Activity Report 2013

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

Keywords: Biological Images, Medical Images, Virtual Physiology, Image Processing, Simulation

Creation of the Project-Team: 2005 November 01.

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2. Overall Objectives

2.1. Introduction

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

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

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

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

2.2. Highlights of the Year

- Nicholas Ayache the received MICCAI 2013 “Enduring Impact Award” for his scientific contributions since the inception of the conference in 1998.
- Nicholas Ayache was elected by the Collège de France to the Chair “Informatics and Computational Sciences” for the academic year 2013-2014.
- The company Therapixel, spin-off of the Inria project teams Asclepios (Olivier Clatz) and Parietal (Pierre Fillard), received an OSEO award in the category "Creation-Development" of start-up companies.

3. Research Program

3.1. Introduction

Tremendous progress has been made in the automated analysis of biomedical images during the past two decades [93]. 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 [84], [82]. Regarding target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [80], in N. Ayache’s article [88] and in the more recent syntheses [89] [93]. The scientific journals *Medical Image Analysis* [74], *Transactions on Medical Imaging* [81], and *Computer Assisted Surgery* [83] are also good reference material. One can have a good vision of the state of the art with the proceedings of the most recent conferences MICCAI’2010 (Medical Image Computing and Computer Assisted Intervention) [77], [78] or ISBI’2010 (Int. Symp. on Biomedical Imaging) [76].

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 [94], [106]. It is also possible to obtain from a Magnetic Resonance Image (MRI) of the head a reasonable segmentation into skull tissues, white matter, grey matter, and cerebro-spinal fluid [109], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [87], Ultrasound or Nuclear Medicine images [95].

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 physical modeling of the image acquisition process, only a few actually model the physical or even 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 comprehension 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 multi-sequence (or multi-parametric) [1] and multi-modal images [2] for each single patient.

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 3.4 and 3.5.

We plan to pursue our efforts on the following problems:

1. Multi-dimensional, multi-sequence and multi-modal image segmentation,
2. Image Registration/Fusion,

3.3. Biological Image Analysis

In biology, a huge number of images of living systems are produced every day to study the basic mechanisms of life and pathologies. If some bio-imaging *principles* are the same as the ones used for medical applications

[1] Multisequence (or multiparametric) imaging consists in acquiring several images of a given patient with the same imaging modality (e.g. MRI, CT, US, SPECT, etc.) but with varying acquisition parameters. For instance, using Magnetic Resonance Imaging (MRI), patients followed for multiple sclerosis may undergo every six months a 3-D 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 MR images of the brain can be acquired by exploiting the so-called Bold Effect (Blood Oxygen Level Dependency): slightly higher blood flow in active regions creates a subtle higher T2* signal which can be detected with sophisticated image processing techniques.

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

(e.g. MR, CT, US, PET or SPECT), bio-imaging *devices* are usually customized to produce images of higher resolution [3] for the observation of small animals (typically rodents). In addition, Optical Imaging (OI) techniques and biophotonics are developing very fast. This includes traditional or Confocal Microscopy (CM), multi-photon confocal microscopy, Optical Coherent Tomography (OCT), near-infrared imaging, diffuse optical imaging, phased array imaging, etc. A very new and promising development concerns micro-endoscopy, which allows cellular imaging at the end of a very small optical fiber [100].

Most of these imaging techniques can be used for *Molecular Imaging*, an activity aiming at the *in vivo* characterization and measurement of biological processes at cellular and molecular levels. With optical techniques, molecular imaging makes extensive use of the fluorescent properties of certain molecules (in particular proteins, e.g. GFP [4]) for imaging of gene expression *in vivo*. With other modalities (like PET, SPECT, MR, CT and even US), molecular imaging can use specific contrast agents or radioactive molecules. For clinical applications, the ultimate goal of molecular imaging is to find ways to probe much earlier the molecular anomalies that are the basis of a disease rather than to image only its end effects [110].

Some of the recent advances made in Medical Image Analysis could be directly applied (or easily adapted) to Biological Image Analysis. However, the specific nature of biological images (higher resolution, different anatomy and functions, different contrast agents, etc.), requires specific image analysis methods (one can refer to the recent tutorial [104] and to the Mouse Brain Atlas Project [86]). This is particularly true when dealing with *in vivo* microscopic images of cells and vessels.

Our research efforts will be focused on the following generic problems applied to *in vivo* microscopic images:

1. quantitative analysis of microscopic images,
2. detection and quantification of variations in temporal sequences,
3. construction of multiscale representations (from micro to macro).

3.4. Computational Anatomy

The objective of the Computational Anatomy (CA) is the modeling and analysis of biological variability of 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 [5].

Studying the variability of biological shapes is an old problem (cf. the remarkable book "On Shape and Growth" by D'Arcy Thompson [108]). Significant efforts have been made since that time to develop a theory for statistical shape analysis (one can refer to [92] for a good synthesis, and to the special issue of Neuroimage [107] for recent developments). Despite all these efforts, there are a number of challenging mathematical issues which remain largely unsolved in general. A particular issue is the computation of statistics on manifolds which 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 to the following problems:

1. Statistics on anatomical manifolds,
2. Propagation of variability from anatomical manifolds,
3. Linking anatomical variability to image analysis algorithms,
4. Grid-Computing Strategies to exploit large databases.

[3] This is the case with micro-MRI, Micro-CT, Micro-US devices, and to a lesser extent with Micro-SPECT and Micro-PET devices.
[4] Green Fluorescent Protein.
[5] The NIH has lauched 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 objective will be to establish new surrogate end-points from the automated analysis of temporal sequences. This is a challenging objective for researchers in Computational Anatomy. The data will be made available to qualified research groups involved or not in the study.

3.5. 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 and biology, where CP can be used for instance 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.

Quite advanced models have already been proposed to study at the molecular, cellular and organic level a number of physiological systems (see for instance [103], [99], [90], [105], [96]). 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 [91]:

- the first level is mainly geometrical, and addresses the construction of a digital description of the anatomy [85], essentially acquired from medical imagery;
- the second level is physical, involving mainly the biomechanical modeling of various tissues, organs, vessels, muscles or bone structures [97];
- the third level is physiological, involving a modeling of the functions of the major biological systems [98] (e.g. cardiovascular, respiratory, digestive, central or peripheral nervous, muscular, reproductive, hormonal, etc.) or some pathological metabolism (e.g. evolution of cancerous or inflammatory lesions, formation of vessel stenoses, etc.);
- a fourth level would be cognitive, modeling the higher functions of the human brain [75].

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 first level of modeling) to a much more ambitious *Physiological Human project* (see [98], [99]). We will not address all the issues raised by this ambitious project, but instead focus on topics detailed below. Among them, our objective is to identify some common methods for the resolution of the large inverse problems raised by the coupling of physiological models to biological images for the construction of patient-specific models (e.g. specific variational or sequential methods (EKF), dedicated particle filters, etc.). We also plan to develop specific expertise on 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, etc.). Application domains include

1. Surgery Simulation,
2. Cardiac Imaging,
3. Brain tumors, neo-angiogenesis, wound healing processes, ovocyte regulation, ...

3.6. Clinical and Biological Validation

If the objective of many of the research activities of the project is the discovery of original methods and algorithms with a demonstration of feasibility on a limited number of representative examples (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, this is a necessary for the transformation of new ideas into clinical tools and/or industrial products. It is also often the occasion to get access to larger databases of images and signals which in turn help stimulate of new ideas and concepts.

4. Software and Platforms

4.1. SOFA

Participants: Hervé Delingette [correspondant], Brina Goyette, Federico Spadoni, Stéphanie Marchesseau, Hugo Talbot.

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. It was developed mainly by the Inria team projects Shaman, Evasion and Asclepios.
See also the web page http://www.sofa-framework.org/.

- ACM: J.2 Physics, J.3 LIFE AND MEDICAL SCIENCES
- Software benefit:- Simulation of the human body
- License: GPL
- License: LGPL
- Type of human computer interaction: console, opengl, qt
- OS/Middelware: linux, windows, mac
- Required library or software: Qt - GPL - GLEW - BSD/MIT - Tinyxml - zlib
- Programming language: C/C++
- Documentation: - each function of the core API and each class in the SOFA modules - doxygen
- ACM: J.3
- Programming language: C/C++

4.2. MedInria

Participants: Maxime Sermesant [Correspondant], Florian Vichot, Moulay Fadil, Loïc Cadour.

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, 2.1.2, was made in September 2013. See also the web page http://med.inria.fr.

- Version: 2.1.2
- License: BSD
- Keywords: Medical Image Processing
- Dependencies: Qt, DTK, VTK, ITK, TTK, MIPS
- Programming language: C++
- Supported OSes: Windows (XP/Vista/7/8), Linux (Fedora/Ubutu), Mac OS X (10.6-10.9)

5. New Results

5.1. Medical Image Analysis

5.1.1. Segmentation of cardiac images from magnetic resonance

Participants: Jan Margeta [Correspondant], Kristin Mcleod, Antonio Criminisi [MSRC], Nicholas Ayache.

