

Activity Report 2015

Project-Team ASCLEPIOS

Analysis and Simulation of Biomedical Images

RESEARCH CENTER Sophia Antipolis - Méditerranée

THEME

Computational Neuroscience and Medecine

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Project-Team ASCLEPIOS

Creation of the Project-Team: 2005 November 01

Keywords:

Computer Science and Digital Science:

- 3.3. Data and knowledge analysis
- 3.4. Machine learning and statistics
- 5.2. Data visualization
- 5.3. Image processing and analysis
- 5.4. Computer vision
- 5.6. Virtual reality, augmented reality
- 5.9. Signal processing
- 6.1. Mathematical Modeling
- 6.2. Scientific Computing, Numerical Analysis & Optimization
- 6.3. Computation-data interaction
- 7.5. Geometry
- 8.2. Machine learning
- 8.3. Signal analysis

Other Research Topics and Application Domains:

- 2.2. Physiology and diseases
- 2.4. Therapies
- 2.6. Biological and medical imaging

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2. Overall Objectives

2.1. Overall Objectives

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

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

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

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

3. Research Program

3.1. Introduction

Tremendous progress has been made in the automated analysis of biomedical images during the past two decades [90]. Readers who are neophytes to the field of medical imaging will find an interesting presentation of acquisition techniques of the main medical imaging modalities in [81], [79]. Regarding target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [77], in N. Ayache's article [85] and in recent review articles [86], [90]. The scientific journals *Medical Image Analysis* [72], *Transactions on Medical Imaging* [78], and *Computer Assisted Surgery* [80] are also good reference material. One can have a good vision of the state of the art from the proceedings of the MICCAI'2010 (Medical Image Computing and Computer Assisted Intervention [75], [76]) and ISBI'2010 (Int. Symp. on Biomedical Imaging [74]) conferences.

For instance, for rigid parts of the body like the head, it is now possible to fuse in a completely automated manner images of the same patient taken from different imaging modalities (e.g. anatomical and functional), or to track the evolution of a pathology through the automated registration and comparison of a series of images taken at distant time instants [91], [105]. It is also possible to obtain from a Magnetic Resonance Image (MRI) of the head a reasonable segmentation of skull tissues, white matter, grey matter, and cerebro-spinal fluid [108], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [84], Ultrasound or Nuclear Medicine images [92].

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

3.2. Medical Image Analysis

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

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

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

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

We plan to pursue our efforts on the following problems:

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

3.3. Computational Anatomy

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

Studying the variability of biological shapes is an old problem (cf. the book "On Shape and Growth" by D'Arcy Thompson [107]). Significant efforts have since been made to develop a theory for statistical shape analysis (one can refer to [89] for a good summary, and to the special issue of Neuroimage [106] for recent developments). Despite all these efforts, there are a number of challenging mathematical issues that remain largely unsolved. A particular issue is the computation of statistics on manifolds that can be of infinite dimension (e.g the group of diffeomorphisms).

There is a classical stratification of the problems into the following 3 levels [102]:

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

We plan to focus our efforts on the following problems:

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

3.4. Computational Physiology

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

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

Quite advanced models have already been proposed to study at the molecular, cellular and organ level a number of physiological systems (see for instance [103], [97], [87], [104], [93]). While these models and new ones need to be developed, refined or validated, a grand challenge that we want to address in this project is the automatic adaptation of the model to a given patient by comparing the model with the available biomedical images and signals and possibly also some additional information (e.g. genetic). Building such *patient-specific models* is an ambitious goal, which requires the choice or construction of models with a complexity adapted to the resolution of the accessible measurements and the development of new data assimilation methods coping with massive numbers of measurements and unknowns.

There is a hierarchy of modeling levels for CP models of the human body [88]:

- the first level is mainly geometrical, and addresses the construction of a digital description of the anatomy [82], essentially acquired from medical imagery;
- the second level is physical, involving mainly the biomechanical modeling of various tissues, organs, vessels, muscles and bone structures [95];
- the third level is physiological, involving the modeling of the functions of the major organ systems [96] (e.g. cardiovascular, respiratory, digestive, central or peripheral nervous, muscular, reproductive, hormonal) or some pathological metabolism (e.g. evolution of cancerous or inflammatory lesions, formation of vessel stenoses, etc.); and
- a fourth level is cognitive, modeling the higher functions of the human brain [73].

These different levels of modeling are closely related to each other, and several physiological systems may interact with each other (e.g. the cardiopulmonary interaction [101]). The choice of the resolution at which each level is described is important, and may vary from microscopic to macroscopic, ideally through multiscale descriptions.

Building this complete hierarchy of models is necessary to evolve from a *Visible Human project* (essentially the first level of modeling) to a much more ambitious *Physiological Human project* (see [96], [97]). We will not address all the issues raised by this ambitious project, but instead focus on the topics detailed below. Among them, our objective is to identify some common methods for the resolution of the large inverse problem raised by the coupling of physiological models and medical images for the construction of patient-specific models (e.g. specific variational or sequential methods (EKF), dedicated particle filters). We also plan to develop specific expertise in the extraction of geometrical meshes from medical images for their further use in simulation procedures. Finally, computational models can be used for specific image analysis problems studied in section 3.2 (e.g. segmentation, registration, tracking). Application domains include

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

3.5. Clinical Validation

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

4. Highlights of the Year

4.1. Highlights of the Year

4.1.1. Awards

- Thomas Benseghir received a Best Paper Award at the 2015 IPCAI conference, Barcelona, Spain, for his paper entitled "A tree-topology preserving pairing for 3D/2D registration", co-authored by Grégoire Malandain and Régis Vaillant.
- Matthieu Lê received a Young Scientist Award at the 2015 MICCAI conference, Munich, Germany, for his paper entitled "GPSSI: Gaussian Process for Sampling Segmentations of Images", coauthored by Jan Unkelbach, Nicholas Ayache, and Hervé Delingette.
- Bjorn Menze received the Young Scientist Publication Impact Award at the 2015 MICCAI conference, Munich, Germany, for his article "A generative model for brain tumor segmentation in multimodal images", co-authored by Koen Van Leemput, Danial Lashkari, Marc-André Weber, Nicholas Ayache and Polina Golland presented at MICCAI 2010 in Beijing, China [100].
- Marco Lorenzi received an honorary mention at the 2015 Cor Baayen Award for his PhD prepared
 jointly within the Asclepios project team at Inria Sophia Antipolis and the IRCCS San Giovanni
 di Dio Fatebenefratelli (Italy), and for his post-doctoral research performed at University College
 London (UCL).
- Hervé Delingette is the co-recipient of the Dirk Bartz First Prize for Visual Computing in Medicine awarded during the 2015 Eurographics conference. The prize was given to a group of 7 Inria researchers who pioneered the development of medical simulators based on the SOFA software platform.
- Nicholas Ayache received a research medal from the University Côte d'Azur on December 10th 2015.

