partner (Institution - Laboratory - Researcher):

University of Toronto (Canada) - Sunnybrook Research Institute - Mihaela Pop

Start year: 2017

See also: https://team.inria.fr/asclepios/research/associated-team-persocardiolearn/

Multi-scale computer modelling is a powerful tool that could be used to simulate in silico cardiac electrical activity and biomechanical function of individual heart. Imaging and 3D heart models built from images can help us understand the basis of structurally-diseased hearts at organ level and to predict in silico the changes in electro-mechanical function as a consequence of muscle remodelling in pathologic state (e.g. chronic infarction, a major cause of death). We hypothesize that MRI-based predictive models can help us identify new opportunities to intervene or to predict the outcome of ablation therapy, which currently has low clinical success. However, these predictive models need to be validated and thoroughly tested in preclinical experiments prior to their integration into the clinical stage. Hence, the next logical step for our joint Inria-SB efforts is to expand our experimental-theoretical framework and to personalize fast 3D heart models from in vivo MR-EP data. This translational step involves numerous challenging tasks from the modelling perspective since the in vivo imaging and physiological signals are rather noisy and obtained at a poor spatial resolution, potentially leading to erroneous customization of mathematical model parameters. However, this collaboration employs a rare combination of experiments and modelling specialists. Moreover, the originality of the proposed approach is to build upon machine-learning techniques rather than on data assimilation methods that are more explored in the literature but have inherent limitations (robustness to noise, local minima. . .).

8.4.3. Inria International Partners

8.4.3.1. Informal International Partners

8.4.3.1.1. 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.

8.4.3.1.2. 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.

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

Marco Lorenzi is collaborator of the Translational Imaging Group of UCL, and with the UCL Institute od Ophtalmology. His collaboration is around the topic of spatio-temporal analysis of medical images, with special focus on brain imaging analysis and biomarker development. 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.

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

Marco Lorenzi is currently collaborator of IGC for the investigation of the 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.

8.4.3.1.5. Other International Hospitals

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

8.5. International Research Visitors

8.5.1. Visits of International Scientists

8.5.1.1. Internships

- Svenja Hüning, PhD student with Johannes Wallner at Graz University in Austria visited the Epione team in November 2018 to work with Xavier Pennec on subdivision schemes on manifolds.
- Santiago Smith Silva Rincon, Master student at the National University of Bogota (CO), visited the Epione team from May to October 2018 to work with Marco Lorenzi on distributed learning methods in imaging-genetics.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Member of the Organizing Committees

- M. Sermesant was a co-chair of the MICCAI 2018 Workshop Statistical Atlases and Computational Models of the Heart (STACOM 2018), which was held in Granada, September 16, 2018.
- H. Delingette was a member of the organizing committee of the scientific day at Inria Sophia Antipolis (September 10th) including two keynote speakers on "Digital privacy" and presenting the activities of the UCA academy on "Networks, Information and Digital Society".

9.1.2. Scientific Events Selection

9.1.2.1. Member of the Conference Program Committees

- H. Delingette was Workshop and Tutorial co-chair for the international conference Medical Image Computing and Computer Aided Intervention (MICCAI 2018) held in Granada, Spain from Sept. 16-20.

9.1.2.2. Reviewer

- M. Lorenzi was a reviewer for the conferences Neural Information Processing Systems (NIPS 2018), International Conference on Machine Learning (ICML 2018), Medical Image Computing and Computer Aided Intervention (MICCAI 2018), International Conference on Learning Representations (ICLR 2019), IEEE International Symposium of Biomedical Imaging (ISBI 2017-19).
- X. Pennec was a reviewer for Medical Image Computing and Computer Aided Intervention (MICCAI 2018) and the MICCAI workshop on Shape in Medical Imaging (ShapeMI 2018).
- M. Sermesant was a reviewer for Medical Image Computing and Computer Aided Intervention (MICCAI 2018) and the MICCAI workshop STACOM.
- H. Delingette was a reviewer for the International Symposium on Biomedical Imaging (ISBI'18), the international conference on computer-aided interventions (IPCAI'18), the conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2018), the International Conference on Computer Vision and Pattern Recognition (CVPR 2018).

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 journal. 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).
- M. Lorenzi is a member of the editorial board of the journal Scientific Reports (Nature Publishing Group); he is also member of the Board of Statisticians of the Journal of Alzheimer's Disease (IOS Press).

9.1.3.2. Reviewer - Reviewing Activities

- M. Lorenzi was a reviewer for the following journals: Neurobiology of Aging, Alzheimer's and Dementia, Journal of Alzheimer's Disease, Medical Image Analysis, IEEE Transactions on Medical Imaging, NeuroImage, International Journal of Computer Vision, Journal of Mathematical Image and Vision, Scientific Reports.
- Xavier Pennec was a reviewer for IEEE Transactions on Information Theory, The Annals of Applied Statistics, Linear Algebra and its Applications.
- M. Sermesant was a reviewer for the following journals: Nature Cardiology Reviews, 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.
- H. Delingette was a reviewer for the following journals: Medical Image Analysis (Elsevier), IEEE Transactions in Medical Imaging, IEEE Transactions in Biomedical Engineering.

