Activity Report 2012

Project-Team ASCLEPIOS

Analysis and Simulation of Biomedical Images

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Medicine and Neuro-sciences

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Project-Team ASCLEPIOS

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

Creation of the Project-Team: November 01, 2005 .

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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 a more central role everyday, as well as the exploitation of the genetic information attached to each patient.

Facing the need of 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 to extract 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

- N. Ayache, H. Delingette, X. Pennec, M. Sermesant, G. Malandain, I. Strobant, A. Cortell were largely involved in the organization of the MICCAI 2012 conference (Medical Imaging Computing and Computer Assisted Interventions). The conference gathered together 1200 from more than 40 countries between October 1 to October 5, 2012 in Nice Acropolis.
- The ERC Advanced Grant MedYMA on Biophysical Modeling and Analysis of Dynamic Medical Images has started in April 2012 for a period of 5 years.
- **Stéphanie Marchesseau** received the Young Investigator award at the MICCAI 2012 conference held in Nice (Oct. 2012) for her paper [43] .
- **Hervé Lombaert** won the MCV 2012 best paper award at the MICCAI workshop on Medical Computer Vision (Oct. 2012) for his paper [39] .
- **Hervé Lombaert** has received a prize from the research fund of Québec FRQ (http://www.frq.gouv.qc.ca) as the "star research student" of the month January 2013 for his paper [14] .

BEST PAPERS AWARDS :

[43] **Cardiac Mechanical Parameter Calibration based on the Unscented Transform in Proceedings of Medical Image Computing and Computer Assisted Intervention 2012 (MICCAI)**. S. MARCHESSEAU, H. DELINGETTE, M. SERMESANT, K. RHODE, S. DUCKETT, C. ALDO. RINALDI, R. RAZAVI, N. AYACHE.

[39] **Groupwise Spectral Log-Demons Framework for Atlas Construction in Medical Computer Vision (MCV'12) MICCAI workshop**. H. LOMBAERT, L. GRADY, X. PENNEC, J.-M. PEYRAT, N. AYACHE, F. CHERIET.

[14] **Human Atlas of the Cardiac Fiber Architecture: Study on a Healthy Population in IEEE Trans. on Medical Imaging**. H. LOMBAERT, J.-M. PEYRAT, P. CROISILLE, S. RAPACCHI, L. FANTON, F. CHERIET, P. CLARYSSE, I. MAGNIN, H. DELINGETTE, N. AYACHE.

3. Scientific Foundations

3.1. Introduction

Tremendous progress has been made in the automated analysis of biomedical images during the past two decades [92]. Readers who are neophyte to the field of medical imaging will find an interesting presentation of acquisition techniques of the main medical imaging modalities in [83], [81]. Regarding the target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [79], in N. Ayache's article [87] and in the more recent syntheses [88] [92]. The scientific journals *Medical Image Analysis* [74], *Transactions on Medical Imaging* [80], and *Computer Assisted Surgery* [82] 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 [93], [107]. 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 [110], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [86], Ultrasound or Nuclear Medicine images [94].

Despite these advances and successes, one can notice that statistical models of the 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 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 the observed images and signals, but also more efficient tools to detect anomalies, predict evolutions, simulate and assess 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 the images are 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.

[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 acquisition (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 to measure for instance the direction of white matter fibers in the brain (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 subtle higher T2* signal which can be detected with sophisticated image processing techniques.

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 on the physics of image acquisition and observed tissues, as well as on 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 (e.g. MR, CT, US, PET or SPECT), the 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 [99].

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 an 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 the ways to probe much earlier the molecular anomalies that are the basis of a disease rather than to image only its end effects [111].

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 [85]). This is particularly true when dealing with *in vivo* microscopic images of cells and vessels.

Our research efforts will be focused to 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 Computational Anatomy (CA) is the modeling and analysis of biological variability of the human anatomy. Typical applications cover the simulation of average anatomies and normal variations,

[2] Multimodal acquisition consists in acquiring on the same patient images from 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.