BEST PAPERS AWARDS:

[26]

T. BENSEGHIR, G. MALANDAIN, R. VAILLANT. *A tree-topology preserving pairing for 3D/2D registration*, in "International Conference on Information Processing in Computer-Assisted Interventions, IPCAI 2015", Barcelona, Spain, International Journal of Computer Assisted Radiology and Surgery, Springer Berlin Heidelberg, June 2015, vol. 10, n^o 6, pp. 913-923 [*DOI* : 10.1007/s11548-015-1207-0], https://hal.inria.fr/hal-01183573

[38]

M. LÊ, J. UNKELBACH, N. AYACHE, H. DELINGETTE. *GPSSI: Gaussian Process for Sampling Segmentations of Images*, in "MICCAI - Medical Image Computing and Computer Assisted Intervention - 2015", Munich, Germany, A. F. FRANGI, J. HORNEGGER, N. NAVAB, W. M. WELLS (editors), Lecture Notes in Computer Science - LNCS, Springer, October 2015, vol. 9351, pp. 38-46 [*DOI:* 10.1007/978-3-319-24574-4_5], https://hal.archives-ouvertes.fr/hal-01155078

5. New Software and Platforms

5.1. MedInria

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

MedInria is a medical imaging software platform developed by the Asclepios research project in collaboration with the Athena, Parietal and Visages Inria research projects. It aims at providing clinicians with state of the art algorithms dedicated to medical image processing and visualization. Efforts have been made to simplify the user interface, while keeping high-level algorithms.

The core of medInria is Open Source with a BSD license; additional plug-ins can have any license.

The latest release of medInria, 2.2.3, was made in September 2015.

 Participants: Théodore Papadopoulo, Olivier Commowick, René-Paul Debroize, Florian Vichot, Loic Cadour, Michael Buckingham, Maxime Sermesant and Hakim Fadil

• Partners: HARVARD Medical School - IHU - LIRYC - IHU - Strasbourg - NIH

Contact: Olivier CommowickURL: http://med.inria.fr

5.2. MUSIC

KEYWORDS: Health - Cardiac - Computer-Assisted Surgery - Cardiac Electrophysiology - Medical Imaging FUNCTIONAL DESCRIPTION:

MUSIC (Multi-modality Platform for Specific Imaging in Cardiology) is 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.

For more information, see the web page or this video on the MUSIC software application.

- Participants: Loic Cadour, Maxime Sermesant, Hakim Fadil, Florent Collot and Mathilde Merle (Software Engineer at IHU LIRYC)
- Contact: Maxime Sermesant
- URL: https://team.inria.fr/asclepios/software/music/

5.3. SOFA

KEYWORDS: Simulation of the Human Body - Physical Simulation - Health - Biomechanics - GPU - Computer-Assisted Surgery

FUNCTIONAL DESCRIPTION:

SOFA (Simulation Open Framework Architecture) 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 it can also be used as a 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 a 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.

It is developed mainly by the Inria team projects Shacra, Evasion and Asclepios and it is available under the LGPL licence.

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

5.4. **VP2HF**

KEYWORDS: Health - Cardiac - Medical Image Processing - Medical Imaging FUNCTIONAL DESCRIPTION:

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

Participants: Maxime Sermesant, Hakim Fadil and Loic Cadour

Contact: Maxime SermesantURL: http://www.vp2hf.eu

5.5. LSVF

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

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

Sources are available under custom licence.

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

6. New Results

6.1. Medical Image Analysis

6.1.1. Longitudinal Analysis and Modeling of Brain Development

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

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

Processing pipeline - brain development - adolescence - longitudinal analysis - non-rigid registration algorithm - extrapolation

- 1. We proposed and detailed a deformation-based morphometry computational framework, called Longitudinal Log-Demons Framework (LLDF), which estimates the longitudinal brain deformations from image data series, transports them in a common space and performs statistical group-wise analyses (see Fig. 1). This processing pipeline is based on freely available softwares and relies on the LCC log-Demons non-linear diffeomorphic registration algorithm with an additional modulation of the similarity term using a confidence mask to increase robustness with respect to brain boundary intensity artifacts.
- 2. The LLDF framework is applied to the study of longitudinal trajectories during adolescence, for which little is known. The aim of this project is to provide models of brain development during adolescence based on diffeomorphic registration parametrised by SVFs. Our study focused particularly on the link between sexual dimorphism and the longitudinal evolution of the brain. This work was done in collaboration with J.L. Martinot et H. Lemaître (Inserm U1000).

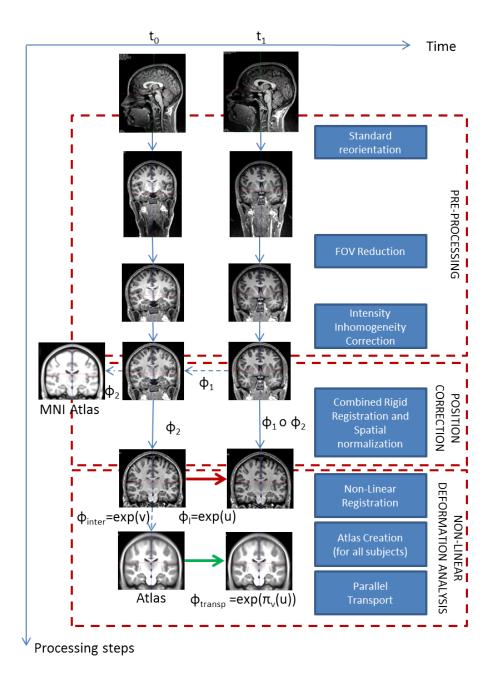


Figure 1. Proposed processing pipeline for longitudinal analysis: the pipeline is composed of three major steps. Starting with raw images, we first pre-process them, then correct the spatial position differences to end up with the longitudinal deformations for each subject in the atlas space.

6.1.2. Inter-Operative Relocalization in Flexible Endoscopy

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

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

Computer Assisted Intervention, Barrett's Esophagus, Biopsy Relocalization, Electromagnetic tracking

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

In an earlier paper, we introduced the first approach to inter-operative relocalization using electromagnetic tracking system. In [21], we propose three incremental experiments to our approach. First, we analyse the error bounds of our system on synthetic data with a realistic noise model. Second, we provide a pseudo ground-truth on *in-vivo* pig data using an optical tracking system. Accuracy results obtained were consistent with the synthetic experiments despite uncertainty introduced due to breathing motion, and remain inside acceptable error margins according to medical experts. Finally, a third experiment was designed using data from pigs to simulate a real task of biopsy site relocalization, and evaluated by ten experts. It clearly demonstrated the benefit of our system towards assisted guidance by improving the biopsy site retrieval rate from 47.5% to 94%.

This inter-operative relocalization framework was then further extended in [53] to provide a constrained image based search as shown in Fig. 2 to obtain the best view point match to the live view. Within this context, we investigate the effect of (a) the choice of feature descriptors and colour-space, (b) filtering of uninformative frames and (c) endoscopic modality, for view point localization. Our experiments indicate an improvement in the best view-point retrieval rate to [92%, 87%] from [73%, 76%] (in our previous approach) for Narrow band imaging and white-light endoscopic image modalities.