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

Cardiac imaging, Magnetic resonance, Image segmentation, Maching learning

- We contributed our previous method to build left ventricle myocardium segmentation consensus based on the STAPLE algorithm [26]
- We enhanced our segmentation method with extra features based on the distance transform and image vesselness measures in order to segment left atria (see Fig. 1) from 3d MRI images [49]. We participated with this method in the left atrium segmentation challenge at MICCAI 2013.

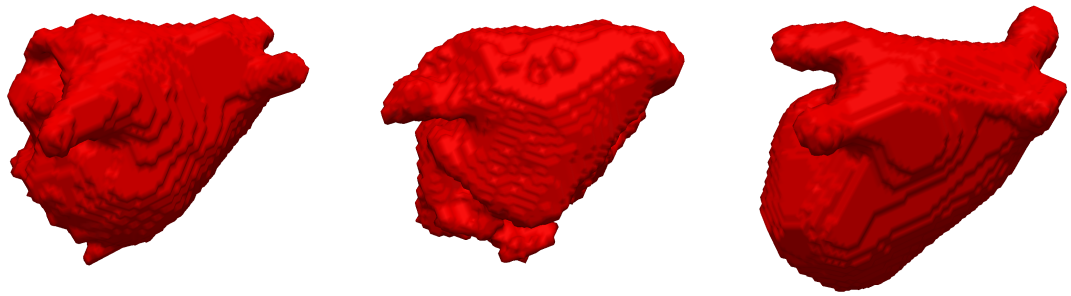

Figure 1. Segmented atria meshes from the validation dataset.

5.1.2. Brain tumor image processing and modeling

Participants: Bjoern Menze [Correspondant], Hervé Delingette, Nicholas Ayache, Nicolas Cordier, Erin Stretton, Jan Unkelbach.

We developed a new non-parametric lesion growth model for the analysis of longitudinal image sequences [59], evaluated the parametric tumor growth model of Konukoglu on longitudinal data, focusing on the relevance of DTI [40], [57], and addressed the question of how to detect tumor growth from longitudinal sequences of patients treated with angiogenesis inhibitors using registration techniques [47]. We also completed work for the 2012 MICCAI Challenge on Brain Tumor Image Segmentation (MICCAI-BRATS 2012) [79], where we also tested some of our own brain tumor image segmentation models based on random forests [42] and patch regression [38], we also participated in MICCAI-BRATS 2013 in Nagoya, Japan [67].

5.1.3. Further developing the random forest framework for medical computer vision tasks

Participants: Bjoern Menze [Correspondant], Matthias Schneider, Ezequiel Geremia, Rene Donner, Georg Langs, Gabor Szekely.

Methodological contributions include the further development of the random forest framework. We introduced the "spatially adaptive" random forest (SARF) classifier [42], and evaluated Hough regression forests for interest point detection in whole body CT image analysis, as well as for vessel detection and tracking [54]. We also evaluated alternative patch-based methods for whole body image registration [41]. As a related community effort, we organized the MICCAI-MCV workshop, also in conjunction with the MICCAI conference in Nagoya, Japan [65].

5.1.4. Statistical Analysis of Diffusion Tensor Images of the Brain

Participants: Vikash Gupta [Correspondent], Nicholas Ayache, Xavier Pennec.

Diffusion Tensor Imaging of the Brain, Tractography, Super-resolution, Statistical analysis

Diffusion tensor imaging (DTI) is gaining interest as a clinical tool for studying a number of brain diseases pertaining to white matter tracts and also as an aid in neuro-surgical planning. Unfortunately, in a clinical environment, diffusion imaging is hampered by the long acquisition times, low signal to noise ratio and a prominent partial volume effect due to thick slices. We are developing a framework for increasing the resolution of the low-resolution clinical CTI images. The method uses a maximum likelihood strategy to account for the noise and an anisotropic regularization prior to promote smoothness in homogeneous areas while respecting edges. The technique is called Higher Resolution Tensor Estimation and it uses a single clinical acquisition to produce high resolution tensor images. We aim to replace resampling techniques used for tensor normalization in population based studies, with the present method. The method itself along with quantitative results on tractography 2 were presented in MICCAI 2013 [45].

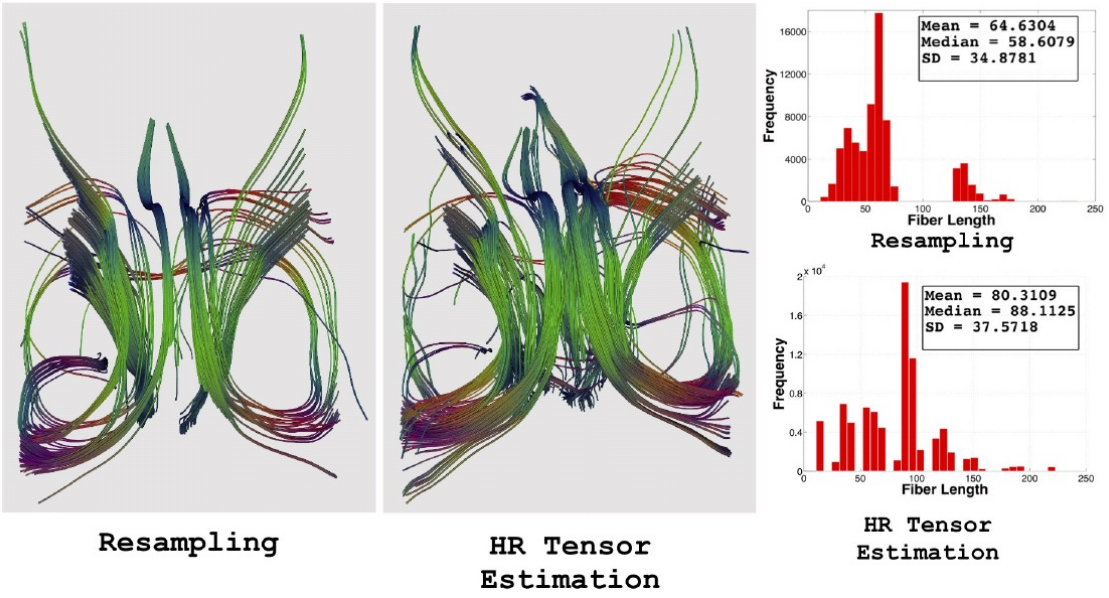

Figure 2. Middle column shows a comparatively dense fiber bundle in the fornix region for the Higher Resolution Tensor Estimation method (superior-inferior view) compared to tensor resampling (left column). Right column shows a quantitative comparison of fiber lengths.

5.1.5. 3D/2D coronary arteries registration

Participants: Thomas Benseghir [Correspondant], Grégoire Malandain, Régis Vaillant [GE-Healthcare], Nicholas Ayache.

This work is done in collaboration with GE-Healthcare (Buc).

3D/2D registration; computed tomography angiography; CTA; X-ray fluoroscopy; coronary arteries

Endovascular treatment of coronary arteries involves catheter navigation through patient vasculature. Projective angiography guidance is limited in the case of chronic total occlusion where the occluded vessel can not be seen. Integrating standard preoperative CT angiography information with live fluoroscopic images addresses this limitation but requires alignment of both modalities.

We published the Iterative Closest Curve (ICC) algorithm [36] in the MICCAI 2013 conference :

- The ICC-algorithm mimics the ICP-algorithm [6], curves being considered instead of points.
- Contrary to closest point pairing, the resulting pairings assure a topological and geometrical coherence since a curve is paired to another one (cf Figure 3).
- The developed method can deal with differences in both datasets by considering outlier rejection at the level of curve and the level of point.

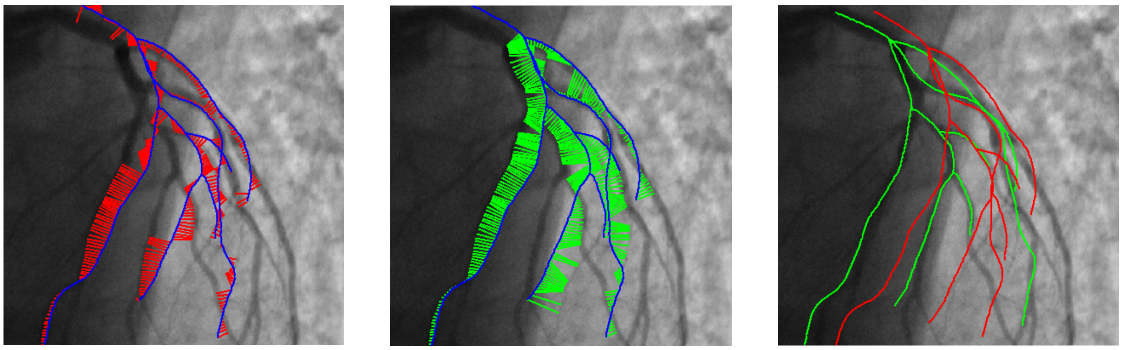

Figure 3. Left : Pairing obtained with the ICP algorithm, Middle : Pairing obtained with the ICC algorithm, Right : ICC (green) and ICP (red) registration results.

