Activity Report 2019

Project-Team EPIONE

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

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Project-Team EPIONE

Creation of the Team: 2018 January 01, updated into Project-Team: 2018 May 01

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1. Team, Visitors, External Collaborators

Research Scientists
 Nicholas Ayache [Team leader, Inria, Senior Researcher, HDR]
 Hervé Delingette [Inria, Senior Researcher, HDR]
 Marco Lorenzi [Inria, Researcher]
 Xavier Pennec [Inria, Senior Researcher, HDR]
 Maxime Sermesant [Inria, Researcher, HDR]

Post-Doctoral Fellows
 Sara Garbarino [Univ Côte d'Azur, Post-Doctoral Fellow]
 Fanny Orlhac [Inria, Post-Doctoral Fellow, until Nov 2019]

PhD Students
 Clement Abi Nader [Univ de Nice - Sophia Antipolis, PhD Student]

Luigi Antelmi [Univ Côte d'Azur, PhD Student]
Benoit Audelan [Univ Côte d'Azur, PhD Student]
Tania Marina Bacoyannis [Inria, PhD Student]
Jaume Banus Cobo [Univ de Nice - Sophia Antipolis, PhD Student]
Nicolas Cedilnik [Inria, PhD Student]
Mikael Chelli [Centre hospitalier universitaire de Nice, PhD Student, from Aug 2019]
Hind Dadoun [Inria, PhD Student, from Dec 2019]
Nicolas Guigui [Inria, PhD Student]
Shuman Jia [Inria, PhD Student]
Florent Jousse [Quantificare, PhD Student, from Apr 2019, granted by CIFRE]
Julian Krebs [Inria, PhD Student]
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Paul Tourniaire [Inria, PhD Student, from Dec 2019]
Zihao Wang [Inria, PhD Student]
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Qiao Zheng [Inria, PhD Student, until Mar 2019]

Interns and Apprentices
Paul Blanc Durand [Hôpital Henri Mondor, from May 2019 until Sep 2019]
Gaëtan Desrues [Inria, from Mar 2019 until Aug 2019]
Julien Moreira [Univ Côte d'Azur, from Apr 2019]
Yingyu Yang [Inria, from Apr 2019 until Aug 2019]
Yann Fraboni [Inria, from Dec 2019]

Visiting Scientists
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Peter Wijeratne [University College London, from Sep 2019 until Oct 2019]

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Philippe Robert [Cobtek Laboratory, Univ. Côte d'Azur]
Clair Vandersteen [Centre hospitalier universitaire de Nice, from Mar 2019]
Wilhelm Wimmer [Bern University, until Oct 2019]

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.
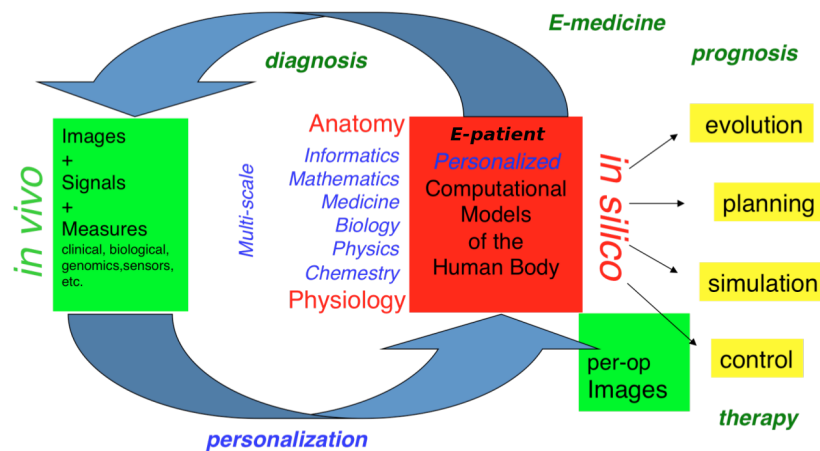
Figure 1. The e-patient for e-medicine

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.

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
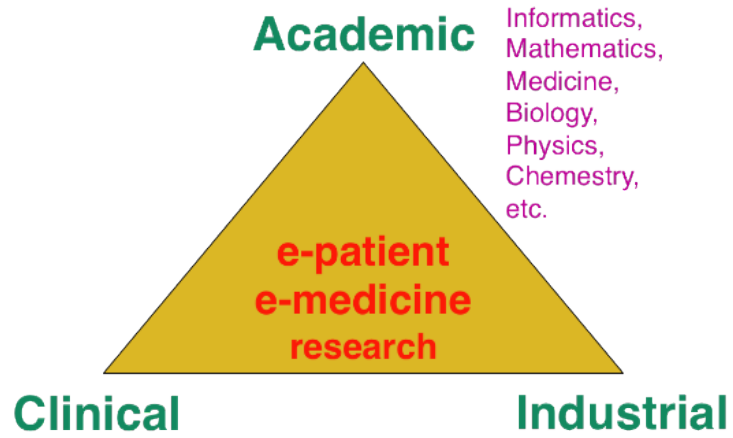
Figure 2. A pluridisciplinary research triangle
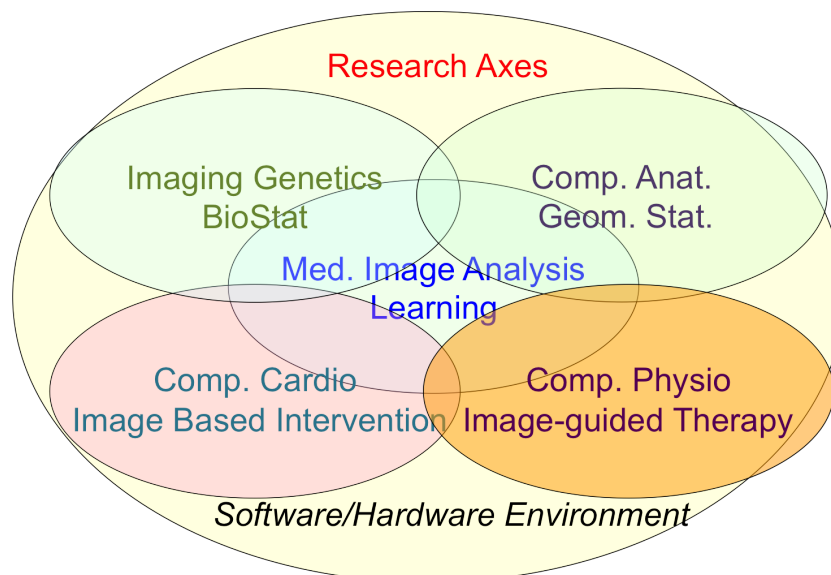
Figure 3. Epione's five main research axes

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.

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.

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

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[1] http://www.ukbiobank.ac.uk/

[2] http://enigma.ini.usc.edu/.

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

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 *federated* 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.

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*

- Nicholas Ayache, Hervé Delingette, Marco Lorenzi, Xavier Pennec, and Maxime Sermesant were awarded a chair at the institute *3IA Côte d'Azur* focused on artificial intelligence.

- Hervé Delingette was elected a Fellow of MICCAI society at MICCAI 2019 : http://www.miccai.org/about-miccai/miccai-fellows/

- Julian Krebs received the Best Presenter Award at the workshop STACOM for his presentation of the paper

- Marco Lorenzi was awarded a Contrat jeune chercheur by the National Research Agency (ANR) for his Fed-BioMed project.

- Sara Garbarino was awarded the IPMI 2019 Erbsmann Award for her paper entitled "Modeling and inference of spatio-temporal protein dynamics across brain networks".

- Nicholas Ayache was awarded the Grand Prize of the City of Nice by the Mayor of Nice, at the Villa Masséna, on May 24, 2019.

- Maxime Sermesant received the Innovator of the Year Award by CentraleSupelec on January 21st, 2019.

- Yann Thanwerdas was nominated among the 5 running papers for the best paper award at the Geometric Sciences of Information conference GSI' 2019 at ENAC in Toulouse.

4.1.2. *Dissemination*

- Publication of the book *Riemannian Geometric Statistics in Medical Image Analysis* [53] edited by Xavier Pennec, Stefan Sommer and Tom Fletcher, 3rd volume of "The Elsevier and MICCAI Society book series". The book contains 5 introductory chapters on the methodological foundations by Xavier Pennec, Tom Fletcher, Stefan Sommer, Stephen Marsland and Marco Lorenzi, and 11 contributed chapters on applications, including a chapter by Nina Miolane, Loic Devillier and Xavier Pennec.

- Publication of the book *Voir l'invisible - Tome 2, Comprendre, Agir* by the Collectif Amir with Maxime Sermesant as one of the scientific contributors. The second version of the book informs the public reader of the latest innovations in science and technology from different fields.
- Organization of the scientific program of the conference "The Academie des sciences in Nice and Sophia Antipolis" by N. Ayache in June 20-21, 2019.