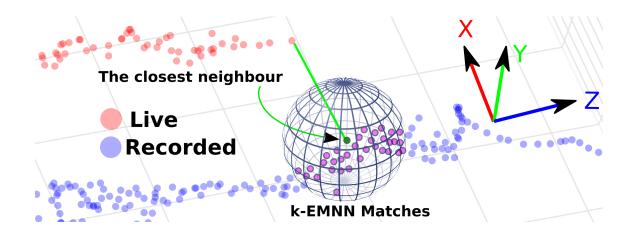


Figure 2. ElectroMagnetic tracker Nearest Neighbour (EMNN) matches. Firstly, the EMNN is obtained using the 3D position match. Then, in a radius r around this match, all the points on the trajectory are considered as the k-EMNN matches. For the images in the k-EMNN matches, scene matching is performed.

6.1.3. Segmentation and anatomic variability of the cochlea and other temporal bone structures from medical images

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

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

image segmentation; surgery planning; shape modelling; anatomic variability; cochlear implant; temporal bone

- We designed a parametric shape model of the intracochlear anatomy with anatomical prior learned from temporal bones high-resolution images, see Fig. 3.
- We evaluated the cochleostomy location regarding two surgical approaches (endaural compared to conventional posterior tympanotomy) [20].

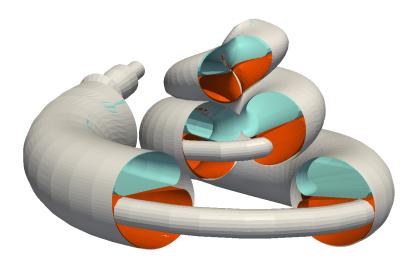


Figure 3. Cochlear implant electrode-array with respect to scala tympani (red) and scala vestibuli (blue).

6.1.4. Structured sparse Bayesian modelling for non-rigid registration and cardiac motion tracking

Participants: Loic Le Folgoc [Correspondent], Hervé Delingette, Antonio Criminisi, Nicholas Ayache.

This work has been partly supported by the Inria – Microsoft Research Joint Center and by the European Research Council through the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Non-rigid Registration - Structured Sparse Bayesian Learning - Automatic Relevance Determination - Reversible-jump Markov Chain Monte Carlo - Cardiac Motion Tracking - Uncertainty Quantification

We developed a generic structured sparse Bayesian model of image registration with three main contributions: an extended image similarity term, the automated tuning of registration parameters and uncertainty quantification. We proposed an approximate inference scheme that is tractable on 4D clinical data. We demonstrated the performance of our approach on cine MR, tagged MR and 3D Ultra Sound cardiac images, and showed state-of-the-art results on benchmark datasets evaluating accuracy of motion and strain.

Moreover, we evaluated the quality of uncertainty estimates returned by the approximate inference scheme. We compare the predictions of the approximate scheme with those of an inference scheme developed on the grounds of reversible jump Markov Chain Monte-Carlo [94](see Fig. 4). We provided more insight into the theoretical properties of the sparse structured Bayesian model and into the empirical behaviour of both inference schemes.

This work is described in the PhD manuscript of Loïc Le Folgoc, defended at Université Nice Sophia Antipolis, 2015 [6].

Probabilistic cardiac registration: three displacement samples

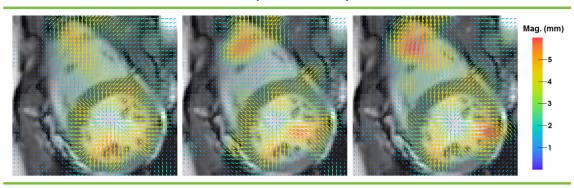


Figure 4. Three displacement fields sampled from the same posterior distribution of coefficients associated with the registration of two cardiac images.

6.1.5. Image Segmentation and Synthesis of brain tumor MR images

Participants: Nicolas Cordier [correspondent], Hervé Delingette, Nicholas Ayache.

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

Brain, MRI, Glioma, Patch-based Segmentation, Image synthesis

The segmentation of glioblastoma, the most severe case of brain tumors, is a crucial step for diagnostic assessment and therapy planning. In order to perform the manual delineation of the tumor compartments, the clinicians have to concurrently screen multi-channel 3D MRI, which makes the process both time-consuming and subject to inter-expert delineation variability.

We have developed 2 contributions for the analysis of MR brain tumor images:

- A patch-based multi-atlas automatic glioma segmentation algorithm[13]. Unlike prior work on patch-based multi-atlas segmentation, our approach does not assume any prior knowledge about the location of pathological structures (no local search window).
- A patch-based image synthesis algorithm (see Fig.5) [4], which generates multi-sequence MR images of the brain with glioma from a single label image. The synthesis of images may be useful to benchmark segmentation algorithms or to increase the size of annotated medical image databases.

6.1.6. Infarct localization from myocardial deformation

Participants: Nicolas Duchateau [Correspondent], Maxime Sermesant.

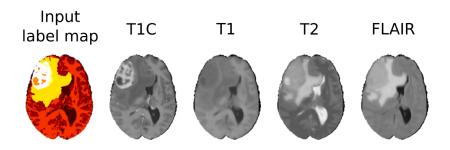


Figure 5. Synthesis of high-grade glioma MR image from a single label map.

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

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

- We investigate new methods for predicting the location of myocardial infarcts from local wall deformation [31], which is useful for risk stratification from routine examinations such as 3D echocardiography. In a broader perspective, this project also aims at determining relevant biomarkers to study cardiac function [54], and eventually at combining several of those markers in an efficient manner [59].
- Non-linear dimensionality reduction aims at estimating the Euclidean space of coordinates encoding deformation patterns, and is combined with multi-scale kernel regressions to infer the low-dimensional coordinates and the infarct location of new cases.
- These concepts were tested on 500 synthetic cases with infarcts of random extent, shape, and location, generated from a realistic electromechanical model. Our prediction goes beyond the current diagnosis of infarct either achieved at the global or segmental level, and significantly outperforms the clinically-used thresholding of the deformation patterns.

6.2. Computational Anatomy

6.2.1. Geometric generative model of organ shapes: statistical properties of template shape estimation

Participants: Nina Miolane [Correspondent, Inria - Stanford], Xavier Pennec [Inria], Susan Holmes [Stanford].

This work is conducted jointly with the Department of Statistics of Stanford, in the context of the associated team GeomStats and the FSCIS (France-Stanford Center for Interdisciplinary Studies) fellowship of Nina Miolane

template, atlas, consistency, estimation theory, Expectation-Maximization algorithm, shapes, quotient space, lie group, sub-Riemannian, in-painting, neuro-geometry, visual cortex, diffusion

This work focuses on the interaction between statistics and geometry, for applications in Medical Imaging. The first part deals with a generative model of (organ) shapes and, more precisely, on the estimation of the mean shape or template. The second part of this work surveys and unveils the mathematical framework needed to extend Neurogeometry, used in 2D Computer Vision, to applications in 3D imaging.

• In the first part, we define a geometric statistical framework of an organ shapes generative model (see Figure 7). This is done through the differential geometry of quotient spaces.