5.1.6. Automatic Registration of Endoscopic Images

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

This work is performed in collaboration with IHU Strasbourg.

Image registration; Endoscopic imaging; Biopsy Relocalization

The screening of cancer lesions in the oesophagus involves obtaining biopsies at different regions along the oesophagus. The localization and tracking of these biopsy sites inter-operatively poses a significant challenge for providing targeted treatments.

Our work [61] introduces a novel framework for accurate re-positioning of the endoscope at previously targeted sites:

- it includes an electromagnetic tracking system in the loop and provides a framework for utilizing it for re-localization inter-operatively.
- We have shown on three in-vivo porcine interventions that our system can provide accurate guidance information, which was qualitatively evaluated by five experts.

[6] P.J. Besl and N.D. McKay. A method for registration of 3-D shapes

5.2. Biological Image Analysis

5.2.1. Pre-clinical molecular imaging: motionless 3D image reconstruction in micro-SPECT

Participants: Marine Breuilly [Correspondant, Inria], Grégoire Malandain [Inria], Nicholas Ayache [Inria], Jacques Darcourt [UNS-CAL], Philippe Franken [UNS-CAL], Thierry Pourcher [CEA].

This work is jointly conducted with the Transporter in Imagery and Oncologic Radiotherapy team (TIRO, CEA-CAL-UNSA) located in Nice.

SPECT/CT, small animal, respiratory motion, respiratory gating, 4D images, stomach, 99mTc-pertechnetate biodistribution, compartmental analysis

This work has been conducted on SPECT images acquired with a small animal device. Dynamic SPECT images provide functional information targeted by a specific radiotracer (99mTc-pertechnetate) that permit the tracking and quantifying of evolving phenomena.

- Respiratory motion induces an artificial enlargement of the moving structures (tumours, organs) in SPECT images, and biases the quantification.
- A full ad-hoc method was presented that allows the reconstruction of a single 3D SPECT image without motion artefacts [37], [6], [1].

5.2.2. Pre-clinical molecular dynamic imaging: ^{99}mTc-pertechnetate biodistribution model of murine stomach with micro-SPECT

Participants: Marine Breuilly [Correspondant, Inria], Grégoire Malandain [Inria], Nicholas Ayache [Inria], Jacques Darcourt [UNS-CAL], Philippe Franken [UNS-CAL], Thierry Pourcher [CEA].

This work is jointly conducted with the Transporter in Imagery and Oncologic Radiotherapy team (TIRO, CEA-CAL-UNSA) located in Nice.

SPECT/CT, small animal, 4D images, stomach, ^{99}mTc-pertechnetate biodistribution, compartmental analysis

Using the coupled SPECT and CT device dedicated to small animals, functional information targeted by a specific radiotracer (^{99}mTc-pertechnetate) can be imaged dynamically.

- ^{99}mTc-pertechnetate is an iodide analog related to the NIS gene. Thus iodide uptake kinetics can be studied through the study of ^{99}mTc- pertechnetate biodistribution.
- Dynamic SPECT images exhibit a progressive accumulation of ^{99}mTc-pertechnetate in the stomach wall and diffusion in the stomach cavity.
- A first simplified model for stomach ^{99}mTc-pertechnetate biodistribution was proposed and studied with a compartmental analysis approach using a simplified two-compartment (stomach wall and cavity) model with one input (blood) (see Figure 4) [1].
- Time activity curves of each compartment were obtained from dynamic images thanks to an original layer-based decomposition of the stomach [1].
- The first estimation of the model transfer parameters K_{ij} was performed by numerically solving the inverse problem [1].

5.3. Computational Anatomy

5.3.1. Longitudinal brain morphometry: statistical analysis and robust quantification of anatomical changes

Participants: Marco Lorenzi [Correspondant], Xavier Pennec, Nicholas Ayache.

Longitudinal analysis, Alzheimer's Disease, non-linear registration, brain morphometry

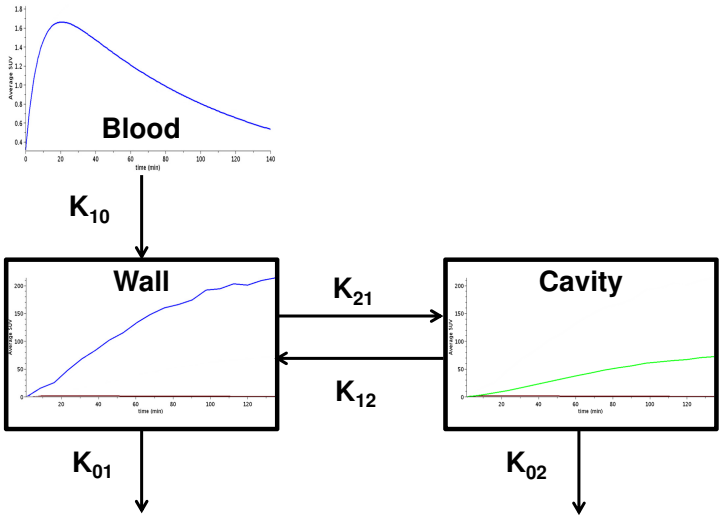

Figure 4. Simplified two-compartment model of ^{99}mTc-pertechnetate biodistribution in murine stomach with time-activity curves for each compartment.

This project is based on the PhD thesis defended in 2012 by Marco Lorenzi, and aims at developing robust and effective instruments for the analysis of longitudinal brain changes, with special focus on the study of brain atrophy in Alzheimer's disease. The project relies on the analysis of follow-up magnetic resonance images of the brain by means of non-linear registration. During 2013 the main scientific achievements were the following:

- We developed and distributed the LCC-logDemons, an accurate and robust diffeomorphic non-linear registration algorithm [14], [16]. The algorithm implements the symmetric Local Correlation Coefficient (LCC) and is suited for both inter and intra-subject registration. The software is freely available for research purposes here.
- We investigated the problem of comparing the trajectories of longitudinal morphological changes estimated in different patients. Based on our previous work on parallel transport in diffeomorphic registration, we proposed the "pole ladder" for the efficient normalization of longitudinal trajectories in a common reference space [15], [48].
- We defined an effective framework for the statistical analysis of longitudinal brain changes in clinical groups. The proposed framework enabled the characterization of abnormal morphological changes in healthy subjects at risk for Alzheiemer's disease [46].
- We addressed the multi-scale analysis of longitudinal volume changes encoded by deformation fields. We provided a probabilistic framework for the consistent definition of anatomical regions of longitudinal brain atrophy across spatial scales, in order to robustly quantify regional volume changes in populations or in single patients. The framework was applied to the longitudinal analysis of group-wise atrophy in Alzheimer's disease (Figure 5), and to the tracking and quantification of treatment efficacy on brain tumors [47].

5.3.2. Longitudinal Analysis and Modeling of Brain Development during Adolescence

Participants: Mehdi Hadj-Hamou [Correspondant], Xavier Pennec, Nicholas Ayache.

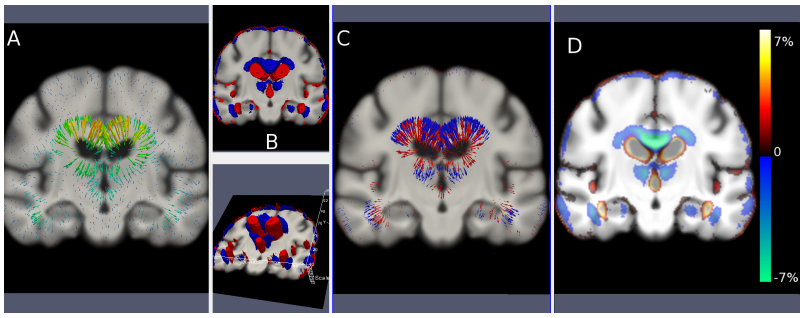

Figure 5. Group-wise scale-space analysis for the 1-year brain atrophy in 30 AD patients.

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

Brain development, adolescence, longitudinal analysis, non-rigid registration algorithm

Due to the lack of tools to capture the subtle changes in the brain, little is known about its development during adolescence. The aim of this project is then to provide quantification and models of brain development during adolescence based on non-rigid registration of longitudinal MRIs (enabling us to capture these changes). The analysis pipeline is the following (Figure 6) :

- Register each patient's pair of images in order to get access to the longitudinal changes defined by a transformation field (parameterized by a Stationary Velocity Field).
- Transport every deformation field in a common space (template) to obtain the mean scenario and quantify the changes.
- Propose simplified models of the anatomical changes occurring during adolescence abstracting the results of the analysis.