BEST PAPERS AWARDS:

[40]

J. KREBS, T. MANSI, N. AYACHE, H. DELINGETTE. *Probabilistic Motion Modeling from Medical Image Sequences: Application to Cardiac Cine-MRI*, in "STACOM 2019 - 10th Workshop on Statistical Atlases and Computational Modelling of the Heart", Shenzhen, China, October 2019, https://arxiv.org/abs/1907.13524 - Probabilistic Motion Model, Motion Tracking, Temporal Super-Resolution, Diffeomorphic Registration, Temporal Variational Autoencoder, https://hal.inria.fr/hal-02239318

[48]

S. GARBARINO, M. LORENZI. *Modeling and Inference of Spatio-Temporal Protein Dynamics Across Brain Networks*, in "IPMI 2019 - 26th International Conference on Information Processing in Medical Imaging", Hong-Kong, China, LNCS, Springer, 2019, vol. 11492, pp. 57-69, https://hal.inria.fr/hal-02165021

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: 3D Consistent & Robust Segmentation of Cardiac Images by Deep Learning with Spatial Propagation

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 Empenn 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: https://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. 2019 Apr 15,190:56-68. doi: 10.1016/j.neuroimage.2017.08.059. Epub 2017 Oct 24. HAL Id : hal-01617750 https://hal.archives-ouvertes.fr/hal-01617750/

RELEASE FUNCTIONAL DESCRIPTION: - New interface and output - Completely based on pytorch

- Participant: Marco Lorenzi
- Contact: Marco Lorenzi
- Publication: Probabilistic disease progression modeling to characterize diagnostic uncertainty: application to staging and prediction in Alzheimer's disease
- 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: Hugo Talbot
- 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/

5.8. MC-VAE

Multi Channel Variational Autoencoder

KEYWORDS: Machine learning - Artificial intelligence - Medical applications - Dimensionality reduction - High Dimensional Data - Unsupervised learning - Heterogeneity

SCIENTIFIC DESCRIPTION: Interpretable modeling of heterogeneous data channels is essential in medical applications, for example when jointly analyzing clinical scores and medical images. Variational Autoencoders (VAE) are powerful generative models that learn representations of complex data. The flexibility of VAE may come at the expense of lack of interpretability in describing the joint relationship between heterogeneous data. To tackle this problem, in this work we extend the variational framework of VAE to bring parsimony and interpretability when jointly account for latent relationships across multiple channels. In the latent space, this is achieved by constraining the variational distribution of each channel to a common target prior. Parsimonious latent representations are enforced by variational dropout. Experiments on synthetic data show that our model correctly identifies the prescribed latent dimensions and data relationships across multiple testing scenarios. When applied to imaging and clinical data, our method allows to identify the joint effect of age and pathology in describing clinical condition in a large scale clinical cohort.

FUNCTIONAL DESCRIPTION: This software implements the work published in the paper "Sparse Multi-Channel Variational Autoencoder for the Joint Analysis of Heterogeneous Data" presented at the conference ICML 2019 (Long Beach, California, USA).

The software extends classical variational autoencoders by identifying a joint latent code associated to heterogeneous data represented in different channels. The software is implemented in python and is based on pytorch. It can be applied to any kind of data arrays, and provides functions for optimisation, visualisation and writing of the modelling results.

RELEASE FUNCTIONAL DESCRIPTION: First release

NEWS OF THE YEAR: Method presented in the International Conference on Machine Learning (ICML 2019).

- Participants: Luigi Antelmi, Marco Lorenzi and Nicholas Ayache
- Partner: CoBteK
- Contact: Luigi Antelmi
- URL: https://gitlab.inria.fr/epione_ML/mcvae

5.9. SOFA-CardiacReduction

KEYWORDS: Simulation - 3D modeling - Model Order Reduction - Cardiac

SCIENTIFIC DESCRIPTION: Modification of a finite element deformation model : meshless approach and frame-based description, reduction in the number of affine degrees of freedom and integration points.

FUNCTIONAL DESCRIPTION: This SOFA plugin is intented to build a reduced model for deformable solids (especially cardiac simulations).

- Participants: Gaetan Desrues, Hervé Delingette and Maxime Sermesant
- Contact: Gaetan Desrues

6. New Results

6.1. Medical Image Analysis

6.1.1. *Learning a Probabilistic Model for Diffeomorphic Registration and Motion Modeling*

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 motion modeling, artificial intelligence, latent variable model, deformation transport

We developed a probabilistic approach for multi-scale deformable image registration in 3-D using conditional variational autoencoder [16], [58] and extended it to a motion model by using cardiac MRI image sequences [40]. This includes:

- A probabilistic formulation of the registration problem through unsupervised learning of an encoded deformation model.
- A generative motion model using explicit time-dependent temporal convolutional networks (Fig. 4).
- Demonstration on cardiac cine-MRI for cardiac motion tracking, simulation, transport and temporal super-resolution.

6.1.2. *Predicting PET-derived demyelination from multimodal MRI using sketcher-refiner adversarial training for multiple sclerosis*

Participants: Wen Wei [Correspondent], Nicholas Ayache, Olivier Colliot [ARAMIS].
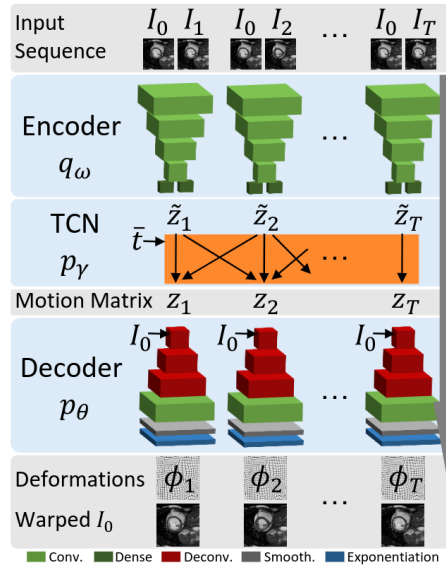
Figure 4. Probabilistic motion model: the encoder q_ω projects the image pair (I_0, I_t) to a probabilistic low-dimensional deformation encoding $\widetilde{z}_t$ from which the temporal convolutional network p_γ constructs the motion matrix $z \in \mathbb{R}^{d \times T}$. The decoder p_θ maps the motion matrix to the deformations ϕ_t.

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

By using multiparametric MRI, we proposed to use a 3D FCNN to predict FLAIR MRI which is used clinically for the detection of WM lesions [26]. In addition, we proposed Sketcher-Refiner GANs to predict PET-derived demyelination from multiparametric MRI [25] with the following contributions:

- Learning the complex relationship between myelin content and multimodal MRI data;
- Comparing quantitatively our approach to other state-of-the-art techniques;
- Proposing visual attention saliency maps to better interpret the neural networks;
- Comparing different combinations of MRI modalities and features to assess which is the optimal input;

6.1.3. Patch Based Bayesian Mesh Registration

Participants: Paul Blanc-Durand [Correspondant], Hervé Delingette.

A 1 year grant from APHP

Bayesian Modeling, Mesh deformation, Mechanical model

The objective of this work is to co-register two lung CT scans of the same patient acquired at different breathing cycle based on an elastic and Bayesian model of lung deformation. Its originality stems from the joint estimation of a displacement fields and its derivatives (gradient matrix) defined from a tetrahedral mesh. Inference is performed in two alternating steps including the optimization of local affine transforms and the global optimiztion of the displacement.
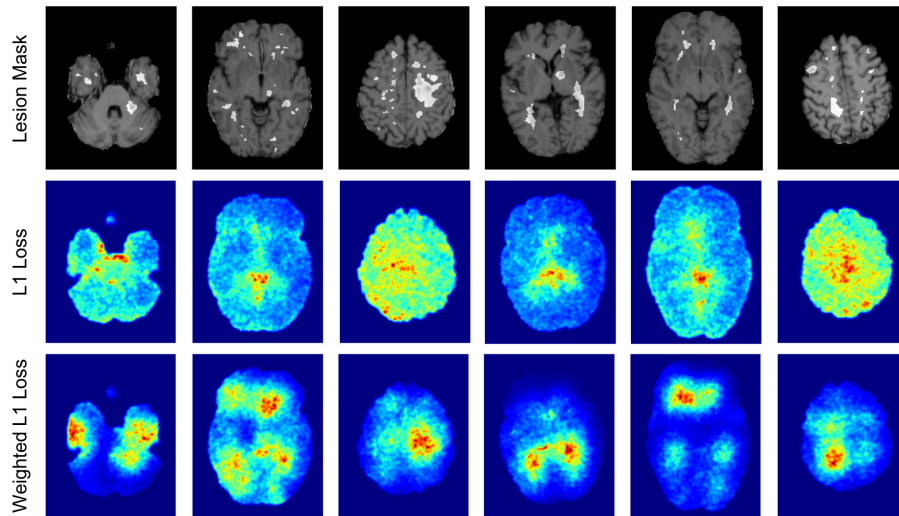
Figure 5. The proposed visual attention saliency map. The white regions shown in first row are MS lesion masks. The second row shows some examples of the attention of neural networks when L1 loss is used as the traditional constraint in the loss function, without the specific weighting scheme that we proposed. The third row shows the corresponding attention of neural networks when our proposed weighted L1 loss is applied. It is clear that our designed loss function is able to effectively shift the attention of neural networks towards MS lesions.
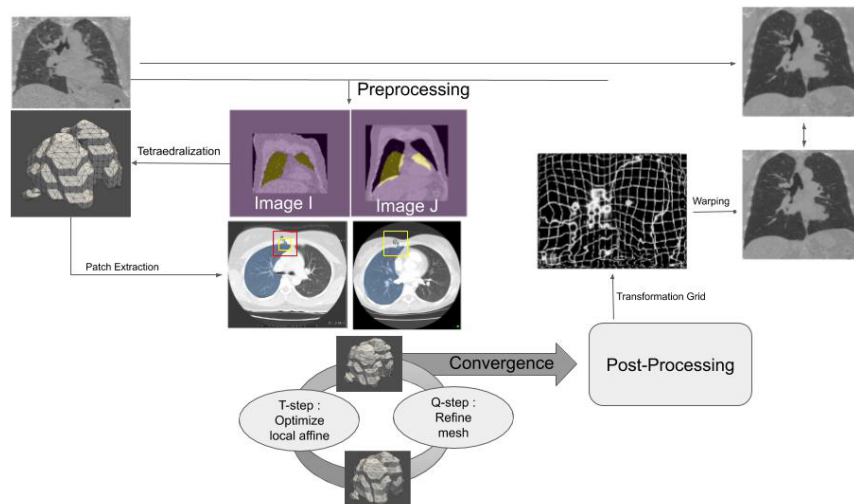
Figure 6. Patches are extracted around vertices of mesh. During T-step, we aim to optimize an affine transform centered on a vertice of image I (the moving image) to image J (the fixed image). The affine transform is regularized under a probabilistic model taking into account the deformation of the mesh. During Q-step, we developed an elastical model of lung which homogenize predictions. After few epochs, convergence is achieved.