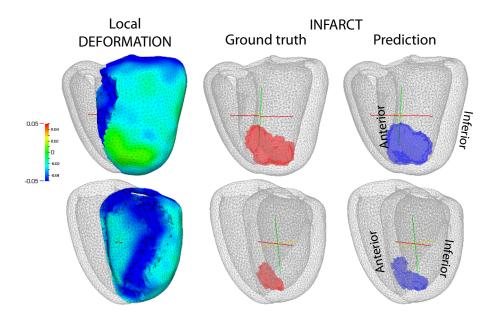


Figure 6. Examples of myocardial deformation patterns, ground truth infarct location, and estimated infarct location.

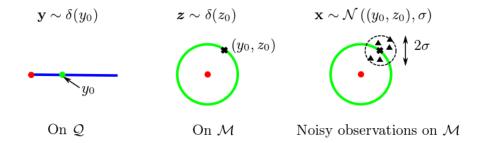


Figure 7. A schematic representation of the generative model of organ shapes.

- Then, we interpret the computation of the mean organ shape (or template) through the max-max algorithm, as an approximate maximum likelihood estimation in this framework.
- Finally, we study the statistical properties of the template computed with this procedure. More precisely, we show that the estimation is inconsistent and that the inconsistency cannot be neglected when the real template is close to the singularity of the quotient space at the scale of the ambient noise on the images [44].
- In the second part, the particularities of a 3D neurogeometry are highlighted with respect to the 2D case. They rely on the fact that 2D neurogeometry is inspired by the primary visual cortex, which codes for our 2D visual field (our retina is 2D). Imagining a 3D visual field or a 3D retina would give rise to a 3D neurogeometry.
- The conceptual framework of a 3D neurogeometry is more subtle, and a new level of mathematical structures arises (see Figure 8). Thus, inpainting (sub-Riemannian diffusion) have to be generalized.
- Applications for in-painting or super-resolution in 3D medical images are described [43].

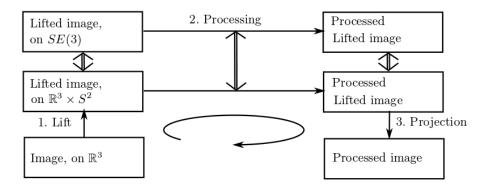


Figure 8. The 3 steps of an image processing pipeline in 3D neurogeometry.

6.2.2. Compact representation of longitudinal deformations

Participants: Raphaël Sivera [Correspondent], Hervé Delingette, Nicholas Ayache.

This work is supported by a PhD fellowship from the University Nice Sophia Antipolis and by the European Research Council through the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Longitudinal modeling, Learning in manifolds, Structured sparsity.

The analysis of dynamic or longitudinal series of medical images is important to better understand the observed evolutions of the organs but also to provide robust computer aided diagnosis tools. This analysis can be performed through a reduced representation of geometric transformations capturing the deformation between 2 time points.

In the context of cardiac motion analysis, we proposed a framework to represent arbitrary diffeomorphisms described as Stationary Velocity Fields (SVF) in a low dimensional linear space (see fig. 9).

To this end, we first improved the Inverse Scaling and Squaring (ISS) algorithm from [83] to transform displacement fields into SVFs. Second, through a structured sparse decomposition of these deformations over the cardiac cycle, we provided a preliminary approach for comparing trajectories of cine-MR images between two patients.

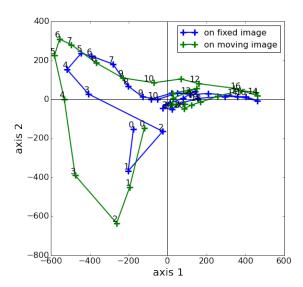


Figure 9. Trajectories of two registered cardiac cycles projected on a 2D space using dimensionality reduction tools.

6.2.3. Statistical analysis of heart motion

Participants: Marc-Michel Rohé [Correspondent], Nicolas Duchateau, Maxime Sermesant, Xavier Pennec.

This work is partly supported by the FP7 European project MD-Paedigree and by the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Statistical analysis, Registration, Reduced order models, Machine learning

This work aims at developing statistical tools to analyze cardiac motion. In particular, we are interested in approximating complex motion models with few parameters or modes that are clinically relevant (reduced models). To this end, we have introduced a polyaffine cardiac motion model that reduces the deformation parameters to a few interpretable parameters, and the most important modes to represent the variability seen in a population are automatically selected. We then performed a group-wise statistical analysis, which relates the model parameters to clinical indices specific to a given pathology. This method was used to classify a population of healthy/infarcted hearts [48] (see Fig. 10), as well as to study cardiac motion of adolescents with cardiomyopathies within the European project "MD-Paedigree".

6.2.4. Statistical Learning via Synthesis of Medical Images

Participants: Hervé Lombaert [Correspondent], Héloise Bleton, Hervé Delingette, Nicholas Ayache, Antonio Criminisi.

This work is partly supported by a grant from Microsoft Research-Inria Joint Centre and by the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

statistical learning, synthesis

Machine learning approaches typically require large training datasets in order to capture as much variability as possible. Application of conventional learning methods on medical images is difficult due to the large variability that exists among patients, pathologies and image acquisitions. The project aims at exploring how realistic image synthesis could be used to improve existing machine learning methods.

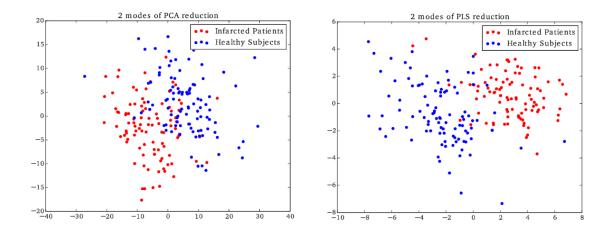


Figure 10. Projection of healthy/infarcted patients cardiac motions on two modes extracted from PCA (left) and PLS (right) methods.

We tackled the problem of better exploiting existing training sets, via a smart modeling of the image space, and applying conventional random forests using guided bagging [99]. Synthesis of complex data, such as cardiac diffusion images (DTI), was also done, with a refined version of [98].

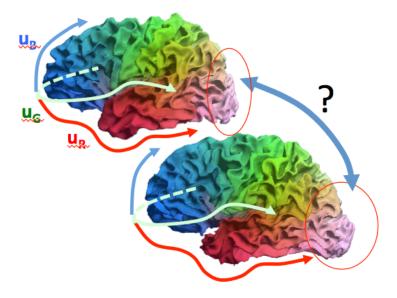


Figure 11. Spectral Representation – How to find an intrinsic representation of shapes for finding fast point correspondences and for learning surface data.

Then, we tackled the problem of exploiting *Geometry in Data*, via intrinsic representations of shapes and data [27]. Spectral decomposition (Fig. 11) of shapes provides a new intrinsic framework for synthesizing complex shapes such as cerebral surfaces [35], and describing functions efficiently on these complex surfaces. This framework establishes the basics for machine learning of surface data [36]. An early application was conducted on retinotopy [57] (the study of functions in the visual cortex).

6.2.5. Consistency of the estimation of the template in quotient spaces

Participants: Loïc Devilliers [Correspondent], Stéphanie Allassonnière [Ecole Polytechnique], Xavier Pennec.