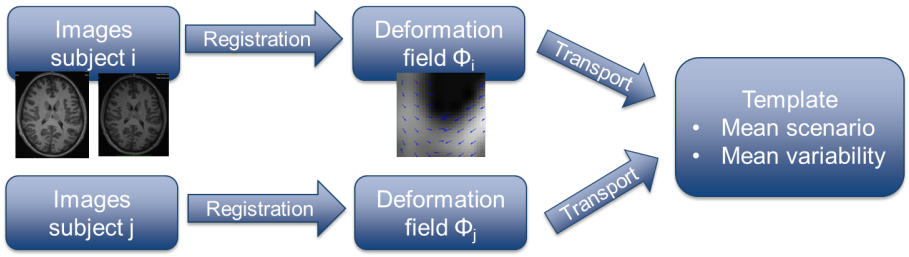

Figure 6. Pipeline for the longitudinal analysis of brain development during adolescence.

5.3.3. Reduced-Order Statistical Models of Cardiac Growth, Motion and Blood Flow

Participants: Kristin Mcleod [Correspondant], Maxime Sermesant, Xavier Pennec.

This work was partially funded by the EU projects Care4me (ITEA2) and MD-Paedigree (FP7).

Statistical analysis, image registration, Demons algorithm, reduced models, CFD, Polyaffine, cardiac motion tracking

This work involves developing reduced models of cardiac growth, motion and blood flow, with application to the Tetralogy of Fallot heart [28].

- Extending the 2012 reduced order model of cardiac motion based on a polyaffine log-demons registration proposed at the 2012 STACOM MICCAI workshop, an additional cardiac-specific prior was added to the model to give more physiologically meaningful weight functions. Using this method, the trace of the affine matrix per region was plotted over time to establish differences between healthy subjects and asynchronous heart failure patients. The method and results were presented at the 2013 FIMH conference [52].
- Going further in analysing the affine parameters per region, statistical methods were applied to the registration parameters of the method proposed at the 2012 STACOM MICCAI workshop [50]. By applying principal component analysis to the transformation parameters stacked either column-wise or row-wise, population-based descriptors of motion in terms of the temporal or spatial components were obtained. The method was applied to 15 healthy subjects and 2 heart failure patients and presented at the 2013 MICCAI conference [51].
- The analysis of a statistical model for reduced blood flow simulations in the pulmonary artery proposed in the 2010 STACOM workshop was extended to a journal version [10], [64]. The previous work was extended to re-solve the obtained pressure and velocity bases for the subject-specific geometry by solving the Navier Stokes equations on the reduced bases. The method was applied to a data-set of 17 Tetralogy of Fallot patients.

5.3.4. Geometric Statistics

Participants: Xavier Pennec [Correspondant], Nina Miolane, Christof Seiler [Stanford], Susan Holmes [Stanford].

This work is partly funded through a France Stanford collaborative project grant (2013-2014).

Statistics, manifolds, Lie groups

The study of bi-invariant means on Lie groups [53] was further pushed by looking for the conditions of existence of bi-invariant semi-Riemannian metrics, thus relaxing the positivity constraint of Riemannian metrics [4]. This idea was based on the fact that such a bi-invariant semi-Riemannian metric exists of SE(3). Unfortunately, this does not generalize to higher dimensions. Other results on geometric statistics on regions for in the context of group-valued trees for deformation analysis were presented in [55].

5.4. Computational Physiology

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

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

Alzheimer's Disease (AD), modeling atrophy, bio-physical model, simulation

We have implemented a 3D bio-physical model for the deformation of the brain with Alzheimer's Disease (AD).The model produces a deformation field of the brain when a known distribution of local volume change (atrophy) is given as the input. The obtained deformation is then used to warp the original 3D MR image. The major contribution of this work corresponds to the block "Brain Deformation" in Figure 7.

5.4.2. Registration of time series of cardiac images

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

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

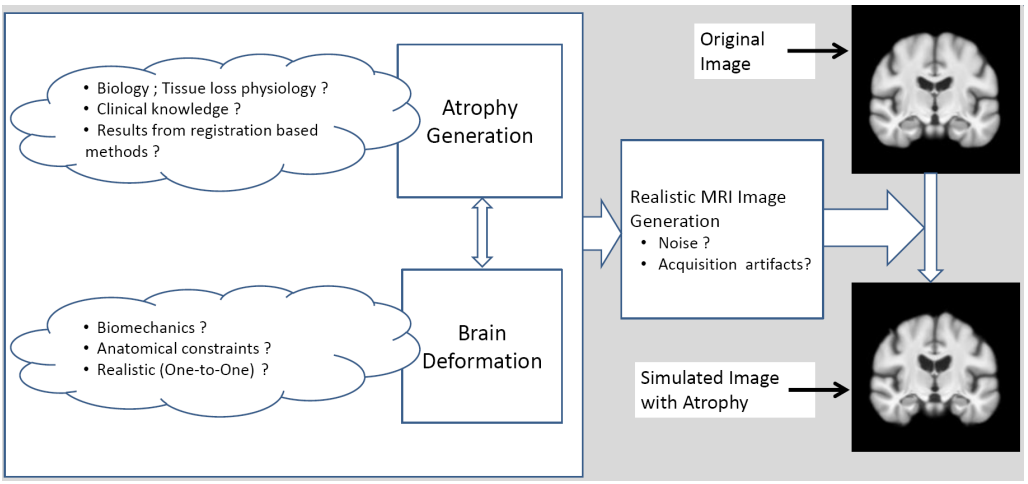

Figure 7. Modeling and simulation of longitudinal brain MRIs with atrophy in Alzheimer's Disease

Registration, Automatic Relevance Determination, Magnetic resonance, 3D-US

- We developed a generic approach to registration building on the framework of Automatic Relevance Determination. We applied this framework to the tracking of heart motion throughout time series of images from cine-MR, tagged-MR and 3D-US modalities.
- Our approach allows for the joint determination of model parameters, such as noise and regularization parameters, decreasing the need for manual tuning and preprocessing. Moreover, it is suitable for further analysis of uncertainty in the output of the registration.

Figure 8. An instance of motion tracking on a cine MR frame. (Left) Mesh contour propagated to end systole via the registration output (Right) Computed displacement field.

5.4.3. Real-Time Cardiac Electrophysiology Computing for Training Simulator

Participants: Hugo Talbot [Correspondant], Hervé Delingette, Stephane Cotin, Maxime Sermesant, Christian Duriez.

This work was performed in collaboration with the SHACRA team in Lille.

Cardiac electrophysiology simulation, Cryoablation simulation, SOFA framework, GPU computing, patient-specific study

- Cardiac arrhythmia is a very frequent pathology that comes from abnormal electrical activity in the myocardium. This work aims at developing a training simulator for cardiologists in the context of catheterization and thermo-ablation of these arrhythmias. After tackling the issue of fast electrophysiology computation [27], a first version of our training simulator was proposed which combines virtual catheterization and interactive GPU electrophysiology modeling [70]. This year, the simulator has been improved by tackling the issue of interactive catheter navigation inside a moving venous system and a beating heart [70]. The simulator was demonstrated during the VRIPHYS 2013 workshop in Lille and the Inria-industry meeting in Paris. Personalization of the electrophysiological model using the data assimilation library Verdandi has been initiated.

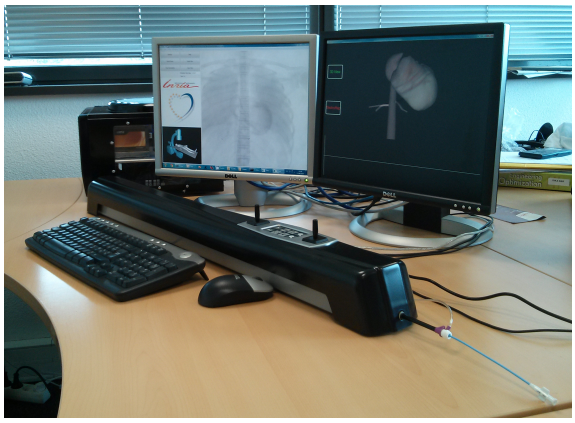

Figure 9. Setup of our simulator dedicated to thermo-ablation for cardiac electrophysiology.

- Cryotherapy simulation in collaboration with the IHU Strasbourg has been performed. This technique consists in inserting needles that freeze the surrounding tissues, thus immediately leading to cellular death of the tissues. We built a simulator able to place the cryoprobes and run a simulation representing the evolution of iceballs in living tissues [58].

5.4.4. Personalized model of the heart for cardiac therapy planning

Participants: Stéphanie Marchesseau [Correspondant], Maxime Sermesant, Hervé Delingette, Nicholas Ayache.