6.2. Imaging & Phenomics, Biostatistics

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

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

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.

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 probabilistic latent variable model able to account for heterogeneous data modalities jointly [6]. In the latent space, this is achieved by constraining the variational distribution of each modality to a common target prior. Moreover, we added *ad hoc* prior distribution and parameterization for the latent space to induce sparsity (Fig. 7a). This approach is capable to highlight meaningful relationships among biomarkers in the context of Alzheimer's disease (Fig. 7b) that can be used to develop optimal strategies for disease quantification and prediction.
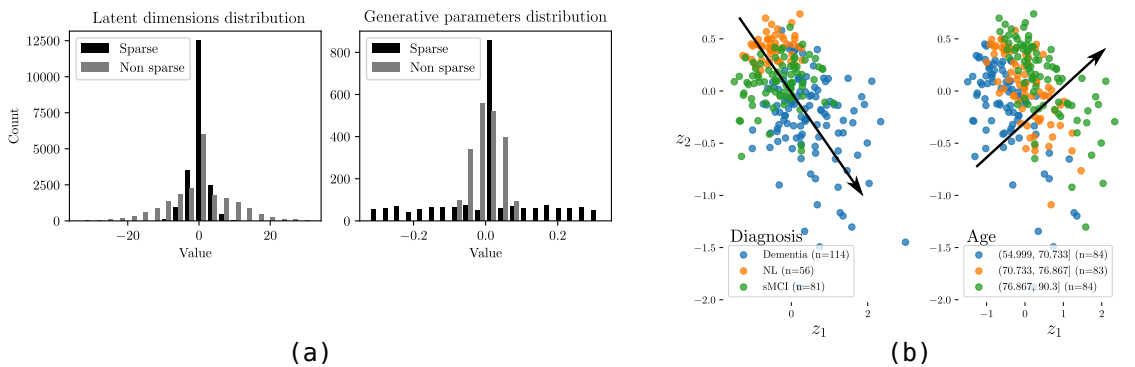
Figure 7. (a) Effect of variational dropout on a synthetic experiment modeled with the Multi-Channel VAE. As expected, the minimum amount of non-zero components of the latent variables (left) and generative parameters (right) is obtained with the sparse model. (b) Stratification of the ADNI subjects (test data) in the sparse latent space. In the same space it is possible to stratify subjects in the test-set by disease status (left) and by age (right) in almost orthogonal directions.

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

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

Lung cancer, Early detection, Biomarkers, Segmentation quality control

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

Lung cancer is among the most common cancer and is considered to be one of the most important public health problem. In recent years, immunotherapy has revolutionized cancer treatments but its efficiency is varying among patients. To prevent possible negative side effects there is a critical need in reliable biomarkers capable of predicting the response to immunotherapy treatments. We analyzed the performance of different biomarkers and studied their combination through logistic regression and decision tree models, as part of a joint project with the IRCAN laboratory (Pr P. Hofman, Dr S. Heeke) at Nice hospital [13].

Furthermore, we investigated the issue of automated quality control assessment of image segmentations, which are a key point of medical image processing pipelines. We propose a novel unsupervised quality control approach based on simple intensity and smoothness assumptions [30]. We introduce a novel spatial prior which allows an automatic estimation of all parameters through Bayesian learning. The approach was tested on various medical imaging datasets (Fig. 8).
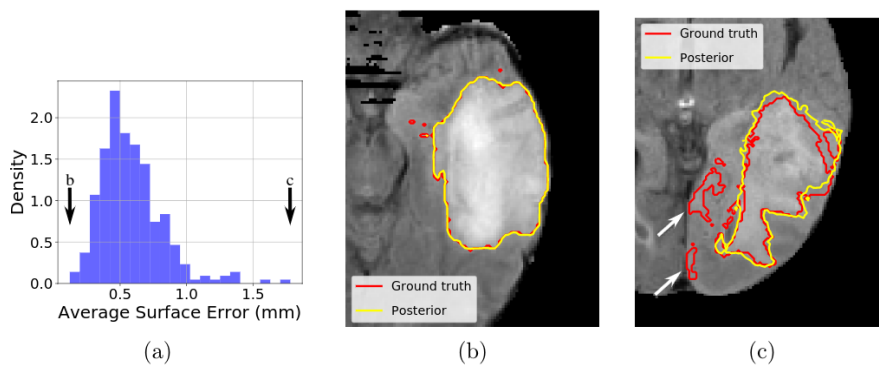
Figure 8. Unsupervised quality control of the BRATS 2017 challenge training set. Distribution of the Average Surface Error (a). Example of a segmentation explained by the model (b). Example of a segmentation not explained by the model (c).

6.2.3. *Modelling and inference of protein dynamics in neurodegenerative diseases across brain networks*

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 "AtroProDem: A data-driven model of mechanistic brain Atrophy Propagation in Dementia".

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

In this project we propose the first unified framework for the joint estimation of long term neurodegenerative disease progression and kinetic parameters describing pathological protein dynamics across brain networks [48]. The model is expressed within a constrained Gaussian Process regression setting. We use stochastic variational inference for scalable inference and uncertainty quantification. Experiments on simulated data and on AV45-PET brain imaging data measuring topographic amyloid deposition in Alzheimer's disease show that our model accurately recovers prescribed rates along graph dynamics and precisely reconstructs the underlying progression.

6.3. Computational Anatomy & Geometric Statistics

6.3.1. *Riemannian Geometric Statistics in Medical Image Analysis*

Figure 9. Schematic representation of the proposed framework. Regional protein concentrations are collected for a number of subjects over a short term time span (A). The dynamics of such concentrations are described in terms of a dynamical system for the vector of concentratio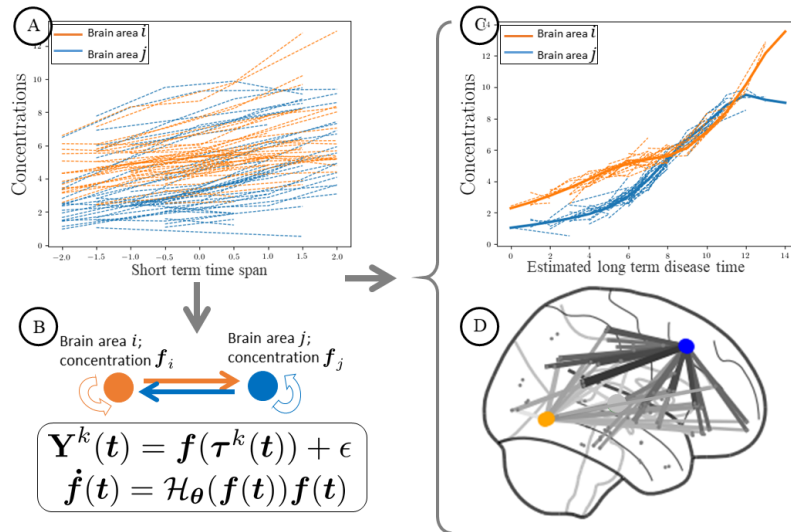ns (B). The proposed framework estimates such parameters encoding the strength of propagation (D) and the long term protein concentrations with respect to the estimated long term time axis (C).

Participants: Xavier Pennec [Correspondant], Stefan Sommer [CPH Univ, DK], Tom Fletcher [University of Virginia at Charlottesville, USA].

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

Geometric statistics, Riemannian geometry, medical image analysis, computational anatomy

There has been a growing need in the medical image computing community for principled methods to process nonlinear geometric data. Riemannian geometry has emerged as one of the most powerful mathematical and computational frameworks for analyzing such data. In the book *Riemannian Geometric Statistics in Medical Image Analysis* [53], we provided an introduction to the core methodology for performing statistics on Riemannian manifolds and more general nonlinear spaces followed by a presentation of state-of-the-art methods in medical image analysis.

We provided more specifically an introduction chapter on differential and Riemannian geometry [56] (with S. Sommer and T. Fletcher), a comprehensive chapter on symmetric positive definite matrices (SPD) and manifold value image processing [55], and reference chapter on the affine connection setting for transformation groups including the stationary velocity fields parametrisation of diffeomorphisms and its use in medical image registration for longitudinal modeling of Alzheimer's disease [54] (with M. Lorenzi) and a chapter on the statistical bias on the estimation in quotient space [52] (with N. Miolane and L Devillier).

6.3.2. Effect of curvature on the Empirical Fréchet mean estimation in manifolds
Participant: Xavier Pennec [Correspondant].

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

Geometric statistics, empirical Fréchet mean

Statistical inference in manifolds most often rely on the Fréchet mean in the Riemannian case, or on exponential barycenters in affine connection spaces. The uncertainty of the empirical mean estimation with a fixed number of samples is a key question. In sufficient concentration conditions, a central limit theorem was established in Riemannian manifolds by Bhattacharya and Patrangenaru in 2005. We propose in [62] an asymptotic development valid in Riemannian and affine cases which better explain the role of the curvature in the modulation of the speed of convergence of the empirical mean. We also establish a non-asymptotic development in high concentration which shows a statistical bias on the empirical mean in the direction of the average gradient of the curvature. These curvature effects become important with large curvature and can drastically modify the estimation of the mean. They could partly explain the phenomenon of sticky means recently put into evidence in stratified spaces, notably in the case of negative curvature.

6.3.3. *Shape Analysis with diffeomorphisms*

Participants: Nicolas Guigui [Correspondant], Shuman Jia, Maxime Sermesant, Xavier Pennec.