Template estimation, Fréchet mean, quotient spaces

In [24], we studied the estimation of the template (the mean shape of our data) when the data is transformed by unknown group elements. In the case of a finite group acting isometrically on a linear space, we proved that the estimation of the template using the Fréchet mean in the quotient space is not always consistent.

6.3. Computational Physiology

6.3.1. Computational modeling of radiofrequency ablation for the planning and guidance of abdominal tumor treatment

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

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

Radiofrequency Ablation Modeling, Patient-Specific Simulation, Lattice Boltzmann Method, Computer Model, Computational Fluid Dynamics, Heat Transfer, Cellular Necrosis, Parameter Estimation, Therapy Planning, Liver, Pre-clinical Study, Medical Imaging

Radio Frequency Ablation (RFA) is a minimally invasive therapy suited for liver tumor ablation. However, a patient-specific predictive tool is needed to plan and guide the treatment.

We developed a computational framework for patient-specific planning of RFA, which includes the following contributions:

- A detailed computational model of the biophysical mechanisms (heat transfer, cellular necrosis, hepatic blood flow) involved in RFA of abdominal tumors based on patient images.
- A new implementation of the bio-heat equations coupled with a cellular necrosis model using the Lattice Boltzmann Method (LBM) on Graphics Processing Units (GPU), which allows near real-time computation.
- A Computational Fluid Dynamics (CFD) and porous media solver using LBM algorithm to compute
 the patient-specific blood flow in the hepatic circulatory system and the blood flow distribution inside
 the parenchyma.
- A complete patient-specific geometry including hepatic venous and arterial circulation system.
- The automatic estimation of the main parameters of the model. Two personalization strategies tested and evaluated on clinical and pre-clinical data.
- The evaluation of the proposed model on a clinical dataset of ten patients (see Fig. 12).
- The evaluation on a preclinical dataset of five swines from a comprehensive experimental set-up specially designed for RFA model validation.

The proposed RFA model and its evaluation on clinical data are presented in [10], and the evaluation of the RFA model on pre-clinical data is presented in [25]. The proposed model, its personalisation and its evaluation against clinical and preclinical data are presented in Chloé Audigier's PhD thesis [1].

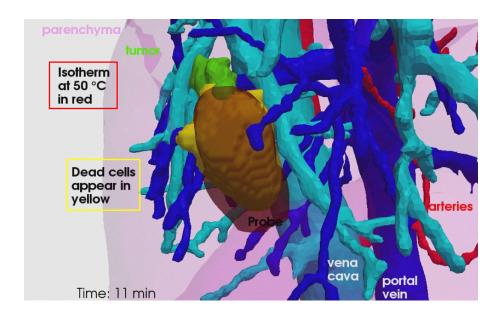


Figure 12. Computed isotherm at 50°C and computed necrosis in a subject-specific geometry.

6.3.2. Learning Cardiac Ablation Targets from Image Data and Simulation

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

This work was supported by the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Cardiac electrophysiology modeling, Intracardiac electrogram modeling, Machine learning, Radiofrequency ablation planning, electroanatomical mapping, local abnormal ventricular activities (LAVA)

Ventricular radiofrequency ablation can have a critical impact on preventing sudden cardiac arrest but it is challenging due to a highly complex arrhythmogenic substrate. We used advanced delayed enhanced-MR image characteristics in a machine learning framework to predict the presence of local abnormal ventricular activities (LAVA). Furthermore, we enriched these predictions through MR image-based patient-specific electrophysiology simulations and the modeling of normal and LAVA-like intracardiac electrograms using the dipole approach and their incorporation in the learning framework (see Fig. 13). Confidence maps can then be generated and analyzed prior to RFA to guide the intervention.

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

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

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

Alzheimer's Disease (AD), modeling brain deformation, biophysical model, simulation

- We developed a framework to generate patient specific multiple time-point images based on our biophysical model of brain deformation due to atrophy in Alzheimer's Disease (AD)[34]. From two time-point brain MRIs of a patient, we used the framework to simulate a new time-point brain MRI with the personalized atrophy for the patient (see Fig. 14).
- The framework can be used to evaluate methods that study the temporal relationships, ordering and co-evolution of atrophy in different structures of the brain.

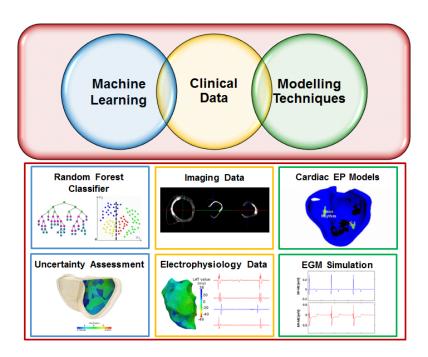


Figure 13. Coupled learning and simulation framework for LAVA identification.

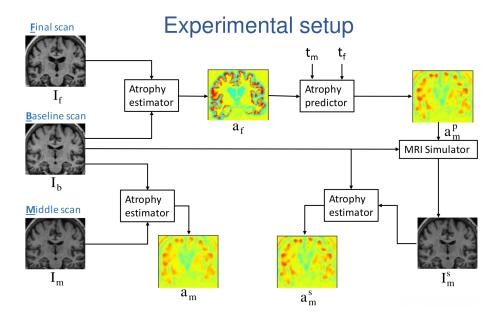


Figure 14. From a given baseline scan and a final scan at time t_f , a middle scan at time t_m is predicted and simulated. An experimenatal setup that allows comparing the atrophy (a_m^s) estimated from a simulated middle-scan against the atrophy (a_m) estimated from the real middle scan is shown.

6.3.4. Brain Tumor Growth Personalization and Segmentation Uncertainty

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

This work is carried out between Asclepios research group, Inria Sophia Antipolis, France and the Department of Radiation Oncology of the Massachusetts General Hospital, Boston, USA. It is supported by the ERC Advanced Grant MedYMA 2011-291080 (on Biophysical Modeling and Analysis of Dynamic Medical Images).

Tumor growth, radiotherapy, modeling, personalization, segmentation, uncertainty, Bayesian

- We developed a method for the Bayesian personalization of a brain tumor growth model based on clinical MRIs [37] (see Fig. 15 Left).
- We proposed an algorithm for the sampling of several plausible segmentations, based on a single clinical segmentation (see Fig. 15 Right). This allows the uncertainty quantification of the radiotherapy plan based on several sample clinical target volumes [38]. This paper received the Young Scientist Award at the 2015 MICCAI conference in Munich, Germany.

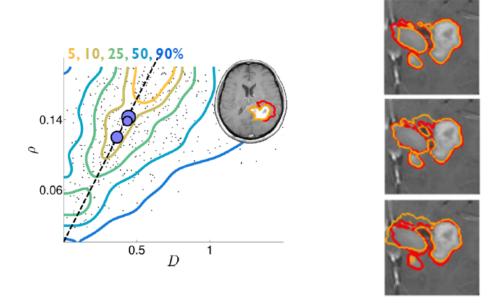


Figure 15. (Left) Bayesian personalization of a glioblastoma patient. Isocontours of the posterior probability of the diffusion parameter D and the proliferation parameter ρ ; (Right) Different sampled plausible segmentations in orange based on the clinical segmentation in red.