This work is performed in the context of the PhD of Stéphanie Marchesseau in collaboration with St Thomas Hospital in London and was partially funded by ERC MedYMA.

- Personalization of the mechanical function of the heart from time series of cardiac images has been achieved by combining global calibration of a few global parameters [18] with estimation of regional contractility parameters [17] using data assimilation techniques.
- Personalized cardiac models were used to create synthetic images [22] of cardiac motion thus allowing the benchmarking of motion tracking algorithms [8], [39].

5.4.5. Cardiac Arrhythmia Radio-frequency Ablation Planning

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

This work is performed in the context of the PhD of Rocío Cabrera Lozoya in collaboration with the CHU LIRYC Bordeaux and is funded by ERC MedYMA.

- Biophysical model development for the prediction of radio frequency ablation sites for ventricular tachycardias.
- Target site map generation for ablation therapy guidance
- Structural and functional characterization of target sites using 3D imaging and EP measurements through machine learning algorithms.
- Prediction validation with acquired clinical data

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

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

This PhD is carried out jointly between the Asclepios research group, Inria Sophia Antipolis, France and the Image Analytics and Informatics global field, Siemens Corporate Research, Princeton, USA.

Radio Frequency Abation, Patient-Specific Simulation, Lattice Boltzmann Method, Computational Fluid Dynamics, Heat Transfer, Therapy Planning, Liver

- In order to obtain a computational framework for patient-specific planning of radiofrequency ablation, a patient-specific detailed anatomical model of the liver has been extracted from a standard CT image and then meshed with tetrahedra. The structures of interest include : parenchyma, lesion, hepatic vein and vena cava.
- A computational fluid dynamic model is used to estimate the patient-specific blood flow in the hepatic circulatory system. It was combined with a porous media model to compute the patient-specific blood flow distribution inside the parenchyma using the results of the CFD solver (pressures).
- Bio-heat equations and a cell death model to account for cellular necrosis have been implemented with FEM using SOFA and a Lattice Boltmann Model to model heat propagation in biological tissues [35] leading to improved accuracy and computational efficiency.

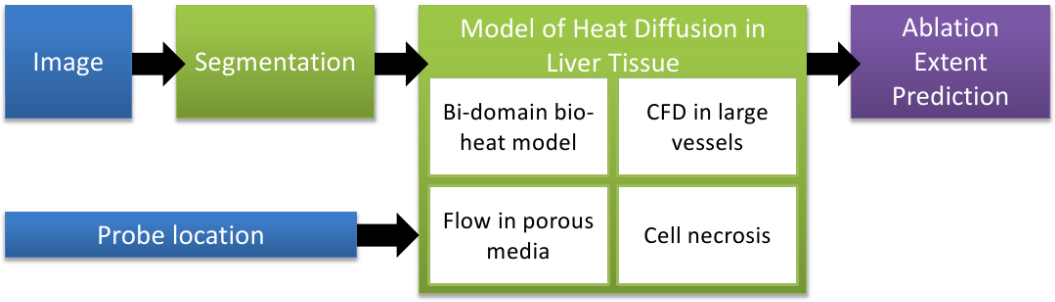

Figure 10. Steps of the proposed method (blue: input, green: processes, purple: output).

5.4.7. Tumor growth assessment based on biophysical modeling

Participants: Erin Stretton [Correspondant], Bjoern Menze, Nicholas Ayache, Hervé Delingette.

This work was carried out during the Phd of Erin Stretton and was funded by the Care4Me project. It was performed in collaboration with Pr Mandonnet, Lariboisière hospital in Paris, and the German Cancer Research Center (DKFZ)

Glioma simulation, tumor growth.

We aim at developing image analysis methods [23] using tumor growth models in order to guide the planning of therapies (surgical removal and chemotherapy) for brain cancer (glioma) patients. Our work is focused on these objectives :

- Predicting the location of glioma recurrence after a resection surgery;
- Determining the description the of tumor cell diffusion tensor in white matter (patient-based, atlas based or isotropic) which leads to the most accurate results for predicting future tumor growth [57];
- Comparing tumor growth speeds between 8 patient cases based on biophysical modeling and various manual methods.

5.4.8. Brain tumor growth modeling : Application to radiation therapy

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

This work is carried out between Asclepios research group, and the Department of Radiation Oncology of the Massachusetts General Hospital, Boston, USA. Part of this work was funded by the European Research Council through the ERC Advanced Grant MedYMA.

Glioma simulations, radiation therapy, target delineation, vasogenic edema

- We developed a tumor growth model for high grade gliomas, based on different types of cell and the vascularization of the brain.
- We studied multimodal brain tumor images to evaluate tumor infiltration.
- We used a Fisher-Kolmogorov model to improve target volume delineation for radiation therapy (see Figure 11)

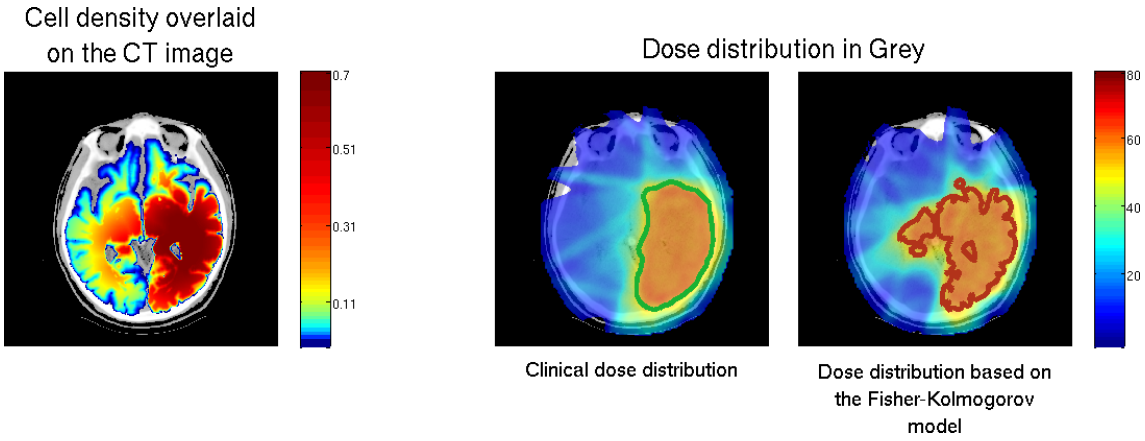

Figure 11. Comparison of the dose distribution (in Grey) clinically delivered and based on the Fisher-Kolmogorov model.

5.4.9. Multimodal patch-based glioma segmentation

Participants: Nicolas Cordier [Correspondant], Bjoern Menze, 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, Tumor Simulation

- A patch-based approach was developed for glioma segmentation based on multi-channel 3D MRI. The method is fully automatic and does not require any learning step.
- Features: multi-channel MR intensities in local neighborhoods.
- A heuristic label fusion strategy was introduced and showed promising results, as shown in Figure 12.
- The algorithm was ranked 5th in the Brain Tumor Segmentation Challenge (BraTS) at MICCAI 2013 [67].
- Large unlabeled glioma MRI databases are being incorporated in the framework.

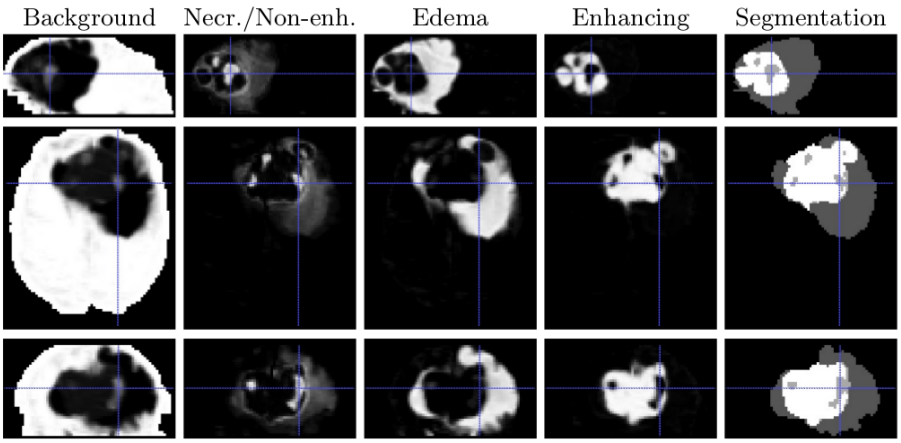

Figure 12. Real high-grade case. From left to right: Vote maps for background, necrosis and non-enhancing tumor (merged), edema, enhancing tumor; Segmentation map. From top to bottom: saggital, axial, and coronal views.