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

Shape Analysis, parallel transport, LDDMM, symmetry

The statistical analysis of temporal deformations and inter-subject variability relies on shape registration and parallel transport of deformations (Figure 10). However, the numerical integration and optimization required lead to important numerical errors. This work aims at improving the numerical consistency and reproducibility of the Pole Ladder scheme to perform parallel transport. We propose a modification of this scheme using registration errors [39] and define different types of errors to evaluate the accuracy: the involutivity and transvectivity. We test our method on 138 cardiac shapes and demonstrate improved numerical consistency for both types of errors.
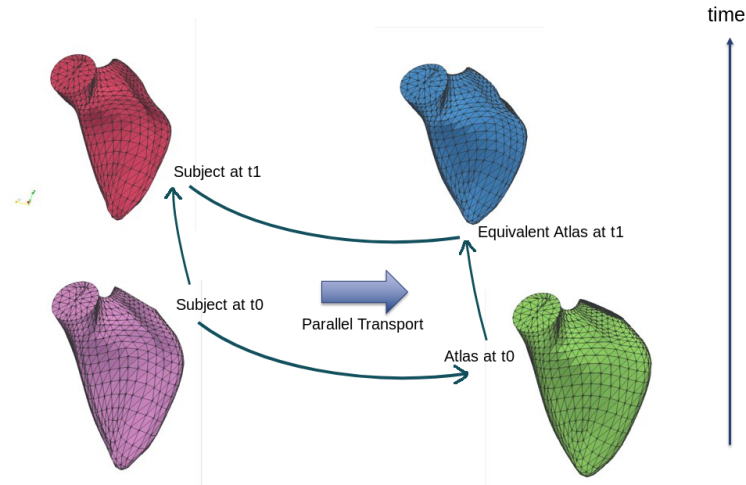

Figure 10. Illustration of our framework using parallel transport to normalize individual temporal deformations to an atlas.

6.3.4. *Classification of Riemannian metrics on the manifold of symmetric positive definite matrices*

Participants: Yann Thanwerdas [Correspondant], Xavier Pennec.

Symmetric Positive Definite matrices, Riemannian metrics, dually flat manifolds

Symmetric Positive Definite matrices have been used in many fields of medical data analysis. Many Riemannian metrics have been defined on this manifold but the choice of the Riemannian structure lacks a set of principles that could lead one to choose properly the metric. We introduced several families of Riemannian metrics supported by a deformation principle and a principle of balanced metrics:

1. Power-Affine and Deformed-Affine metrics [43], that highlight relations between the affine-invariant, the polar-affine and the log-Euclidean metrics ;

2. Mixed-Power-Euclidean and Mixed-Power-Affine metrics [42], that highlight relations between many Riemannian metrics, as shown on Figure 11.
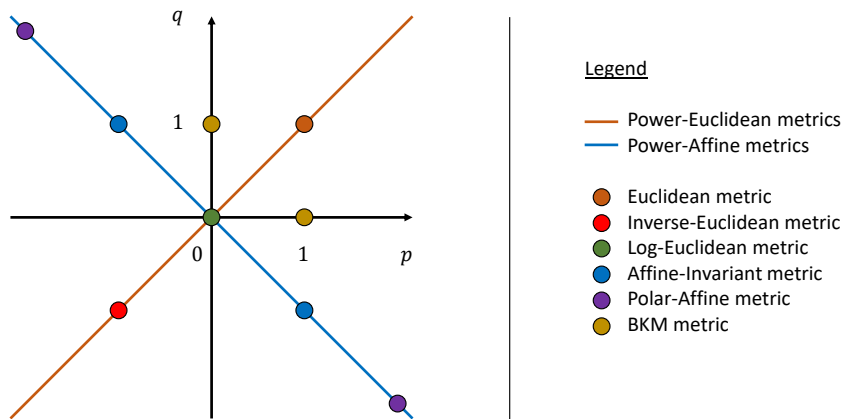
Figure 11. The family of Mixed-Power-Euclidean metrics

6.3.5. *Statistical shape analysis of faces for computer aided dermatology and plastic surgery*

Participants: Florent Jousse [Correspondant], Xavier Pennec, Hervé Delingette, Matilde Gonzalez.

Gaussian Processes, non rigid registration

The objective of this work is to model complex face deformations related to natural aging, facial expressions, surgical interventions or posture motions to improve the 3D reconstruction of faces and to normalize their analysis. It includes the development of non-rigid registration methods of textured meshes and their statistical modeling through Gaussian processes.

6.3.6. *Brain Morphometry in the MAPT clinical trial*

Participants: Raphaël Sivera [Correspondant], Hervé Delingette, Marco Lorenzi, Xavier Pennec, Nicholas Ayache.
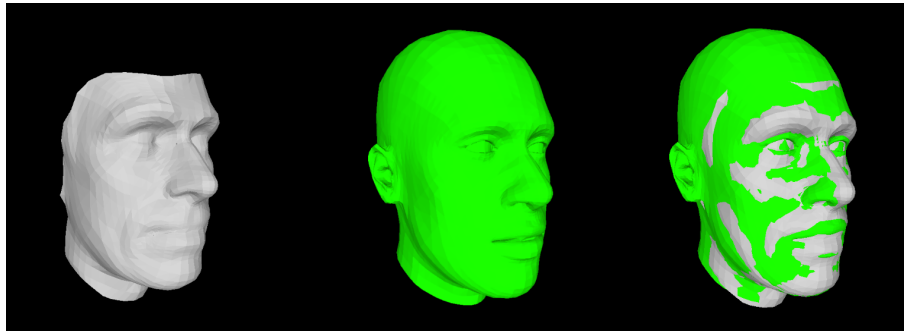
Figure 12. Example of facial template fitting. The white mesh (target) has been acquired by stereoscopy while the green one is a template mesh that has been deformed to fit the target.

Longitudinal deformation modeling, multivariate statistics, brain morphology, Alzheimer's disease, clinical trial.

- We proposed a complete framework for statistical hypothesis testing on mass-multivariate data. This framework builds on the recent works on multivariate statistics in neuroimaging to propose a generic approach adapted to the study of longitudinal deformations [3].
- This framework is used in the context of the MAPT study to highlight a significant effect of the multidomain intervention on the brain morphological changes (see Figure 13) [22].

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

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

Gaussian Process, Alzheimer's Disease, Disease Progression Modelling

The aim of this thesis is to develop a spatio-temporal model of Alzheimer's Disease (AD) progession based on multi-modal brain data. 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 Gaussian processes (Figure 14). We also compute an individual time-shift parameter to assess the disease stage of each subject. This work has been accepted for publication in the journal NeuroImage [5]

6.4. Computational Physiology

6.4.1. *Deep Learning based Metal Artifacts Reduction in post-operative Cochlear Implant CT Imaging*

Participants: Zihao Wang [Correspondant], Clair Vandersteen, Thomas Demarcy, Dan Gnansia, Charles Raffaelli, Nicolas Guevara, Hervé Delingette.

Generative Adversarial Network, Metal Artifacts Reduction, Cochlea Implantation
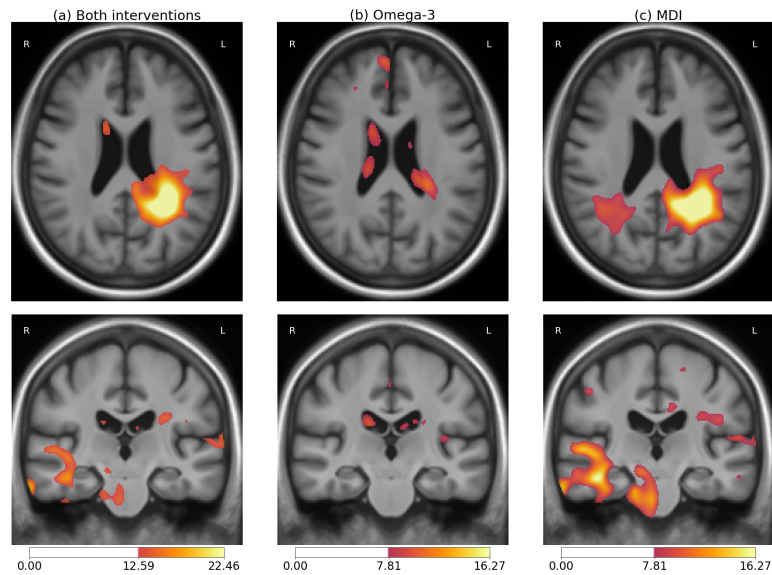
Figure 13. Localization of the MAPT treatments effect on the longitudinal morphological changes for: (a) both categorical variables associated with the omega-3 supplementation and the multidomain intervention, (b) omega-3 only, (c) multidomain intervention only. Color bars indicate the magnitude of the z-values for the likelihood-ratio test. High values indicate a difference in the morphological changes that is associated with the treatment status.

We propose a 3D metal artifact reduction method using convolutional neural networks for post-operative cochlear implant imaging.[44]

- Learn metal artifacts reduction by using pre-operative images and metal artifacts simulation to create image pairs for training GANs.
- Metal artifacts simulation starts from a cochlea implantation fusion image and ends with the simulated post-operative image.(Fig. 15)
- A 3D generative adversarial network (MARGANs) to create an image with a reduction of metal artifacts.
- Evaluations on ten patients show the effectiveness of artefact reduction compared to two classical methods.

6.4.2. Kinematic Spiral Shape Recognition in the Human Cochlea

Participants: Wilhelm Wimmer [Correspondant], Clair Vandersteen, Nicolas Guevara, Marco Caversaccio, Hervé Delingette.