6.3.5. Uncertainty quantification in personalised Cardiac models. Application to myocardial fiber uncertainty.

Participants: Roch-Philippe Molléro [Correspondent], Dominik Neumann [Siemens], Marc-Michel Rohé, Hervé Delingette, Maxime Sermesant, Xavier Pennec, Nicholas Ayache, Tommaso Mansi [Siemens].

This work was partly supported by the FP7 European project MD-Paedigree and was done in collaboration with Siemens Corporate Technology, Erlangen, Germany and Siemens Corporate Research, Princeton, New Jersey.

Heart Modeling - Myocardial Fibers - Biophysical Simulation - Uncertainty Quantification

Computational models of the heart are of increasing interest for clinical applications due to their discriminative and predictive power. However, the personalisation step to go from a generic model to a patient-specific one is still challenging. In particular, it is still difficult to quantify the uncertainty on the estimated parameters and predicted values.

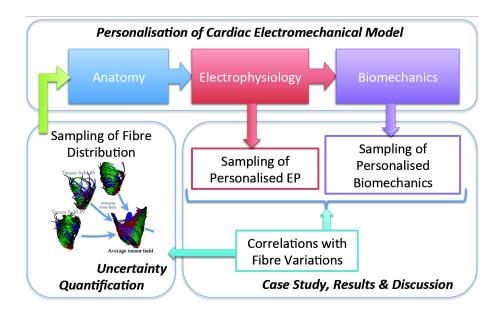


Figure 16. Global scheme of fibre variability propagation along the personalisation pipeline.

We developed a pipeline (see Fig. 16) to evaluate the impact of myocardial fibre uncertainty on the personalisation of an electromechanical model of the heart from ECG and medical images:

- We studied how to estimate the variability of the fibre architecture among a given population (from a myocardial fiber atlas).
- Then, we showed the variability of the personalised simulations, in electrophysiology (EP) and in biomechanics, with respect to the principal variations of the fibres.
- Finally, we discussed how the variations in this population of fibres impact the parameters of the personalised simulations.

This work led to a paper at FIMH 2015 conference in Maastricht, The Netherlands [45].

6.3.6. Non-invasive personalisation of the electrical heart model

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

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

Cardiac Modelling, Personalised Simulation, Electrical Simulation

Non-invasive cardiac electrical data has been acquired at St Thomas' Hospital, London. It consists in Body Surface Potential Mapping (BSPM), which are recordings of the electrical potential on several locations on the surface of the torso (see Fig. 17). From BSPMs and MRI data of the heart, we aim at personalizing the electrical propagation model of the heart previously developed within the Asclepios team.

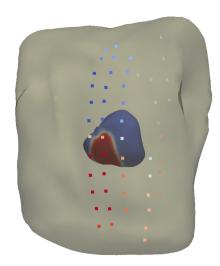


Figure 17. Torso representation used for personalizing cardiac electrical parameters from non-invasive observations.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

7.1.1. CIFRE PhD Fellowships

7.1.1.1. Neurelec/Oticon Medical

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

7.1.2. Inria - Mauna Kea Technologies I-Lab SIWA

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

This I-lab involves the Mauna Kea Technologies company.

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

For more information, see this link ⁴.

7.1.3. Microsoft Research

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

⁴https://lisa.sophia.inria.fr/siwa-loasis-numerique-dinria-et-de-mauna-kea-706.html

⁵http://www.msr-inria.fr/projects/4d-cardiac-mr-images

⁶http://www.msr-inria.fr/projects/medilearn

7.1.4. Spin-off company Therapixel

Therapixel⁷ is a spin-off of the Asclepios (Inria Sophia Antipolis) and Parietal (Inria Saclay) project teams founded in 2013. Therapixel makes surgical information systems. It relies on depth sensing, advanced software processing and innovative user interfaces to provide touchless control of the computer. This technology allows for a direct control of the computer, which sterility constraints made impractical in the past. In 2015, Therapixel obtained the CE marking of its product on touchless visualization of medical images.

7.1.5. Other contracts

Contracts with Philips and Siemens are described in our previous activity reports.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. Consulting for Industry

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

8.1.2. Collaboration with national hospitals

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

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

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

8.2. European Initiatives

8.2.1. FP7 & H2020 Projects

8.2.1.1. MD PAEDIGREE

Title: Model-Driven European Paediatric Digital Repository

Programme: FP7

Period: March 2013 - February 2017

Coordinator: Ospedale Pediatrico Bambini Gesù, Rome.

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

Biomolecular Research Genomics (Italy)

Deutsches Herzzentrum Berlin (Germany)

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

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

Haute Ecole Specialisée de Suisse Occidentale (Switzerland)

Istituto Giannina Gaslini (Italy)

Katholieke Universiteit Leuven (Belgium)

⁷http://www.therapixel.com/

Lynkeus (Italy)

Motek Medical B.V. (Netherlands)

Ospedale Pediatrico Bambino Gesu (Italy)

Siemens Aktiengesellschaft (Germany)

Siemens Corporation (United States)

Technische Universiteit Delft (Netherlands)

University College London (United Kingdom)

Universitair Medisch Centrum Utrecht (Netherlands)

Universita Degli Studi di Roma Lapienza (Italy)

The University of Sheffield (United Kingdom)

Universitatea Transilvania Din Brasov (Romania)

Stichting Vu-Vumc (Netherlands)

Maat Francerl (France)

Inria contact: Xavier Pennec

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

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

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

8.2.1.2. VP2HF

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

Programme: FP7

Period: October 2013 - September 2016 Coordinator: King's College, London.

Partners:

Centron Diagnostics Ltd (United Kingdom)

CHU Côte de Nacre, Caen (France)

King's College London (United Kingdom)

Philips Technologie (Germany)

Philips France (France)

Simula Research Laboratory As (Norway)

Université Catholique de Louvain (Belgium)

Universitat Pompeu Fabra (Spain)

Inria contact: Dominique Chapelle / Maxime Sermesant

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

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

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

8.2.1.3. MedYMA

Title: Biophysical Modeling and Analysis of Dynamic Medical Images

Programme: FP7
Type: ERC

Period: April 2012 - March 2017

Coordinator: Inria

Inria contact: Nicholas Ayache

During the past decades, exceptional progress was made with in vivo medical imaging technologies to capture the anatomical, structural and physiological properties of tissues and organs in patients, with an ever increasing spatial and temporal resolution. Physicians are now faced with a formidable overflow of information, especially when a time dimension is added to the already hard to integrate 3-D spatial, multimodal and multiscale dimensions of modern medical images. This increasingly hampers the early detection and understanding of subtle image modifications, which can have a vital impact on the patient's health. To change this situation, a new generation of computational models for the simulation and analysis of dynamic medical images is introduced. Thanks to their generative nature, they will allow the construction of databases of synthetic and realistic medical image sequences simulating various evolving diseases, producing an invaluable new resource for

training and benchmarking. Leveraging on their principled biophysical and statistical foundations, these new models will bring an added clinical value once they have been personalized with innovative methods to fit the medical images of any specific patient. By explicitly revealing the underlying evolving biophysical processes observable in the images, this approach will yield new groundbreaking image processing tools to correctly interpret the patient's condition (computer aided diagnosis), to accurately predict the future evolution (computer aided prognosis), and to precisely simulate and monitor an optimal and personalized therapeutic strategy (computer aided therapy). First applications concern high impact diseases including brain tumors, Alzheimer's disease, heart failure and cardiac arrhythmia and will open new horizons in computational medical imaging.