6. Bilateral Contracts and Grants with Industry

6.1. Inria - Mauna Kea Technologies I-Lab SIWA

6.1.1. Inria - Mauna Kea Technologies I-Lab SIWA

Participants: Nicholas Ayache [Correspondant], Xavier Pennec, Irina Vidal-Migallón, Marzieh Kohandani Tafreshi, Julien Dauguet, Tom Vercauteren, Barbara André.

GPU, registration, OpenCL

The I-Lab SIWA (Stitching Images and Wisdom into the Atlas) aims at maturating two key image processing technologies into real products for confocal fibered-microscopy. The first axis on content-based image retrieval (CBIR) will develop efficient and friendly tools for helping diagnosis and for user training. The second axis on image registration will develop near real-time and robust image registration tools for mosaicking, image stabilization and super-resolution. Both goals are built on GPU implementations of widely used algorithms (e.g. [33]).

For more information, see here.

6.2. CIFRE PhD Fellowships

6.2.1. General Electric

The work of Thomas Benseghir, *3D/2D Coronary Registration for Interventional Cardiology Guidance*, is supported by a PhD fellowship from the General Electric company.

6.3. Other contracts

The contracts Cancéropôle PACA, Philips, and Siemens are described in our previous activity reports.

6.4. Creation of spin-off company Therapixel

Therapixel is a spin-off of the Asclepios (Inria Sophia Antipolis) and Parietal (Inria Saclay) project teams. It was founded in June 2013 by a team of 11 partners and the IT-Translation investment fund. Therapixel makes information systems for image guided therapy designed for operating theaters: interventional radiology or surgery. 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 that sterility constraints made impractical in the past. It also opens up new opportunities for image guided surgery and allows for more integration in the management of digital information before, during and after intervention.

Two prototypes are undergoing testing for 18 months at the Centre Antoine Lacassagne (interventional radiology) and the University Hospital of Nice (neurosurgery). The development started in 2011 as a specialisation of the MedInria software. From early 2012, a dedicated team composed of 2 researchers and 3 engineers worked on the project. Therapixel received 2 awards at the OSEO national contest for the creation of start-up companies.

6.5. National initiatives

6.5.1. Consulting for Industry

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

6.5.2. Collaboration with national hospitals

Asclepios is collaborating with the following 3 IHU (University Hospital Institute) in France : the IHU-Strasburg (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 Salpétriére (Dr. O. Colliot and S. Durrleman) on neuroimaging.

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

Asclepios is part of the EQUIPEX MUSIC with Bordeaux University Hospital in order to build an XMR interventional room equipped with a medInria workstation.

7. Partnerships and Cooperations

7.1. European Initiatives

7.1.1. FP7 Projects

7.1.1.1. VPH NOE

Participants: Maxime Sermesant [correspondant], Moulay Fadil, Florian Vichot, Nicholas Ayache.

medinria registration toolbox VPH NOE standards

Title: VPH NoE

Type: COOPERATION (ICT)

Defi: Virtual Physiological Man

Instrument: Network of Excellence (NoE)

Duration: June 2008 - November 2012

Coordinator: University College London, UK

Others partners: Core members include UCL (UK), Oxford (UK), CNRS (FR), ULB (BE), U. of Nottingham (UK), UPF (ES), U. Auckland (NZ), EMBL (DE), U. Sheffield (UK), Karolinka (SE), ERCIM (FR), IOR (IT).

See also: http://www.vph-noe.eu/

Abstract: The Virtual Physiological Human Network of Excellence (VPH NoE) is a EU seventh Framework funded project, working to connect and support researchers in the VPH field within Europe and beyond. Inria is one of the core members, and is mostly dedicated, through Asclepios, to the data fusion part of the VPH toolkit. More precisely, a registration toolbox has been delivered which aims at including registration algorithms from the team and elsewhere in the new version of medInria (2.x). During the extension of the project through 2013, we participated in a hackfest on software interoperability (May 20-24, 2013 in Kingston, Canada and Nov 4-8, 2013 in London, UK).

7.1.1.2. MedYMA

Title: Biophysical Modeling & Analysis of Dynamic Medical Images

Type:ERC

Instrument: ERC Advanced Grant (Advanced)

Duration: April 2012 - March 2017

Coordinator: Inria (France)

See also: http://www.inria.fr/en/centre/sophia/news/medical-imagery-and-i.t.-the-personalised-digital-patient

Abstract: During the past decades, exceptional progress was made with in vivo medical imaging technologies for capturing the anatomical, structural and physiological properties of tissues and organs in a patient, with an ever increasing spatial and temporal resolution. The physician is 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 changes which can have a vital impact on the patient's health. To change this situation, this proposal introduces a new generation of computational models for the simulation and analysis of dynamic medical images. Thanks to their generative nature, they will allow the construction of databases of synthetic, realistic medical image sequences simulating various evolving diseases, producing an invaluable new resource for training and benchmarking. Leveraging their principled biophysical and statistical foundations, these new models will bring remarkable added clinical value after they are 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 future evolution (computer aided prognosis), and to precisely simulate and monitor an optimal and personalized therapeutic strategy (computer aided therapy). First applications will concern high impact diseases including brain tumors, Alzheimer's disease, heart failure and cardiac arrhythmia and will open new horizons in computational medical imaging.

7.1.1.3. MD PAEDIGREE

Type: COOPERATION

Defi: ICT for Health

Instrument: Integrated Project

Objectif: validating and advancing patient-specific, computer-based predictive models of six paediatric pathologies into clinical acceptance.

Duration: March 2013 - February 2017

Coordinator: Ospedale Pediatrico Bambino Gesu, Rome, Italy.

Partners: Siemens AG (DE), Siemens SCR (USA), Maat France (FR), MOTEK (NL), EMP (DE), VUmc (NL), Lynkeus (IT). Universities: KU Leuven (BE), Fraunhofer (DE), UMC Utrecht (NL), TU Delft(NL), Sheffield (UK), Athens (GR), Genoa (IT), Transilvania din Brasov (RO); Hospitals: OPBG (Roma, IT), Gaslini (Genoa, IT), GOSH/UCL (London, UK), JHU (Baltimore, USA).

See also: http://www.md-paedigree.eu/

Inria contact: Xavier Pennec

Abstract: MD-Paedigree is a clinically-driven and strongly VPH-rooted project, where 7 world-renowned clinical centres of excellence pursue improved interoperability of paediatric biomedical information, data and knowledge by developing together a set of reusable and adaptable multi-scale models for more predictive, individualised, effective and safer paediatric healthcare, being scientifically and technologically supported by one of the leading industrial actors in medical applications in Europe operating in conjunction with highly qualified SMEs and some of the most experienced research partners in the VPH community.

MD-Paedigree validates and brings to maturity patient-specific computer-based predictive models of various paediatric diseases, thus increasing their potential acceptance in the clinical and biomedical research environment by making them readily available not only in the form of sustainable models and simulations, but also as newly-defined workflows for personalised predictive medicine at the point of care. These tools can be accessed and used through an innovative model-driven infostructure powered by an established digital repository solution able to integrate multimodal health data, entirely focused on paediatrics and conceived of as a specific implementation of the VPH-Share project, planned to be fully interoperable with it and cooperating, through it, also with p-Medicine.

MD-Paedigree's goals are to integrate and share highly heterogeneous biomedical information, data and knowledge, using best practices from the biomedical semantic Web; develop holistic search strategies to seamlessly navigate through and manage the integrative model-driven infostructure and digital repository; jointly develop reusable, adaptable and composable multi-scale VPH workflow models, support evidence-based translational medicine at the point of care, and ultimately facilitate collaborations within the VPH community.

7.1.1.4. VP2HF

Type: COOPERATION

Defi: ICT for Health

Instrument: Specific Targeted Research Project

Objectif: New Patient Management for Heart Failure using Modelling

Duration: October 2013 - September 2016

Coordinator: King's College London (UK)

Partner: Philips Research Hamburg (DE), Universitat Pompeu Fabra (SP), Inria, French National Research Institute in Informatics and Mathematics (FR), Université Catholique de Louvain (BE), Caen University Hospital (FR), Philips Research Paris (FR), Simula Research Laboratory (NO), Centron Diagnostics (UK)

Inria contact: Dominique Chapelle

Abstract: 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 the 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 in 200 patients (including 50 historical datasets) across 3 clinical sites, including a prospective clinical study in 50 patients in the last year of the project. The key innovations in VP2HF that make it likely that the project results will be commercially exploited and have major clinical impact are: 1) all tools to process images and signals, and 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; and 2) by utilising a decision tree stratification approach, only the appropriate parts of the tool chain, that will add maximum value to the predictions, 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 results of substantial improved efficacy of decision making over current guidelines, and 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.

7.1.2. Collaborations in European Programs, except FP7

7.1.2.1. Care4Me

Participants: Xavier Pennec [Correspondant], Nicholas Ayache, Hervé Delingette, Kristin Mcleod, Erin Stretton, Maxime Sermesant, Marco Lorenzi.