Approximate maximum likelihood, kinematic surface recognition, natural growth

To improve therapies for hearing loss and deafness, e.g., with auditory neuroprostheses, we developed a reliable detection algorithm for the cochlear modiolar axis in CT images (Fig. 16). The algorithm was tested in an experimental study with 4 experts in 23 human cochlea CT data sets [45] [27]. Our experiments showed that the algorithm reduces the alignment error providing more reliable modiolar axis detection for clinical and research applications.
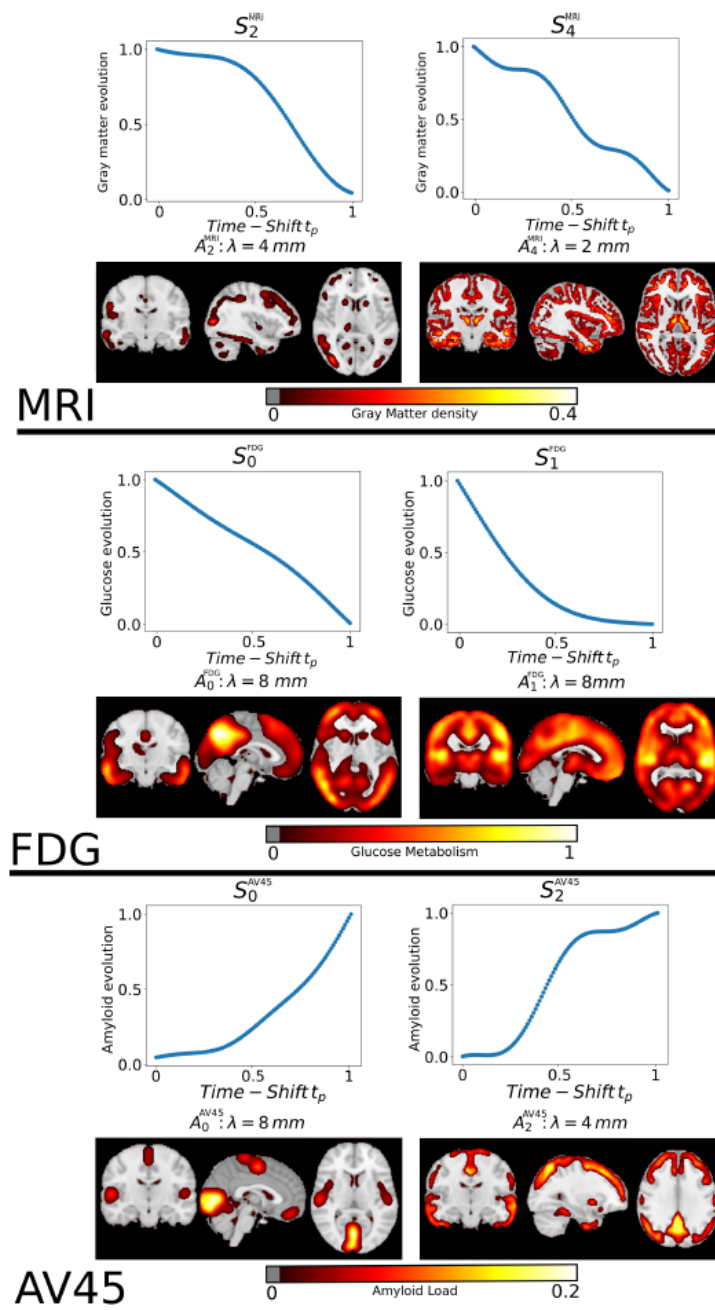
Figure 14. Estimated spatio-temporal processes affecting the brain during Alzheimer's Disease for three different imaging markers.
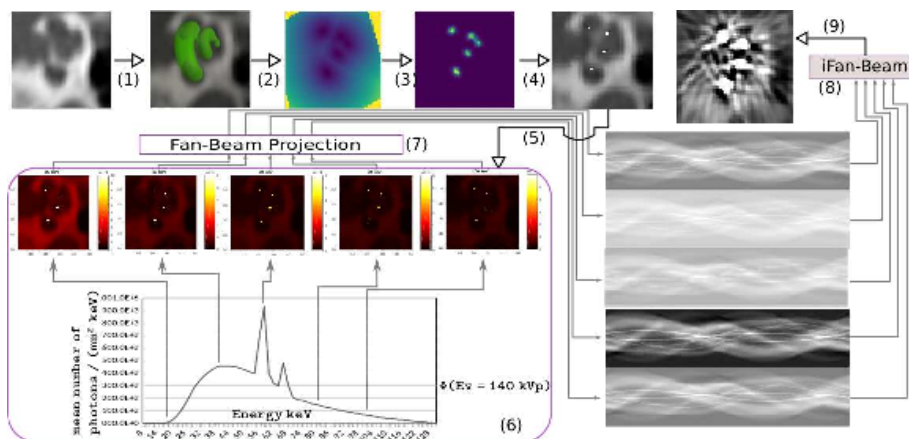
Figure 15. CI metal artifacts simulation workflow starting from a pre-operative image and ending with the simulated post-operative image after 9 processing steps.
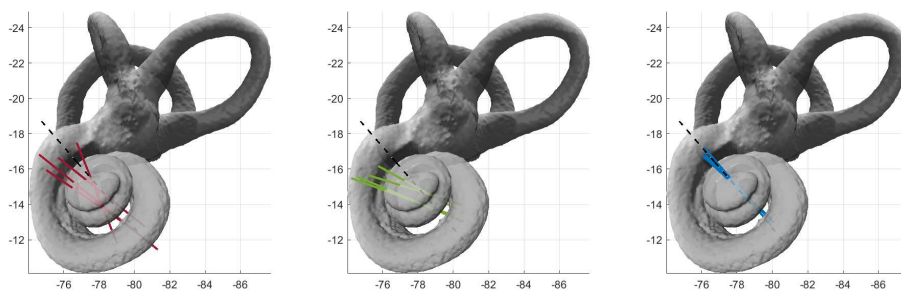
Figure 16. Visualization of the bony labyrinth with reference modiolar axis (dashed line). Modiolar axes after manual landmark-based (left), PCA-based (middle), and robust kinematic detection (right) in CT data are shown for comparison.

6.5. Computational Cardiology & Image-Based Cardiac Interventions

6.5.1. *Cardial Electrophysiological Model Learning and Personalisation*

Participants: Nicolas Cedilnik [Correspondant], Ibrahim Ayed [Sorbonne, LIP6, Paris], Hubert Cochet [IHU Liryc, Bordeaux], Patrick Gallinari [Sorbonne, LIP6, Paris], Maxime Sermesant.

This work is funded by the IHU Liryc, Bordeaux.

modelling, electrophysiology, ventricular tachycardia, ischemic cardiomyopathy

This project aims at making electrophysiological model personalisation enter clinical practice in interventional cardiology. During this year:

- we evaluated a fully automated computed tomography-based model personalisation framework in the context of post-ischemic ventricular tachycardia [35],

- we developped a model personalisation methodology based on invasive data in our participation in the STACOM2019 modelling challenge [37],

- we proposed a deep learning based approach to replace numerical integration of partial differential equations used in cardiac modelling [32], see Figure 17.
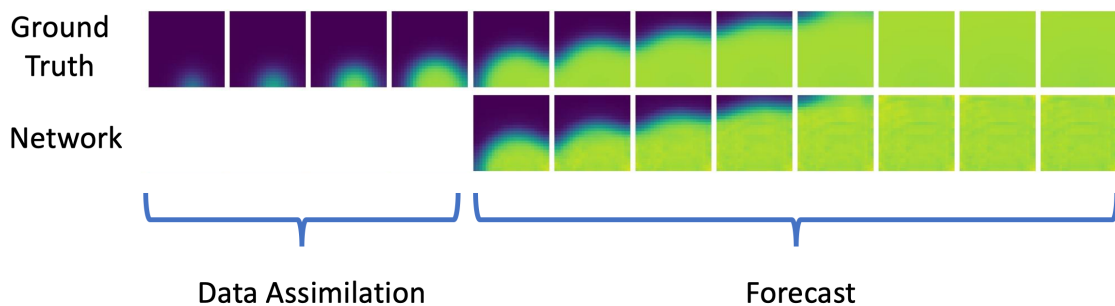
Figure 17. Transmembrane potential obtained with a reaction diffusion model (top) and forecasted by EP-Net (bottom) for one slice of a tissue slab

6.5.2. *Deep Learning Formulation of ECGI for Data-driven Integration of Spatiotemporal Correlations and Imaging Information*

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.

Deep Learning, Electrocardiographic Imaging, Inverse problem of ECG, Electrical simulation, Generative Model.

Electrocardiographic imaging (ECGI) aims at reconstructing the electrical activity of the heart using body surface potentials.To achieve this one has to solve the ill-posed inverse problem of the torso propagation. We propose in [33] a novel Deep Learning method based on Conditional Variational Autoencoder able to solve ECGI inverse problem in 2D. This generative probabilistic model learns geometrical and spatio-temporal information and enables to generate the corresponding activation map of the specific heart.

120 activation maps and the corresponding Body Surface Potentials (BSP) were generated using the dipole formulation. 80% of the simulated data was used for training and 20% for testing.We generate 10 propbable solutions for each given input using our model. The Mean Squarre Error (MSE) metric over all the tests was 0.095. As results we were able to observe that the reconstruction performs well. Next, we will extend the model in 3D and test it on real data provided by the IHU Liryc.
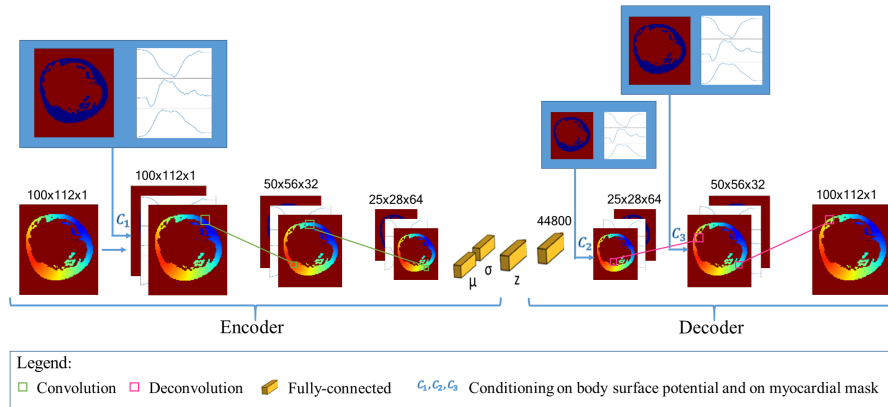
Figure 18. Architecture of our conditioned generative model (encoder) and our conditioned variational approximation (decoder)
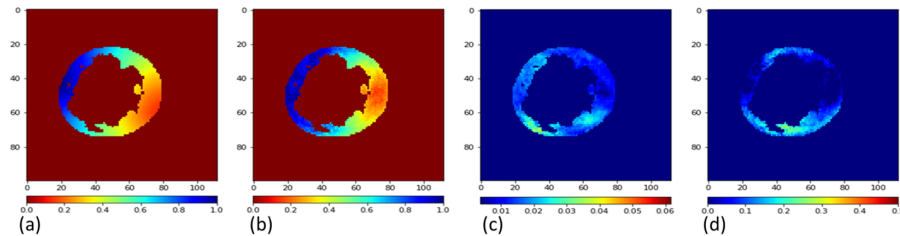
Figure 19. (a) Simulated and (b) predicted mean activation maps for proposed deep learning based ECGI, (c) Standard deviation map calculated over 10 predictions, (d) error map, difference between predicted and simulated activation maps.