[3] This is the case with micro-MRI, Micro-CT, Micro-US devices, and to a less extent with Micro-SPECT and Micro-PET devices.

[4] Green Fluorescent Protein.

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 [109]). Significant efforts have been made since that time to develop a theory for statistical shape analysis (one can refer to [91] for a good synthesis, and to the special issue of Neuroimage [108] for recent developments). Despite all these efforts, there is 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 [101]: 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.

3.5. 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 apparition 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], [98], [89], [105], [95]). 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 confronting the model with the available biomedical images and signals and possibly also from 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 (e.g. [106], [102]) 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 [90]:

- the first level is mainly geometrical, and addresses the construction of a digital description of the anatomy [84], essentially acquired from medical imagery;
- the second level is physical, involving mainly the biomechanical modeling of various tissues, organs, vessels, muscles or bone structures [96];
- the third level is physiological, involving a modeling of the functions of the major biological systems [97] (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].

[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.

These different levels of modeling are closely related to each other, and several physiological systems may interact together (e.g. the cardiopulmonary interaction [100]). 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 [97], [98]). 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 a 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 condition to see new ideas transformed 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 participate to the stimulation of new ideas and concepts.

4. Software

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 newer algorithms, but can also be used as an efficient prototyping tool. based on an advanced software architecture, it allows to:- create complex and evolving simulations by combining new algorithms with algorithms already included in SOFA- modify most parameters of the simulation (deformable behavior, surface representation, solver, constraints, collision algorithm, etc.) by simply editing an XML file- build complex models from simpler ones using a scene-graph description- efficiently simulate the dynamics of interacting objects using abstract equation solvers- reuse and easily compare a variety of available methods. It is mainly developed 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: Benoît Bleuzé, Florian Vichot, Hakim Fadil, Loic Cadour, Agata Krason, Maxime Sermesant [correspondant], Nicolas Toussaint.

MedInria is a free collection of softwares developed by the Asclepios research project in collaboration with the Athena, Parietal and Visages Inria research projects. It aims at providing to clinicians 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. MedInria is available for Microsoft windows XP/Vista/7, Linux Fedora Core, MacOSX, and is fully multithreaded.

The first release of Medinria 2.0 was done in April 2012.

See also the web page http://med.inria.fr.

- Version: 2.0
- Keywords: Medical Image Processing
- License: Proprietary Licence
- Type of human computer interaction: QT
- OS/Middleware: Windows - Linux - MacOSX
- Required library or software: DTI Track (Proprietary), vtkInria3D (CeCillB), Baladin (Proprietary)
- Programming language: C++

5. New Results

5.1. Medical Image Analysis

5.1.1. Brain tumor cell density estimation from multi-modal MR images based on a synthetic tumor growth model

Participants: Ezequiel Geremia [Correspondant, Inria], Nicholas Ayache [Inria], Antonio Criminisi [MSRC], Bjoern Menze [Inria,ETHZ], Marcel Prastawa [University of Utah].

Published in the proceedings of the MCV Workshop at MICCAI 2012 [36]

biophysiological tumor growth simulator, multi-variate regression random forests, gliomas, MRI

- A generative-discriminative framework is presented to learn model-based estimations of the tumor cell density
- The ground truth for tumor cell density is very hard to obtain
- A biophysiological tumor growth simulator is used to generate the ground truth tumor cell densities and associated MRIs
- A multi-variate regression random forests is trained to estimate the voxel-wise distribution of tumor cell density from input MR images
- The training data contains 500 synthetic cases and their associated ground truth generated by the brain tumor simulator
- The method was tested on 200 synthetic cases with excellent results
- The method also provided very promising results for estimating the tumor cell density on 16 clinical cases showing low grade gliomas from the DKFZ (German Cancer Research Center)