Program: ITEA2

Project acronym: Care4Me

Project title: Cooperative Advanced REsearch for Medical Efficiency

Duration: September 2009 - September 2013

Coordinator: Philips, NL.

Other partners: Alma (ES), Bull (FR), CEA (FR), CIMNE (ES), Compasiss (ES), CVSS (ES), Duodecim (FI), Erasmus MC (NL), ESI (NL), HSP (ES), Helsinki Hosp. (FI), ISI (GGR), LUMC (NL), MediConsult (FI), MEDIS (NL), Nokia (FI), Philips (NL), Pie Medical Imag. (NL), Pohjola (FI), Prowellness (FI), Robotiker (ES), UMC (NL), VTT (FI)

Abstract: This project aims at increasing quality and productivity in the healthcare care cycle by using more advanced medical imaging and decision support methods while combining them with different knowledge sources, from early diagnosis to treatment and monitoring. The final outcome of this project were clinical prototypes of novel medical image analysis and decision support systems for three specific disease areas (cancer, cardio-vascular and neurodegenerative diseases), that connect to hospital information systems using a new system architecture. In this project, the role of the Asclepios team is to develop an atlas of the ageing brain and the beating heart, and to model tumor growth.

7.2. International Initiatives

7.2.1. Inria Associate Teams

7.2.1.1. CAPNEONATES

Title: Analysis of structural MR and DTI in neonates

Inria principal investigator: Bertrand Thirion [Parietal]

Asclepios investigator: Xavier Pennec

International Partner (Institution - Laboratory - Researcher):

Institution: University of Southern California (United States)

Laboratory: Image Lab at Children Hospital at Los Angeles

Researcher: Natasha Leporé

Duration: 2011 - 2013

See also: http://www.capneonates.org/

While survival is possible at increasingly lower gestational ages at birth, premature babies are at higher risk of developing mental disorders or learning disabilities than babies born at term. A precise identification of the developmental differences between premature and control neonates is consequently of utmost importance. Nowadays, the continuously improving quality and availability of MR systems makes it possible to precisely determine, characterize and compare brain structures such as cortical regions, or white matter fiber bundles. The objective of this project is to understand the developmental differences between premature and normal neonates, using structural and diffusion MRI. This work consists in identifying, characterizing and meticulously studying the brain structures that are different between the two groups. To do so, we join forces with the Parietal team at Inria and the University of Southern California. Parietal has a recognized expertise in medical image registration and in statistical analyses of groups of individuals. USC has a broad knowledge in MR image processing. In particular, the Children's Hospital at Los Angeles (CHLA), which is part of USC, is in the process of collecting a unique database of several hundred MR scans of premature and normal neonates. This joint collaboration consequently offers a unique chance of addressing key questions pertaining to neonatal and premature development. It will make it possible to elaborate new tools for analyzing neonate MR images while tremendously increasing our knowledge of neuroanatomy at an early stage in life.

7.2.2. Inria International Partners

7.2.2.1. Declared Inria International Partners

7.2.2.1.1. Stanford, Statistics Department

France Stanford collaborative project grant (2013-2014):*Understanding Lower Back Pain through Geometric Statistical Analysis of computed tomography (CT) Images*. Stanford, Statistics Dept & Nice Univ. Hospital. Principal investigators X. Pennec (Inria) and S. Holmes (Stanford). Collaboration on statistics on group-valued trees and geometric subspace learning [55].

7.2.2.2. Collaboration with international hospitals

7.2.2.2.1. 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.

7.2.2.2.2. 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. Matthieu Lê spent 2013 in the department of Radiation Physics at MGH.

7.2.2.2.3. Other International Hospitals

Collaborations with several other European hospitals have been established through the European projects VP2HF, Care4Me and MD PAEDIGREE.

8. Dissemination

8.1. Scientific Animation

8.1.1. Journal editorial boards

N. Ayache is the co-founder and the Co-Editor in Chief with J. Duncan (Professor at Yale) of *Medical Image Analysis* [7]. This scientific journal was created in 1996 and is published by Elsevier.

N. Ayache is Associated Editor of *IEEE Transactions on Medical Imaging* [8] 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) and of the SIAM *Journal on Imaging Sciences (SIIMS)*.

8.1.2. Participation in the organization of conferences

H. Delingette was area chair of the MICCAI 2013 conference held in Nagoya, program committee member of the International Symposium on Biomedical Imaging (ISBI'12), the conference on Virtual Reality Interactions and Physical Simulation (VRIPHYS'13), the MICCAI Workshop on Mesh Processing in Medical Image Analysis (MeshMed'13), the conference on Functional Imaging and Modeling of the Heart (FIMH'13).

X. Pennec was the general chair of the MICCAI workshop MFCA'13 (Mathematical Foundations of Computational Anatomy), which was held at Nagoya (JP) on Sept. 22; area chair of the MICCAI 2013 conference held in Nagoya (JP), Sept. 23-25; member of the paper selection committee of IMPI 2013 (Information processing in Medical Images), Asilomar, CA, USA, June 28, July 3rd, 2013; member of the program committees of: MICCAI 2013; GSI 2013 (Geometric Science of Information), Paris, FR, August 28-30, 2013; Workshop on computational diffusion MRI (CDMRI'13).

M. Sermesant was a co-organizer of the MICCAI 2013 Workshop on Statistical Atlases and Computational Models of the Heart and the medInria hands-on workshop.

8.1.3. Scientific animation

Nicholas Ayache is member of the Aviesan national alliance on biosciences. He is also a member of the "Comité de la Recherche Biomédicale en Santé Publique (CRBSP)" of the Nice hospitals since 2008. He was invited to Fukuoka, Japan in February 2012 to evaluate a national program on "Computational Anatomy" funded by the MEXT.

Xavier Pennec has been a member of the MICCAI Society Board of Directors for the period 2012-2016 and of the Doctoral follow-up Commitee (CSD) at Inria Sophia Antipolis since 2010. In 2013, he was an evaluator for the European Research Concil (math panel), the Council of Physical Science of the Netherlands Organisation for Scientific Research (NWO), for several project proposals submitted to the French research agency ANR.

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. He was an evaluator for the integrated European project ARTREAT, for the Austrian center of excellence ACMIT, for several project proposals submitted to the French research agency ANR, to the National Commission for Scientific and Technological Research of the Government of Chile (CONICYT). He was involved

[7] http://www.elsevier.com/wps/find/journaleditorialboard.cws_home/620983/editorialboard
[8] http://www.ieee-tmi.org/

in the redaction of the report for the evaluation of Inria Sophia Antipolis research center by the national evaluation agency (AERES). He was the coordinator for the national evaluation of the Inria theme "Computational Medicine and Neuroscience" by the Inria evaluation committee and a panel of experts.

M. Sermesant acted as an evaluator for the ANR, CNRS and the Dutch and UK Research Councils. He is a member of the Medical Simulation Working Group of Aviesan, CUMIR (local committee representing the users of computer services) and of the CCC (local committee in charge of the selection of funding for courses and conferences organisation). He also participates in scientific animation in high schools, presenting research and medical imaging (2 times in 2013).

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

Master 2 MVA and École Centrale de Paris. H. Delingette and X. Pennec are jointly responsible for 2 modules on medical imaging (formation and analysis of medical images) (45 hours of lectures) at the Master MVA of ENS Cachan "Mathematiques, Vision et Apprentissage". The second module is common to the 3rd year of Ecole Centrale Paris.

Master CBB - Computational Biology and Biomedicine, Univ. Nice-Sophia-Antipolis. X. Pennec is responsible for a 21h module on Computational Anatomy and Physiology, with the participation of H. Delingette (9h)

Diplôme Inter Universitaire - Radiothérapie externe Haute Technicité, Univ. Nice-Sophia-Antipolis. X. Pennec gave a 1 h course.

8.2.2. Supervision

8.2.2.1. PhD defended in 2013

1. Marine Breuilly, *Imagerie TEMP 4D du petit animal - Estimation du Mouvement Respiratoire et de la Biodistribution de l'Iode*. Nice Sophia-Antipolis University, November 2013, [1].
2. Ezequiel Geremia, *Spatial random forests for brain lesions segmentation in MRIs and model-based tumor cell extrapolation*. Nice Sophia-Antipolis University, January 2013, [2].
3. Stephanie Marchesseau *Simulation de modèles personnalisés du coeur pour la prédiction de thérapies cardiaques*. Ecole des Mines de Paris, January 2013, [3].
4. Kristin Mc Leod, *Modeling of Cardiac Growth and Deformation from Medical Images*. Nice-Sophia Antipolis University, November 2013.
5. Adityo Prakosa, *Analysis and simulation of multimodal cardiac images to study the heart function*. Nice-Sophia Antipolis University, January 2013, [5].