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

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

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. [34]
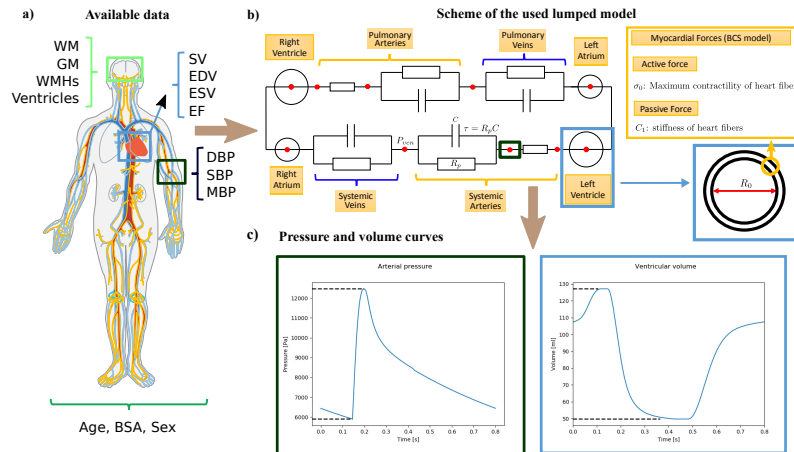
Figure 20. a) Summary of the available data for each subject, including cardiac data, socio-demographic information, blood pressure measurements and brain volumetric indicators. b) Simplified representation of the lumped model showing the parameters used in the personalisation. τ characterizes the contractility of the main systemic arteries, R_p the peripheral resistance, P_{ven} the venous pressure right after the capillaries, R_0 the radius of the left ventricle, σ_0 the contractility of the cardiac fibers and C_1 their stiffness. A more detailed representation of the myocardial forces is omitted for the sake of clarification. c) Example of the pressure and volume curves that can be obtained from the model, from these curves we extract scalar indicators to match the available clinical data.

6.5.4. *Parallel transport of surface deformations from pole ladder to symmetrical extension*

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

We proposed a general scheme to perform statistical modeling of the temporal deformation of the heart, directly based on meshes. We encoded the motion and the intersubject shape variations, with diffeomorphisms parameterized either by stationary SVFs or by time-varying velocity fields in the LDDMM framework.

Experiments on a 4D right-ventricular endocardial meshes database demonstrated the stability of our transport algorithm, of importance for the assessment of pathological changes. The method is adaptable to other anatomies with temporal or longitudinal data.

6.5.5. *Machine Learning and Pulmonary hypertension*

Participants: Yingyu Yang [Correspondant], Stephane Gillon, Jaume Banus Cobo, Pamela Moceri, Maxime Sermesant.

cardiac modelling, machine learning
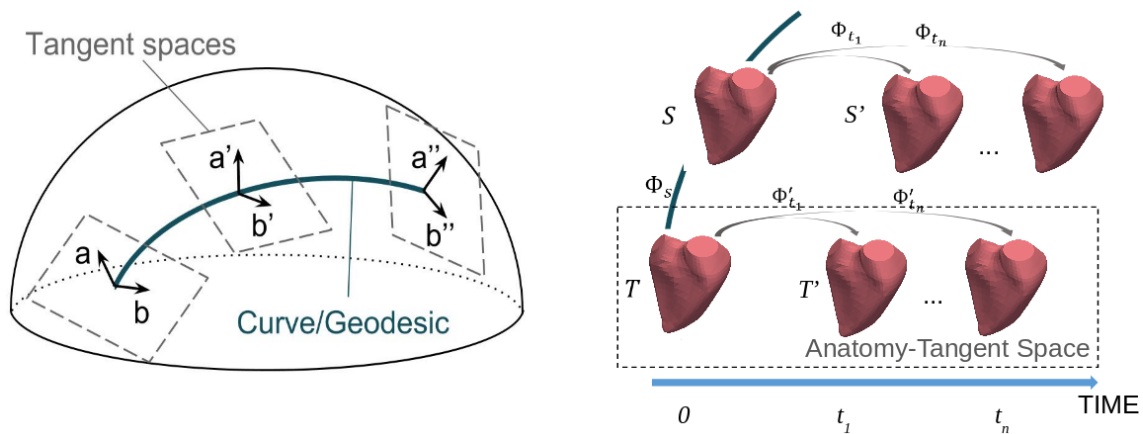
Figure 21. Illustration of parallel transport of vectors a and b along a curve (left) and its application to cardiac imaging (right) with a focus on surfaces.

Right heart catheterisation is considered as the gold standard for the assessment of patients with suspected pulmonary hyper-tension. It provides clinicians with meaningful data, such as pulmonary capillary wedge pressure and pulmonary vascular resistance, however its usage is limited due to its invasive nature. Non-invasive alternatives, like Doppler echocardiography could present insightful measurements of right heart but lack detailed information related to pulmonary vasculature. In order to explore non-invasive means, we studied a dataset of 95 pulmonary hypertension patients, which includes measurements from echocardiography and from right-heart catheterisation. We used data extracted from echocardiography to conduct cardiac circulation model personalisation and tested its prediction power of catheter data. Standard machine learning methods were also investigated for pulmonary artery pressure prediction. Our preliminary results demonstrated the potential prediction power of both data-driven and model-based approaches. It was published as "Non-Invasive Pressure Estimation in Patients with Pulmonary Arterial Hypertension: Data-driven or Model-based?" accepted at 10th Workshop on Statistical Atlases and Computational Modelling of the Heart, Oct 2019, Shenzhen, China [46]

6.5.6. *Style Data Augmentation for Robust Segmentation of Multi-Modality Cardiac MRI*

Participants: Buntheng Ly [Correspondent], Hubert Cochet [IHU Liryc, Bordeaux], Maxime Sermesant.

Image Segmentation. Multi-modality, Cardiac Magnetic Resonance Imaging, Late Gadolinium Enhanced, Deep Learning

We propose a data augmentation method to improve the segmentation accuracy of the convolutional neural network on multi-modality cardiac magnetic resonance dataset [41].

The strategy aims to reduce over-fitting of the network toward any specific intensity or contrast of the training images by introducing diversity in these two aspects, as shown in figure 23.

6.5.7. *Towards Hyper-Reduction of Cardiac Models using Poly-Affine Deformation*

Participants: Gaëtan Desrues [Correspondant], Hervé Delingette, Maxime Sermesant.

Model Order Reduction, Finite Elements Method, Affine Transformation, Meshless
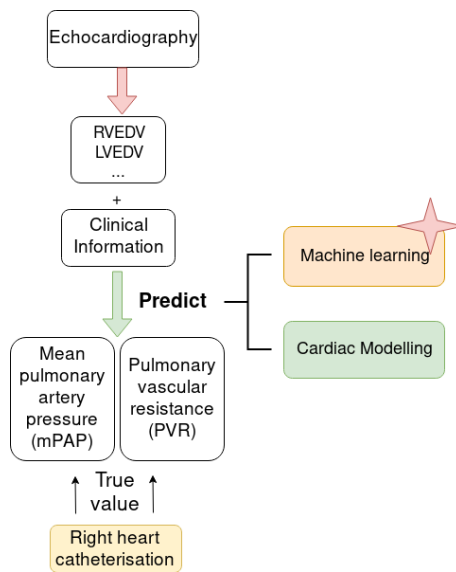
Figure 22. The main idea and logic of this work
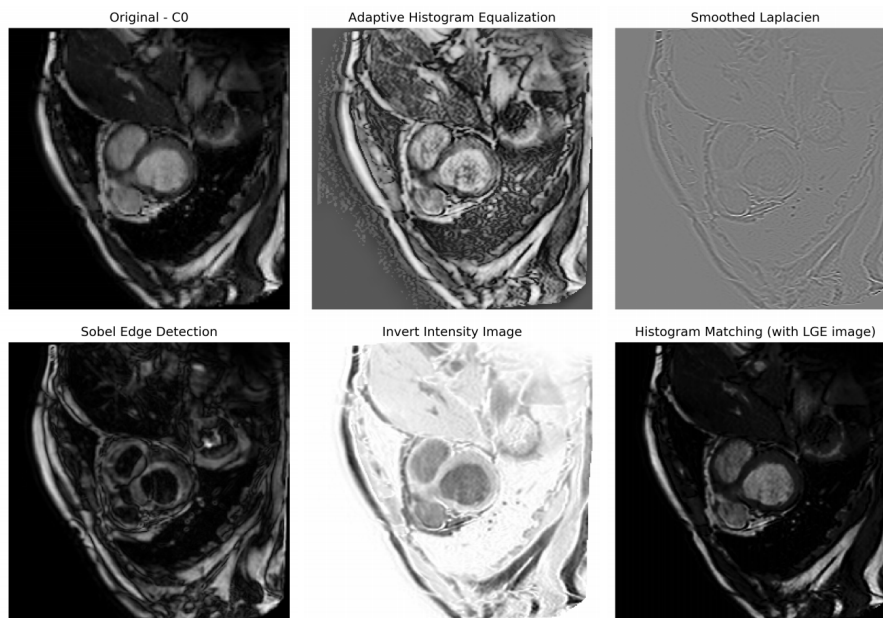
Figure 23. Different variation of input images and the image processing methods used. C0 denotes the steady-state free precessing CMR modality image.