9.1.4. Invited Talks

- **N. Ayache** gave the following plenary invited talks:
  - AI for Digital Patients, Int Conf on Image Comput. and Digital Medicine, Chengdu, China, 2018,
  - IA & Healthcare, IA Summit, Sophia Antipolis, 2018,
  - Patient numérique: images, apprentissage, intelligence artificielle, Collége de France 2018,
  - L'intelligence articifielle au coeur de la médecine de précision, Medicen, Paris, 2018.
- **M. Lorenzi** was a speaker for the panel IA & Santé of the SophIA Summit 2018, Sophia Antipolis, November 7th, 2018. He was also invited to give a lecture to the Armour College of Engineering of the Illinois Institute of Technology, Chicago, July 25th 2018, to the General Assembly of the European Clinical Project AMYPAD, Berlin, October 9th 2018, and to the Disease Progression Modeling Workshop of the European project EUROPOND, Geneva, February 19th, 2018.
- **X. Pennec** was invited speaker at the Mathematics and Image Analysis Conference (MIA 2018), 15-17 January 2018, Berlin (DE), at the MFO workshop on Nonlinear Data: Theory and Algorithms, Oberwolfach (DE), 22-28 April 2018, at the MFO workshop on Statistics for Data with Geometric Structure, Oberwolfach (DE), 21-27 January 2018.
- **M. Sermesant** was an invited speaker at the Fields Institute (Toronto) "Mathematics for Medicine" workshop, at the "Myocardial Function" workshop in Leuven, at the CardioFunxion Winter School in Lyon, at the "New Horizons in Heart Failure" conference in Paris, at the "Computing in Cardiology" conference in Maastricht, at the French Radiology Days meeting of Cardiac Imaging in Paris, at the PIC Marie Curie ITN meeting in Bordeaux.
- **H. Delingette** was a keynote speaker at the NAFEMS conference in Paris November 20th 2018, and an invited speaker at the SOFA workshop in Strasburg in November 2018, at the Data Science structuring program evaluation day in Sept. 2018.
- **N. Miolane** was invited speaker at the MFO workshop on Statistics for Data with Geometric Structure, Oberwolfach (DE), 21-27 January 2018, at the Workshop on Geometry in Machine Learning (GiMLi), July 15, 2018, Stockholm, Sweden and at the Seminar of John Hopkins University, Center of Imaging Science, May 19, 2018, Baltimore, USA.

9.1.5. Leadership within the Scientific Community

- **H. Delingette** is a member of the MICCAI Society Board of Directors.

9.1.6. Scientific Expertise

- **N. Ayache** is a member of the following scientific committes:
  - 2016 -: Scientific advisory committee for Région Ile de France (20 members),
  - 2015 -: Research Committee of Fondation pour la Recherche Médicale (18 members),
  - 2010 -: Scientific Advisory Boards in London (ICL,KCL,UCL), Oxford & Notthingham,
  - 2009 - 2019: Advisory Committee, Japan Initiative in Computational Anatomy, MEXT.
- **M. Lorenzi** was reviewer of the funding agencies ANR (Agence Nationale de la Recherche, France) and an expert panel member for the evaluation of the projects submitted to the Flanders Research Foundation, Belgium. He is providing scientific consulting for the company MyDataModels through an Inria Tech research contract.
- **X. Pennec** was a member of the Junior researcher (CR) recruiting committee for Inria-Sophia Antipolis, for the Inria International Chairs Selection Committee, and an evaluator for the Netherlands Organisation for Scientific Research (NWO).
- **M. Sermesant** was an evaluator for the Wellcome Trust (UK) and the NSF (USA).
- **H. Delingette** was an evaluator for the Dutch research council NWO, and or the Research Council of KU Leuven.

9.1.7. Research Administration

- **Xavier Pennec** is co-director and at the board of the Ecole doctorale STIC of Université Côte d'Azur. He 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 and in charge of the relationships of Inria-Sophia with the Nice University Hospital (CHU). At University Côte d'Azur, he is a member of the executive committee of the Academy 4 (Living systems Complexity and diversity), of the Scientific committee of the Academy 2 (Complex Systems), and of the Advanced Research Program Committee.
- **Marco Lorenzi** is is a member of the local steering committee of the technological platforms (Comités Scientifiques de Pilotage des Plateformes) in charge of Cluster, Grid, Cloud, and HPC technologies. He is also member of the Scientific Board of the UCA NeuroMod Institute.
- **Hervé 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. He is the coordinator of the Academy of excellence on "Networks, Information and Digital Society" at the Université Côte d'Azur. He is member of the executive committee of the "Ecole Universitaire de recherche" entitled *Digital Systems for Humans* at Université Côte d'Azur. He is a representive of Inria at the Federation Hospitalo-Universitaire Oncoage led by the CHU Nice.