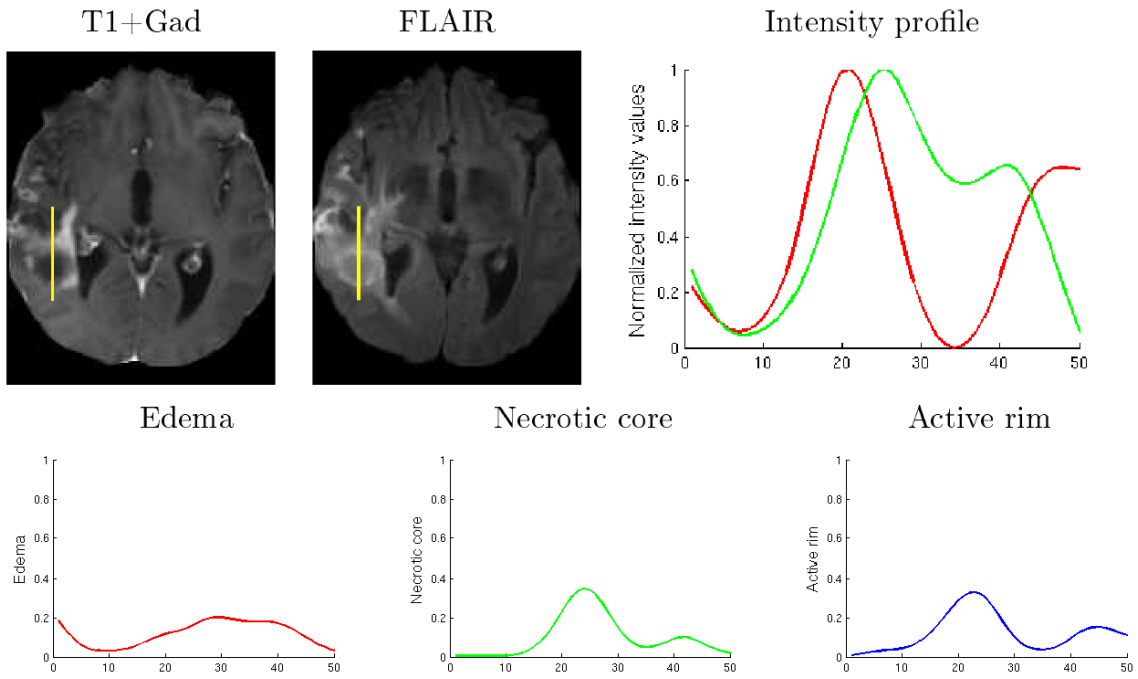

Figure 1. ***Prediction of the cell densities along a section of the tumor.*** *Top, from left to right: T1+Gadolinium, FLAIR image, the intensity profile along the section (yellow). Bottom, from left to right: prediction of the cell density for the edema, necrotic core and active rim, respectively.*

5.1.2. Automatic indexation of cardiac MR images

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

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).

Machine learning, Cardiac MR, MR preprocessing

- A generic random forest framework has been implemented and its recent modifications have been applied to a fully automatic and a semisupervised image segmentation methods, and manifold learning in cardiac MRI.
- We have performed image based cardiac function quantification from preprocessed cardiac cine MRI sequences.