Patient-specific 3D models can help in improving therapy selection, treatment optimization and interventional training. However, these simulations generally have an important computational cost. The aim of this project is to optimize a 3D electromechanical model of the heart for faster simulations [38]. The cardiac deformation is approached by a reduced number of degrees of freedom represented by affine transformations (frames in Figure 24b) located at the center of the AHA regions (Figure 24a). The displacement of the material points are computed using region-based shape functions (Figure 24c).

(a)   (b)   (c)
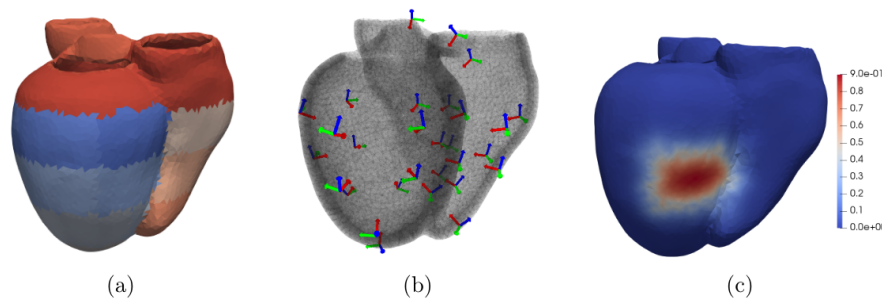
Figure 24. Framework on a cardiac topology. AHA regions (a). Affine degrees of freedom (b). Shape function in one region (c).

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

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 inHEART*

inHEART[7] is a spin-off of the Epione 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. It currently employs 10 people.

7.1.3. *Live Anatomy*

A 3 month InriaTech contract was performed with the Live Anatomy start-up between January and March 2019 in order to develop a remote viewer and to optimise image segmentation.

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

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[5] http://www.msr-inria.fr/projects/4d-cardiac-mr-images
[6] http://www.msr-inria.fr/projects/medilearn
[7] https://www.inheart.fr/

7.1.5. *Quantificare*

The company Quantificare is funding the PhD of Florent Jousse through a CIFRE grant, on the statistical analysis of shapes, deformations and appearance of anatomical surfaces for computer-aided dermatology and plastic surgery. The primary purpose is to model complex face deformations such as natural aging, facial expressions, surgical interventions and posture motions.

7.1.6. *Oticon Medical*

Oticon Medical, Vallauris, France, is co-funding the PhD work of Zihao Wang which aims at developing robust medical image algorithms for cochlea image segmentation.

8. Partnerships and Cooperations

8.1. Regional Initiatives

- Marco Lorenzi is principal investigator of the project Big Data for Brain Research, funded during 2017-20 by the Départment 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.
- 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.
- 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).

8.2. National Initiatives

8.2.1. *Consulting for Industry*

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

8.2.2. *Institute 3IA Côte d'Azur*

The 3IA Côte d'Azur http://univ-cotedazur.fr/institutes/3IA/home is one of the four "Interdisciplinary Institutes of Artificial Intelligence" that were created in France in 2019. Its ambition is to create an innovative ecosystem that is influential at the local, national and international levels, and a focal point of excellence for research, education and the world of AI.

Epione is heavily involved in this institute since its 5 permanents researchers (N. Ayache, H. Delingette, M. Lorenzi, M. Sermesant and X.Pennec) are chair holders in this institute, and N. Ayache is its scientific director.

8.2.3. 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

PI: 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 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. 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.

8.4.3.1.2. 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.

8.4.3.1.3. 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.

8.4.3.1.4. Other International Hospitals

Collaborations with several other European hospitals have been established through the European projects VP2HF, MD PAEDIGREE, SysAFib and with BarcelonaBeta research centre for Alzheimer.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

- Dr. Gabriel Ziegler (German Center for Neurodegenerative Disorder, DE) visited the group from Oct 14th to Oct 18t.
- Guillaume Lajoinie (Physics of Fluid laboratory, University of Twente, NL) visited the team from April until October 2019.
- Wilhelm Wimmer (Center ARTORG, University of Bern, CH) visited the team from Nov. 2018 until Oct. 2019.
- Pr. Dmitri Alekseevky (The Institute for Information Transmission Problems, Moscow) visited the Geometric Statistics group from february 6 to 13 2019.

8.5.1.1. Internships

- Buntheng LY, Master student at the University Claude Bernard Lyon 1, visited the Epione team from March to September 2019 to work with Maxime Sermesant on Machine Learning methods for the prediction of Sudden Cardiac Death.
- YingYu Yang, Master student at Ecole Polytechnique, visited the Epione team from April to September 2019 to work with Maxime Sermesant on Machine Learning and Pulmonary hypertension.
- Gaetan Desrues, Master student at University of Bordeaux, visited the Epione team from March to September 2019 to work with Maxime Sermesant on hyper-reduction of cardiac models using poly-affine deformation.
- Paul Blanc Durand, Master student at University Paris-Est Créteuil, visited the Epione team from April to October 2019 to work with Hervé Delingette on Mesh-based Registration of lung CT scans between inhale and exhale phases.

- Bastien Manach-Perennou, Master student at Ecole Central Supélec, visited the Epione team from September to January 2019 to work with Xavier Pennec on Registration synchronisation.

- Julien Moreira, Master student from University Côte d'Azur, visited the Epione team from April to June 2019 to work with Marco Lorenzi on the analysis of apathy and depression in the UK Biobank. The internship is within a collaboration with Centre de la Memoire de Nice.

- Yann Fraboni visited the Epione team from December 2019 to work with Marco Lorenzi on the analysis of bias of federated learning methods in distributed application. The internship is within a collaboration with Accenture Labs of Sophia Antipolis.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. General Chair, Scientific Chair

- X. Pennec organized the Geometric Statistics workshop in Toulouse from August 30 to September 5 2019, in the framwork of the Associated team GeomStats with Stanford, the ERC G-Statistics and the thematic semester "Statistics with Geometry and Topology" of the CIMI Labex of Toulouse. The workshop featured 6 hours courses by Susan Holmes and Xavier Pennec and talks by Nina Miolane and Yann Thanwerdas.

- N. Ayache organized the scientific program of the conference "The Académie des Sciences in Nice and Sophia Antipolis" in June 20-21 2019.

9.1.2. Member of the Organizing Committees

- X. Pennec was a co-chair of the MICCAI 2019 Workshop on Mathematical Foundations of Computational Anatomy (MFCA 2019), which was held in Shenzen in October 2019 [57].

- M. Sermesant was a co-chair of the MICCAI 2019 Workshop Statistical Atlases and Computational Models of the Heart (STACOM 2019), which was held in Shenzhen, October 2019.

- H. Delingette co-organized the meeting on "Digital Sciences & Technologies" on April 3rd as well as the meeting on "Digital Sobriety" on Dec. 2nd as part of the scientific animation of the UCA Academy of Excellence on Digital Sciences. He was also member of the organizing committee of the 2019 SophIA summit in Sophia Antipolis that was held in Sophia Antipolis from Nov. 20-22nd.

9.1.3. Scientific Events Selection

9.1.3.1. Member of the Conference Program Committees

- X. Pennec was a program committee member and session chair of the Geometric Sciences of Information conference GSI' 2019 at ENAC in Toulouse.

9.1.3.2. Reviewer

- M. Lorenzi was a reviewer for the conferences Neural Information Processing Systems (NeurIPS 2019), International Conference on Machine Learning (ICML 2019), Medical Image Computing and Computer Aided Intervention (MICCAI 2019), International Conference on Learning Representations (ICLR 2020), Information Processing in Medical Imaging (IPMI 2019).

- M. Sermesant was a reviewer for Medical Image Computing and Computer Aided Intervention (MICCAI 2019), the MICCAI workshop STACOM and the Computing in Cardiology conference.

- X. Pennec was a reviewer for Medical Image Computing and Computer Aided Intervention (MICCAI 2019) and for Information Processing in Medical Images (IPMI 2019), the 35th Annual Symposium on Computational Geometry (CG Week 2019).

- H. Delingette was a reviewer for the International Symposium on Biomedical Imaging (ISBI'19), the international conference on computer-aided interventions (IPCAI'19), the International Conference on Computer Vision and Pattern Recognition (CVPR 2019).

9.1.4. Journal

9.1.4.1. Member of the Editorial Boards

- H. Delingette is a member of the editorial board of the journal Medical Image Analysis (Elsevier).
- 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).
- X. Pennec is a member of the editorial board of the journal Medical Image Analysis (MedIA, Elsevier), of the International Journal of Computer Vision (IJCV, Springer), and of the Journal of Mathematical Imaging and Vision (JMIV, Springer).
- 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).
- I. Strobant is editorial coordinator for Medical Image Analysis, Elsevier (since october 2001).

9.1.4.2. 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.
- X. Pennec was a reviewer for the Journal of Computational Dynamics, Annals of Statistics, Communications in Statistics - Simulation and Computation, Linear Algebra and its Applications, Information geometry, Medical Image Analysis, IEEE Transactions on Medical Imaging.
- M. Sermesant was a reviewer for the following journals: Journal of Machine Learning Research, 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, Pattern Recognition, and Computer Vision and Image Understanding.