8.3. International Initiatives

8.3.1. Inria International Labs

Inria@SiliconValley

Associate Team involved in the International Lab:

8.3.1.1. GeomStats

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

International Partner (Institution - Laboratory - Researcher):

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

Starting year: 2015

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

The scientific goal of this associated team is to develop the field of geometric statistics that have key applications in computational anatomy. Computational anatomy is an emerging discipline at the interface of geometry, statistics, image analysis and medicine, which aim is to analyze and model the biological variability of the organs shapes at the population level. An important application in neuroimaging is the spatial normalization of subjects, which is necessary to compare anatomies and functions through images in populations with different clinical conditions.

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

8.3.2. Inria International Partners

8.3.2.1. Informal International Partners

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

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

8.3.2.1.2. Massachusetts General Hospital, Boston

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

8.3.2.1.3. Other International Hospitals

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

8.4. International Research Visitors

8.4.1. Research visits abroad

In the context of the Associated team GeomStats, part of the Inria International Lab Inria@SiliconValley, there were two research visits in 2015 at the Stanford Statistics Department:

- Xavier Pennec: 3 months (April to June 2015)
- Nina Miolane: 8 months (April to June and August to December 2015)

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

- 9.1.1.1. General chair, scientific chair
 - **X. Pennec** was general chair of the Mathematical Foundations of Computational Anatomy (MFCA 2015) workshop, which was held in conjunction with MICCAI at Munich, Germany, on October 9, 2015.
- 9.1.1.2. Member of organizing committees
 - M. Sermesant was a co-chair of the MICCAI 2015 Workshop Statistical Atlases and Computational Models of the Heart (STACOM 2015), which was held in Munich, Germany, on October 9, 2015.

9.1.2. Scientific events selection

- 9.1.2.1. Member of conference program committees
 - X. Pennec was area chair of the International Symposium on Biomedical Imaging (ISBI 2015, New-York, NY, USA), and program committee member of the conference Geometric Sciences of Information (GSI'2015, Palaiseau, France).
 - **H. Delingette** was program committee member of the conference on Medical Image Computing and Computer Assisted Intervention(MICCAI 2015), the FIMH 2015 conference, and the conference on Virtual Reality Interactions and Physical Simulation (VRIPHYS'15). He was an associate editor for the conference IEEE EMBC 2015.

9.1.2.2. Reviewer

- H. Delingette was a reviewer for the International Symposium on Biomedical Imaging (ISBI'15), the international conference on computer-aided interventions (IPCAI'15) the conference on Virtual Reality Interactions and Physical Simulation (VRIPHYS'15), the conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2015), the International Conference on Computer Vision (ICCV 2015), the International Conference on Computer Vision and Pattern Recognition (CVPR 2015).
- M. Sermesant was a reviewer for the MICCAI 2015 and FIMH 2015 conferences.
- **X. Pennec** was a reviewer for the 24th biennial international conference on Information Processing in Medical Imaging (IPMI 2015) and the conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2015).

9.1.3. *Journal*

9.1.3.1. Member of editorial boards

- **N. Ayache** is the co-founder and the Co-Editor in Chief with J. Duncan (Professor at Yale) of *Medical Image Analysis* ⁸. This scientific journal was created in 1996 and is published by Elsevier.
- **N. Ayache** is Associated Editor of *IEEE Transactions on Medical Imaging* ⁹ and a member of the editorial board of the following journals: *Medical Image Technology* (Japanese journal) and *Journal of Computer Assisted Surgery* (Wiley).
- **H. Delingette** is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier).
- **I. Strobant** is editorial coordinator for *Medical Image Analysis*, Elsevier (since october 2001) and editorial assistant for *IEEE Transactions on Medical Image Analysis* (since october 2001).
- **X. Pennec** is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier), of the *International Journal of Computer Vision* (Springer), of the SIAM *Journal on Imaging Sciences* (SIIMS), and of the *Journal of Mathematical Imaging and Vision (JMIV)*.

9.1.3.2. Reviewer - Reviewing activities

- **H. Delingette** was a reviewer for the following journals: *Medical Image Analysis* (Elsevier), IEEE Transactions in Medical Imaging, IEEE Transactions in Biomedical Engineering, Computer Vision and Image Understanding, Biomedical Engineering, Computers in Biology and Medicine and Journal of Fluids and Structures.
- X. Pennec was a reviewer for the following journals: Medical Image Analysis (MedIA), IEEE Transactions in Medical Imaging (TMI), NeuroImage (NIMG), IEEE Transactions on Pattern Analysis (PAMI), International Journal of Computer Vision (IJCV), Journal of mathematical imaging and vision (IJCV), SIAM journal on Imaging Sciences (SIIMS) and International Statistical Review (ISR).
- M. Sermesant was a reviewer for the following journals: Journal of the American College of Cardiology, IEEE Transactions on Medical Imaging, IEEE Transactions on Biomedical Engineering, Medical Image Analysis and Computers in Biology and Medecine.

9.1.4. Invited talks

- Nicholas Ayache gave the following invited lectures:
 - Symposium "Les savoirs de l'ENS", Ecole Normale Supérieure, Paris 2015.
 - First conference CYBERMED, Juan-les-Pins, 2015.
 - Forum Chili-France, La société intelligente, Paris 2015.
 - Conference ENIT organized by the Collège de France in Tunisia, Tunis, 2015.
 - Journées françaises des doubles cursus, Paris 2015.
 - Institut du cerveau et de la moelle épinière, Hôpital de la Pitié Salpêtrière, Paris 2015.
 - Keynote at the Multidisciplinary Computational Anatomy Initiative, Fukuoka, Japan 2015.
- Hervé Delingette gave the following invited lectures at the:
 - IHU Strasbourg Scientific Day on June 3rd in Strasbourg.
 - Biomed Summer School in Paris in July 2015.
 - Metice workshop in Bordeaux in September 2015.
- **Xavier Pennec** gave the following invited lectures:
 - Schrödinger institute Programme on Infinite-Dimensional Riemannian Geometry with Applications to Image Matching and Shape Analysis, Vienna, February 2015: a one week course and one workshop presentation.

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

⁹http://www.ieee-tmi.org/

- 2015 Joint Mathematics Meetings (AMS/MAA): AMS Special Session on Differential Geometry and Statistics, San Antonio, Texas, January 2015.
- Center for Health Sciences, SRI international, Menlo Park, USA, June 4 2015.
- Statistics Department Seminar, Stanford University, April 21, 2015.
- Maxime Sermesant gave an invited lecture at Computing in Cardiology Conference, in Nice September 2015.