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.

9.2.2. Theses Defended

- Pamela Moceri, From normal right ventricle to pathology: shape and function analysis with different loading conditions using imaging and modelling. Started in 2015. Directed by M. Sermesant. Defended on January 25 2018.

9.2.3. PhD in progress

- Raphaël Sivera, Analyse statistique de l'évolution de structures morphologiques partir de séquences temporelles d'IRM, Université Côte d'Azur. Started in October 2015. Co-directed by N. Ayache and H. Delingette and co-supervised by M. Lorenzi and X. Pennec.
- Pawel Mlynarski, Tumor segmentation based on Random Forests and Convolutional Neural Networks trained on partially annotaded data, Université Côte d'Azur. Started in December 2015. Co-directed by N. Ayache and H. Delingette.
- Qiao Zheng, Deep learning for cardiac image analysis, Université Côte d'Azur. 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, Université Côte d'Azur. Started in 2016. Co-directed by M. Sermesant and X. Pennec.
- Wen Wei, Learning Brain Alterations in Multiple Sclerosis from Multimodal Neuroimaging Data, Université Côte d'Azur. Started in 2016. Co-directed by N.Ayache and O.Colliot.
- Julian Krebs, Robust image registration based on machine learning, Université Côte d'Azur. Started in 2016. Co-directed by H. Delingette and N. Ayache.
- Luigi Antelmi, Statistical learning on large databases of heterogeneous imaging, cognitive and behavioural data, Université Côte d'Azur. Started in 2017. Co-directed by P. Robert and N. Ayache and supervised by M. Lorenzi.

- Clément Abi-Nader, Statistical Learning of Heterogeneous Data in Large-Scale Clinical Databases, Université Côte d'Azur. Started in 2017. Co-directed by P. Robert and N. Ayache and supervised by M. Lorenzi.
- Jaume Banús Cobo, Heart & Brain: discovering the link between cardiovascular pathologies and neurodegeneration through biophysical and statistical models of cardiac and brain images, Université Côte d'Azur. Started in 2017. Directed by M. Sermesant and co-supervised by Marco Lorenzi.
- Tania-Marina Bacoyannis, Cardiac Imaging and Machine Learning for Electrostructural Tomography, Université Côte d'Azur. Started in 2017. Co-directed by M. Sermesant and H. Cochet.
- Nicolas Cedilnik, Personalised Modeling for Ventricular Tachycardia Ablation Planning, Université Côte d'Azur. Started in 2017. Co-directed by M. Sermesant and H. Cochet.
- Nicolas Guigui, Statistical estimation on Riemannian and affine symmetric spaces with applications to the statistical survey of the brain anatomy, Université Côte d'Azur. Started in 2018. Directed by X. Pennec.
- Benoît Audelan, Joint biological and imaging markers for the diagnosis of severe lung diseases. Started in 2018. Co-directed by H. Delingette and N. Ayache.
- Zihao WANG, Cochlear Implantation Modeling, Planning & Evaluation. Started in 2018. Directed by H. Delingette.

9.2.4. Juries

- Marco Lorenzi was a jury member for the PhD probation exam of Kurt Kutajar and Remi Domingues (EURECOM), Isa Costantini (Athena, Inria), and Radia Zeghari (CoBTeK, Inria, CHU Nice).
- Xavier Pennec was co-supervisor of the PhD thesis of Pauline Bezivin Frere (U. Orsay) defended in July 2018, reviewer for the PhD of Maël Dugast, INSA Lyon, FR, Dec. 2018 and for the PhD of Baptiste Moreau, University of Montpellier II, FR, March 2018. He was the president of the jury of the HDR of Laurent Risser (HDR), U. Toulouse, FR, November 2018.
- Hervé Delingette was a reviewer in the PhD thesis committee of C. Jaquet (ESIEE- Univ. of Paris-Est).
- Maxime Sermesant was a reviewer and a member of the PhD jury of Josselin Duchateau, Bordeaux University (Dec 20), a reviewer for the PhD of Sergio Sanchez, UPF Barcelona (Sep 21) and a member of the PhD jury of Ketan Bacchuwar, ESIEE (Jun 5).

9.3. Popularization

9.3.1. Interventions

- Nicolas Cedilnik, Pierre Tramaloni, Thomas Demarcy, Hervé Delingette and Maxime Sermesant organised a cardiac intervention simulator demo and a cochlear implant demo for the Science Festival at Inria (Dec 7).
- On April the 10th, during the "mathematics week", 2 PhD students (Nicolas Cedilnik and Raphael Sivera) met young pupils (age 8-10) at the ESPE (école supérieure du professorat et de l'éducation) Nice. The pupils were introduced to mathematical concepts in a practical way through the use of toys.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

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