9.1.5. Invited Talks

- **M. Lorenzi** was invited to give a lecture to: Nice Genomic Winter School, Dec 18th; Imaging-Genetics Winter School, University of Verona, Nov 25th-29th; SophIA Summit of Sophia Antipolis, Nov 19th; International Tau Workshop, Geneva University Hospital, Nov 11th; International Meeting "The future of Medicine Starts Now", Menarini Foundation, Genoa, Italy, Sep 27th; European Glaucoma Society Meeting, Bordeaux, Aug 30th; Big@UCA Summer School, Nice, Jun 26th; Lacassagne Hospital, Jun 20th; VUmc Hospital, Amsterdam, May 23rd; Collége de France, Paris, Apr 23rd; UCA Maison de la Simulation, Apr 18th; International Conference ISBI 2019, Venice, Apr 9th; UPF University, Barcelona, Feb 7th;
- **H. Delingette** was a keynote speaker at the University of Twente (NL) seminar on Nov 6th, at the regional Otology meeting "ORL PACA" on June 15th 2019, and at the Machine Learning Meets Medical Imaging workshop in Shenzhen, China, on Oct 13th.
- **X. Pennec** gave the following plenary invited talks:
  - IPAM program on Geometry and Learning from Data in 3D and Beyond (Los Angeles, USA, 02/04).

- CARS 2019 conference in Rennes (19/06).
- the Academie des Sciences en région in Nice and Sophia Antipolis (21/06).

He also gave invited lectures and seminars at: Copenhagen University (DK 18/03); the Institut Mathematique de Toulouse (27/05); the ENUMATH 2019 conference held in Egmond aan Zee (NL, 04/10); LJK-Deterministic Models and Algorithms: EDP-AIRSEA-CVGI Seminar, Univ Grenoble (16/12).

- **M. Sermesant** was an invited speaker at the European Heart Rhythm Association conference (18/03), eHealth Monaco (27/03), Cardiac Electromechanics workshop (15/04), EuroCMR (03/05), CVPR Medical Imaging workshop (16/05), Innovation Alzheimer summer school (26/06), Académie de Médecine working group on AI & Healthcare (10/09), Inria/SIMULA workshop (26/09), SOPH.I.A Summit (20/11) and TRM Forum (10/12).

- **N. Ayache** gave the following plenary invited talks:
  - AI for Healthcare: Hope & Challenges. Global Forum on AI for Humanity, Paris, 2019.
  - AI for Medical Imaging & Digital Twins, Keynote Lecture, Shezhen University, China 2019.
  - AI for e-medecine, 5th International Symposium on Multi-disciplinary Computational Anatomy, Fukuoka, Japan 2019.
  - Le jumeau numérique: images, modèles et IA. Académie nationale de médecine, Paris, 2019.
  - Intelligence Artificielle et médecine. Académie des Sciences, Nice, 2019.
  - La Santé à l'ère numérique, Institut de l'ENS, 2019.
  - Imaging in Cancer - Multimodal Analysis, iBV, Nice, 2019

9.1.6. Leadership within the Scientific Community

- **H. Delingette** is a member of the MICCAI Society Board of Directors.
- **H. Delingette** is elected as MICCAI Society's Fellows.

9.1.7. Scientific Expertise

- **M. Lorenzi** was reviewer of the funding agency ANR (Agence Nationale de la Recherche, France). He is providing scientific consulting for the company MyDataModels and Flexper through an Inria Tech research contract.

- **X. Pennec** was a reviewer for the funding agency Israel Science Foundation (ISF).

- **M. Sermesant** was an evaluator for the Wellcome Trust (UK), the NSF (USA) and the Netherlands research council.

- **H. Delingette** is a member of the scientific committee of the institute 3IA Côte d'Azur and was reviewer of the funding agency ANR (Agence Nationale de la Recherche, France).

- **N. Ayache** is a member of the following scientific committes:
  - 2016 -: Scientific advisory committee for Région Ile de France (20 members),
  - 2015 - 2019: 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.

9.1.8. Research Administration

- **N. Ayache** is the scientific director of the 3IA Côte d'Azur since its creation in April 2019.

- **Marco Lorenzi** 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.

- **Xavier Pennec** is co-director of the Ecole doctorale STIC of Université Côte d'Azur. He is a member of the committee of EDSTIC, of the Doctoral follow-up Committee (CSD) at Inria Sophia Antipolis, and participated to the PhD fellowship granting committees of EDSTIC, Cofund at UCA, CORDI at Inria. He is a member of the "Comité de la Recherche Biomédicale en Santé Publique (CRBSP)" of the Nice University Hospital (CHU). At University Côte d'Azur / IDEX-JEDI, 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. He was elected member of the Evaluation Committee of Inria (Sep. 2019 to Aug. 2023) and participated to the promotion commission for CRCN, DR1, DR0.
- **M. Sermesant** is an elected member of the Inria Sophia Antipolis research centre committee.
- **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 director of the Academy of excellence on "Networks, Information and Digital Society" at the Université Côte d'Azur. He is the deputy director of the "Ecole Universitaire de recherche" entitled *Digital Systems for Humans* at Université Côte d'Azur. He is a representative 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 Saclay, France.

Master: H. Delingette and X. Pennec, Medical Image Processing, 30h course, M2 Data Science & AI, Univ. Côte d'Azur, France.

Master: H. Delingette, Data Visualization, 6h course, M1 Data Science & AI, Univ. Côte d'Azur, France.

Master: M. Lorenzi, Bayesian Learning, 30h course, Master Data Science, Univ. Côte d'Azur, France.

Master: M. Lorenzi, Model Selection and Resampling Methods, 30h course, Master Data Science, Univ. Côte d'Azur, France.

X. Pennec is a member of the pedagogical council of the Computational biology master QCSBD, Univ. Côte d'Azur, France.

9.2.2. Theses Defended

- Qiao Zheng, Deep learning for cardiac image analysis, Université Côte d'Azur. Started in January 2016. Co-directed by N. Ayache and H. Delingette. Defended on March the 27th, 2019.
- Pawel Mlynarski, Tumor segmentation based on Random Forests and Convolutional Neural Networks trained on partially annotated data, Université Côte d'Azur. Started in December 2015. Co-directed by N. Ayache and H. Delingette. Defended on November the 15th, 2019.
- 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. Defended on November the 29th, 2019.
- 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. Defended on December the 18th 2019.

9.2.3. PhD in progress

- 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.

- 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.

- 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.

- 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.

- 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.

- Nicolas Cedilnik, Personalised Modeling for Ventricular Tachycardia Ablation Planning, Université Côte d'Azur. Started in 2017. Co-directed by M. Sermesant and H Cochet.

- Florent Jousse, Analyse statistique de forme, de déformations et d'apparences de surfaces anatomiques pour l'aide à la dermatologie et à la chirurgie plastique. Started in 2019. Cifre fellowship with Quantificare. Co-directed by X. Pennec and H. Delingette.

- Buntheng Ly, Cardiac Image Analysis for Sudden Cardiac Death Prediction, Université Côte d'Azur. Started in 2019. 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.

- Yann Thanwerdas, Statistical Dimension Reduction in Non-Linear Manifolds for Brain Shape Analysis, Connectomics & Brain-Computer Interfaces, Université Côte d'Azur. Started in 2019. Directed by 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.

- Zihao WANG, Cochlear Implantation Modeling, Planning & Evaluation. Started in 2018. Directed by H. Delingette.

- Hind Dadoun, AI-Based Real Time Diagnosis of Abdominal Ultrasound, Université Côte d'Azur. Started in December 2019. Co-directed by N.Ayache and H.Delingette.

- Paul Tourniaire, AI-based selection of imaging and biological markers predictive of therapy response in lung cancer, Université Côte d'Azur. Started in 2019. Co-directed by N. Ayache and H. Delingette.

9.2.4. Juries

- Marco Lorenzi was invited jury member for the PhD defense of Remi Domingues (EURECOM, Sophia Antipolis).

- Xavier Pennec was reviewer and member of the jury for the PhDs of: Line Kuhnel, Univ. Copenhagen, DK, feb. 2019; Maxime Louis, UPMC, Sorbonne Universités, Paris, sep. 2019; Emilie Buessler, Univ. Grenoble-Alpes, Dec. 2019. He was President of the PhD jury of Emmanuelle Poulain, Univ Cote d'Azur, Oct. 2019, and President of the HDR jury of Olivier Commowick, Univ. Rennes, Jun. 2019.

- Maxime Sermesant was a reviewer for the PhD of Kenny Rumindo (Lyon).

- Hervé Delingette was a reviewer and member of the jury in the PhD thesis committee of H. Bertrand (ENST), defended on Jan. 8th 2019, of H. Oliveri (ENS LYon) defended on May 28th 2019.

9.3. Popularization

9.3.1. Interventions

- Maxime Sermesant did three 45 minutes interventions on Mathematics and Healthcare at the Jules Ferry High School in Cannes.
- Tania Bacoyannis and Nicolas Cedilnik presented AI for high school teachers and interacted with them on this topic during a day.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] S. JIA. *Population-Based Models of Shape, Structure, and Deformation in Atrial Fibrillation*, Université Côte d'Azur, December 2019, https://hal.inria.fr/tel-02428638

[2] P. MLYNARSKI. *Deep Learning for Segmentation of Brain Tumors and Organs at Risk in Radiotherapy Planning*, Université Côte d'Azur, November 2019, https://hal.inria.fr/tel-02358374

[3] R. SIVERA. *Modeling and measuring the brain morphological evolution using structural MRI in the context of neurodegenerative diseases*, Université Cote d'Azur, November 2019, https://hal.inria.fr/tel-02389924

[4] Q. ZHENG. *Deep Learning for Robust Segmentation and Explainable Analysis of 3D and Dynamic Cardiac Images*, Inria - Sophia Antipolis, March 2019, https://hal.inria.fr/tel-02083415

Articles in International Peer-Reviewed Journals

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[6] L. ANTELMI, N. AYACHE, P. ROBERT, M. LORENZI. *Sparse Multi-Channel Variational Autoencoder for the Joint Analysis of Heterogeneous Data*, in "Proceedings of Machine Learning Research", 2019, n° 97, pp. 302–311, https://hal.inria.fr/hal-02395747

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