9.1.5. Leadership within the scientific community

- **Xavier Pennec** is a member of the MICCAI Society Board of Directors from 2012 to 2015.
- Nicholas Ayache is a member of the French Academy of Sciences in the section of Mechanics and Informatics.

9.1.6. Scientific expertise

- **Nicholas Ayache** was invited in Tokyo, Japan in February 2015 to evaluate a national program on the "Multidisciplinary Computational Anatomy Initiative" funded by the MEXT.
- **Xavier Pennec** was a member of the Member of the panel for the joint FLAG-ERA Joint / HBM flagship Transnational Call (JTC), 2015.
- **H. Delingette** was an evaluator for the ECOS Sud France-Chili program. He was involved in the redaction of the second application of the Unversité Côte d'Azur to the IDEX bid.
- **M. Sermesant** is a member of the Medical Simulation Working Group of Aviesan. He organized two hackfests for the medInria software.

9.1.7. Research administration

- Nicholas Ayache has been a member of the "Comité de la Recherche Biomédicale en Santé Publique (CRBSP)" of the Nice hospitals since 2008. He has been a member of the Research Council of the "Fondation pour la Recherche Médicale (FRM)" since January 2015.
- **Xavier Pennec** is a member of the Doctoral follow-up Committee (CSD) at Inria Sophia Antipolis and in charge of the relationships of Inria-Sophia with the Nice University Hospital (CHU).
- **H. Delingette** is a member of the local committee in charge of the scientific selection of visiting scientists (Comité NICE) and the local committee on the immersive platform.
- **M. Sermesant** is a member of the local committee in charge of the selection of funding for courses and conferences organisation and of the local organisation for scientific presentations in high schools.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

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

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

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

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

9.2.2. PhD defended

Vikash Gupta, *Diffusion tensor imaging of the brain: towards quantitative clinical tools*, Nice Sophia Antipolis University, March 2015.[5]

Thomas Benseghir, 3D/2D Coronary Registration for Interventional Cardiology Guidance, Nice Sophia Antipolis University, July 2015.[2]

Rocio Cabrera Lozoya, *Radio frequency ablation planning for cardiac arrhythmia treatment through biophysical modelling and machine learning approaches*, Nice Sophia Antipolis University, September 2015.[3]

Chloé Audigier, *Modeling radio-frequency ablation for the planning of abdominal tumors resection*, Nice Sophia Antipolis University, October 2015.[1]

Loic Le Folgoc, *Biophysical Personalization of Cardiac Models based on Machine Learning*, Nice Sophia Antipolis University, November 2015.[6]

Nicolas Cordier, Simulation and Analysis and Simulation of Brain Tumors Images, Nice Sophia Antipolis University, December 2015.[4]

Jan Margeta, *Indexation of time-series 4D cardiac MR images*, Ecole des Mines de Paris, December 2015.[7]

9.2.3. PhD in progress

Pietro Gori, Statistics on the brain connectivity of patients with neurological diseases, University of Paris. Started in 2012. Thesis in collaboration with the Aramis project-team, co-directed by O. Colliot, S. Durrleman and N. Ayache. Defended on January 8, 2016.

Mehdi Hadj-Hamou, *Biophysical modeling of the anatomical evolution of the brain*, Nice Sophia Antipolis University. Started in September 2012. Co-directed by N. Ayache and X. Pennec.

Bishesh Khanal, *Modeling the atrophy of the brain in Alzheimer's disease*, Nice Sophia Antipolis University. Started in November 2012. Co-directed by X. Pennec and N. Ayache.

Nina Miolane, Geometric Statistics in Computational Anatomy: Template Estimation and Subspace Learning in Manifolds, Lie groups and Stratified Spaces, Nice-Sophia Antipolis University. Started in November 2013. Directed by X. Pennec.

Anant Vemuri, *Augmented reality for image-guidedsurgery*, Nice Sophia Antipolis University. Started in 2012. Co-directed by S. Nicolau and N. Ayache.

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

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

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

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

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

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

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

9.2.4. Juries

N. Ayache was co-supervisor of the PhD theses of Vikash Gupta (U. of Nice Sophia Antipolis), Rocío Cabrera Lozoya (U. of Nice Sophia Antipolis), Chloé Audigier (U. of Nice Sophia Antipolis), Loic Le Folgoc (U. of Nice Sophia Antipolis), Nicolas Cordier (U. of Nice Sophia Antipolis) and Jan Margeta (Ecole des Mines de Paris).

Hervé Delingette was co-supervisor of the PhD theses of Chloé Audigier (U. of Nice Sophia Antipolis), Loic Le Folgoc (U. of Nice Sophia Antipolis) and Nicolas Cordier (U. of Nice Sophia Antipolis). He was a reviewer in the PhD thesis committee of Vasyl Mykhalchuk (U. of Strasburg) and of Romane Gauriau (Telecome ParisTech). He was a member of the PhD thesis committee of Alexandre Abraham (U. of Paris-Saclay) and Jan Margeta (Ecole des Mines de Paris).

Xavier Pennec was examinor of the HDR of Laurence Rouet (U. Paris-Descartes) and of the PhD thesis committee of Thomas Benseghir (U. of Nice Sophia Antipolis). He was co-supervisor of the PhD thesis of Vikash Gupta (U. of Nice Sophia Antipolis).

Maxime Sermesant was co-supervisor of the PhD thesis of R. Cabrera Lozoya (U. of Nice Sophia Antipolis).

9.3. Popularization

Maxime Sermesant gave a presentations about research and medical imaging at Lycée Bristol in Cannes.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

- [1] C. AUDIGIER. Computational modeling of radiofrequency ablation for the planning and guidance of abdominal tumor treatment, Université Nice Sophia Antipolis, October 2015, https://tel.archives-ouvertes.fr/tel-01256010
- [2] T. Benseghir. *Topology Preserving Vascular Registration: Application to Percutaneous Coronary Intervention*, Université de Nice-Sophia Antipolis, July 2015, https://hal.inria.fr/tel-01235141
- [3] R. CABRERA LOZOYA. Radiofrequency ablation planning for cardiac arrhythmia treatment using modeling and machine learning approaches, Université Nice Sophia Antipolis, September 2015, https://tel.archivesouvertes.fr/tel-01206478
- [4] N. CORDIER. Multi-Atlas Patch-Based Segmentation and Synthesis of Brain Tumor MR Images, Université Nice Sophia Antipolis, December 2015, https://hal.inria.fr/tel-01237853
- [5] V. GUPTA. Diffusion tensor imaging of the brain: towards quantitative clinical tools, Université Nice Sophia Antipolis, March 2015, https://tel.archives-ouvertes.fr/tel-01159964
- [6] L. LE FOLGOC. *Statistical learning for image-based personalization of cardiac models*, Université Nice Sophia Antipolis, November 2015, https://hal.inria.fr/tel-01237874
- [7] J. MARGETA. *Machine Learning for Simplifying the Use of Cardiac Image Databases*, MINES ParisTech, December 2015, https://hal.inria.fr/tel-01243340

Articles in International Peer-Reviewed Journals

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