8.2.2.2. Current PhDs

1. Chloé Audigier, *Modeling radio-frequency ablation for the planning of abdominal tumors resection*, Nice Sophia-Antipolis University. Started in April 2012.
2. Thomas Benseghir, *3D/2D Coronary Registration for Interventional Cardiology Guidance*, Nice Sophia-Antipolis University. Started in March 2012.
3. Rocio Cabrera Lozoya, *Radio frequency ablation planning for cardiac arrhythmia treatment through biophysical modelling and machine learning approaches*, Nice Sophia-Antipolis University. Started in February 2012.
4. Nicolas Cordier, *Simulation and Analysis and Simulation of Brain Tumors Images*, University of Lille. Started in February 2012.
5. Vikash Gupta, *Diffusion tensor imaging of the brain: towards quantitative clinical tools*, Nice Sophia-Antipolis University. Started in November 2011.

6. Mehdi Hadj-Hamou, *Biophysical modeling of the anatomical evolution of the brain*, Nice Sophia-Antipolis University. Started in September 2012.
7. Bishesh Khanal, *Modeling the atrophy of the brain in Alzheimer's disease*, Nice Sophia-Antipolis University. Started in November 2012.
8. Loic Le Folgoc, *Biophysical Personalization of Cardiac Models based on Machine Learning*, Nice Sophia-Antipolis University. Started in June 2012.
9. Jan Margeta, *Indexation of time-series 4D cardiac MR images*, Ecole des Mines de Paris. Started in March 2011.
10. 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.
11. Erin Stretton, *Modelling and simulation of brain tumor growth from time-series of 3-D MR images to improve diagnosis and therapy*, Ecole des Mines de Paris. Started in June 2010.
12. Hugo Talbot, *Simulation of Radiofrequency ablation of cardiac cells*, University of Lille. Started in September 2010.
13. Anant Vemuri, *Augmented reality for image-guided surgery*, Nice-Sophia Antipolis University. Started in 2012.

8.2.2.3. Masters Students

1. Nina Miolane: *Defining a mean on Lie groups*. MSc Quantum Fields and Fundamental Forces, Theoretical Physics Dept, Imperial College London, UK. 2013. From July 2013 to August 2013.

8.2.3. Juries

N. Ayache was supervisor of the PhD thesis of Ezequiel Geremia (University of Nice-Sophia Antipolis), co-supervisor of the PhD theses of S. Marchesseau (École des Mines de Paris)) and A. Prakosa (University of Nice-Sophia Antipolis), reviewer of the Phd thesis of R. Prevost (Univ. Paris Dauphine).

Hervé Delingette was supervisor of the Phd theses of S. Marchesseau (École des Mines de Paris) and A. Prakosa (University of Nice-Sophia Antipolis), co-supervisor of the PhD thesis of Ezequiel Geremia (University of Nice-Sophia Antipolis), reviewer of the PhD thesis committee of P-Y. Baudin (Ecole Centrale de Paris).

X. Pennec was a member of the HDR jury of Stéphanie Allassionnière, Ecole Normale Cachan (Reviewer) and to the PhD juries of Kevin Sol, U. Montpelier (Reviewer); Aymeric Stamm, U. Rennes; Fabrice Michel, U. ParisTech (Ecole Centrale) (Reviewer); Jean-Baptiste Fiot, U. Dauphine (Reviewer); Barthelemy Serres, U. Tours (President of the jury); Kristin McLeod, University of Nice-Sophia Antipolis, (Advisor).

Maxime Sermesant was co-supervisor of the PhD theses committee of S. Marchesseau (École des Mines de Paris), A. Prakosa (University of Nice-Sophia Antipolis) and Kristin McLeod (University of Nice-Sophia Antipolis). He was external examiner for the PhD viva of Robert Xi (Oxford University, UK) and Mikael Wallman (Oxford University, UK), and part of the PhD committee of Hubert Cochet MD in Radiology (Bordeaux University).

8.2.4. Invited Lectures

We only list invited talks here. Please refer to general references for regular participation in conferences with a submission process.

- **Nicholas Ayache** gave the following invited lectures:
  - at the *French-Japanese symposium on the future of surgery* in Strasbourg on December 20th 2012.
  - at the *Rank Prize Fund Symposium* on March 21th 2013 on the topic "Medical Imaging meets Computer Vision".

  - at the symposium organized for the 15th anniversary of the Imaging Science Center at Johns Hopkins University on May 18th 2013.
  - at the Ecole Centrale Paris on November 5th 2013 during the session organised around the challenges in Healthcare and Biotechnologies.
- **Hervé Delingette** gave the following invited lectures:
  - at the *MICI international workshop* held in Tokyo (Japan).
  - at the *MICCAI Workshop on Mesh Processing in Medical Image Analysis 2013* in Nagoya (Japan).
  - at the *10th VRIPHYS Workshop on Virtual Reality Interaction and Physical Simulation* in Lille, France.
  - at the session on cardiac imaging organized by the GRIC (Groupe de Recherche en Imagerie Cardiaque) during the Journées Française de radiologie in Paris.
  - at the *ORASIS conference* in Cluny (France).
- **Xavier Pennec** gave the following invited lectures:
  - IMA Annual Program Year Workshop on Topological Structures in Computational Biology, Minneapolis, US, December 9-13, 2013.
  - Advances in Matrix Functions and Matrix Equations (FUN13), Manchester, UK, April 10-12, 2013.
  - Distinguished seminar series, SCI institute, Salt-Lake City, February 13 2013.
  - Geometric Mechanics and Shape, NZMRI workshop 2013, Ohope beach, New Zealand, January 13-19, 2013.
  - Hamiltonian Dynamics Seminar, Chair of Geometric Analysis Section de Mathématiques, EPFL, Lausanne, October 9, 2013.
  - Thematic day on initial stress for geomechanical models at IFP Energies nouvelles (IFPEN), Rueil-Malmaison, Sept. 19, 2013.
- **Maxime Sermesant** was invited to give the closing lecture on "Mathematics for Healthcare" at the 34th Paediatric Cardiology Seminar organised by Necker Hospital, and gave an invited lecture on congenital cardiopathies at the "Printemps de la Cardiologie" in Marseille and an invited lecture on real-time simulation of ablation at the Atrial Fibrillation meeting in London.

8.2.5. Nominations and Prizes

- **Nicholas Ayache** received the MICCAI 2013 “Enduring Impact Award” for his scientific contributions since the inception of the conference in 1998. This award was established four years ago and was previously awarded to Ron Kikinis (Harvard Medical School), Russ Taylor (Johns Hopkins), Chris Taylor (Manchester Univ.) and Jerry Prince (Johns Hopkins). Nicholas took the opportunity to thank the team and all his collaborators.
- **Nicholas Ayache** was elected at the Collège de France to the Chair “Informatics and Computational Sciences” for the academic year 2013-2014. He will teach a course entitled “The Personalized Digital Patient: Images, Medicine and Informatics”. The course will be completed by seminars (2 of them being delivered by H. Delingette and X. Pennec), and an international Colloquium. More details to appear on the web site of the Collège de France: http://www.college-de-france.fr/site/nicholas-ayache/.
- **Tom Vercauteren** won the Young Scientist Publication Impact Award 2013 of the MICCAI Society (Oct 2012) for the paper "Symmetric log-domain diffeomorphic Registration: a demons-based approach", published at MICCAI 2008 co-authored by X. Pennec, A. Perchant, N. Ayache.

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Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] M. BREUILLY. , *Imagerie TEMP 4D du petit animal : estimation du mouvement respiratoire et de la biodistribution de l'iode*, Université Nice Sophia Antipolis, November 2013, http://hal.inria.fr/tel-00908962

[2] E. GEREMIA. , *Spatial random forests for brain lesions segmentation in MRIs and model-based tumor cell extrapolation*, Université Nice Sophia Antipolis, January 2013, http://hal.inria.fr/tel-00838795

[3] S. MARCHESSEAU. , *Simulation de modèles personnalisés du coeur pour la prédiction de thérapies cardiaques*, Ecole Nationale Supérieure des Mines de Paris, January 2013, http://hal.inria.fr/pastel-00820082

[4] N. MIOLANE. , *Defining a mean on Lie group*, Imperial College London, September 2013, http://hal.inria.fr/hal-00938320

[5] A. PRAKOSA. , *Analysis and simulation of multimodal cardiac images to study the heart function*, Université Nice Sophia Antipolis, January 2013, http://hal.inria.fr/tel-00837857

Articles in International Peer-Reviewed Journals

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[7] F. CHUNG, H. DELINGETTE. *Regional Appearance Modeling based on the Clustering of Intensity Profiles*, in "Computer Vision and Image Understanding", 2013, vol. 117, n^{o} 6, pp. 705-717 [*DOI :* 10.1016/J.CVIU.2013.01.011], http://hal.inria.fr/hal-00813880

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