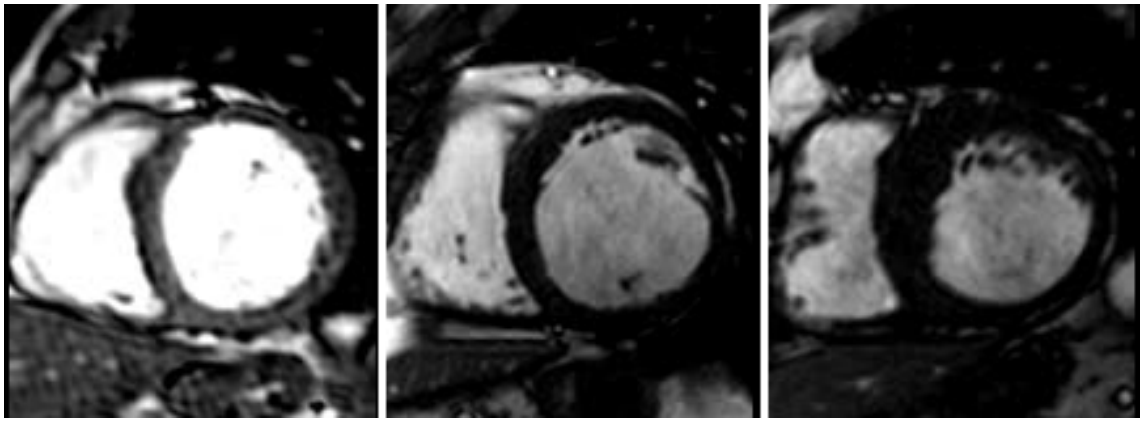

Figure 2. Three different patients with increasing (from left to right) functional deficiency of the heart.

- An image intensity standardization in magnetic resonance images method has been proposed.

5.1.3. Multimodal brain tumor segmentation

Participant: Bjoern Menze [Correspondant].

MICCAI 2012

- Further developed the generative brain tumor segmentation model
- Developed a generative-discriminative model for multimodal brain tumor segmentation
- Developed a new regularization approach for longitudinal tumor segmentation (with Guillaume Charpiat & Yuliya Tarabalka, Inria Sophia-Antipolis)
- Initiated and co-organized an international benchmark on multimodal brain tumor segmentation as a challenge workshop during MICCAI 2012 in Nice (http://www2.imm.dtu.dk/projects/BRATS2012)

5.1.4. Statistical Analysis of Diffusion Tensor Images of Brain

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

Diffusion Tensor Imaging of 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, the diffusion imaging is hampered by the long acquisiton times, low signal to noise ratio and a prominent partial volume effect due to thick slices. The present work aims at robustifying the analysis of clinical images by developing a super-resolution algorithm for DTI and quantifying its improvements with respect to the existing tensor estimation methods. Part of the work was presented at the 1st International Symposium on Deep Brain Connectomics [69].

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 ; coronary arteries ; Chronic Total Occlusion ; X-ray fluoroscopy / CT image fusion

The context of this work is to provide the cardiologist with an advanced guidance application, where a pre-operative 3D CT segmented image will be superimposed on the per-operative 2D live fluoroscopy. Since the relative positions of the 3D image and the 2D projective images are unknown, we are currently investigating robust pose estimation methods before using an upcoming registration algorithm.

5.2. Biological Image Analysis

5.2.1. Pre-clinical molecular imaging: breath-hold reconstruction in micro-SPECT and segmentation of IHC stomach slices

Participants: Marine Breuilly [Correspondant], Grégoire Malandain, Nicholas Ayache, Jacques Darcourt [CAL], Philippe Franken [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, segmentation, immuno-histochemistry

Using the coupled CT and SPECT device, both the anatomy (with the CT) and physiology information targeted by a dedicated radio-pharmaceutical tracer (here the tumors, with the SPECT) can be imaged. However, tumor quantification is impaired by the respiratory motion that induces an artifical enlargement of the moving structures. Thus, the characterization of respiratory motion in dynamic images was studied.

- An ad hoc method for motion detection in dynamic image was developped and tested on two different modalities (4D-SPECT and 4D-CT).
- Image-based motion detection results were compared to the pressure signal and to lung volume variation. A temporal shift between the peak of motion in images and the ones in the pressure signal was observed (see Figure 3).
- The temporal shift suggested to carefully select data from the non moving phase for a motionless 3D-SPECT image reconstruction. This step was incorporated in a breath-hold like reconstruction method [66], [68], [67].

5.3. Computational Anatomy

5.3.1. Statistical Analysis of Transformations on Lie groups and longitudinal studies

Participants: Xavier Pennec [Correspondant], Marco Lorenzi, Nicolas Duchateau [Hospital Clinic, Univ. Barcelona].

Lie groups, transformations, mean value, non-linear registration

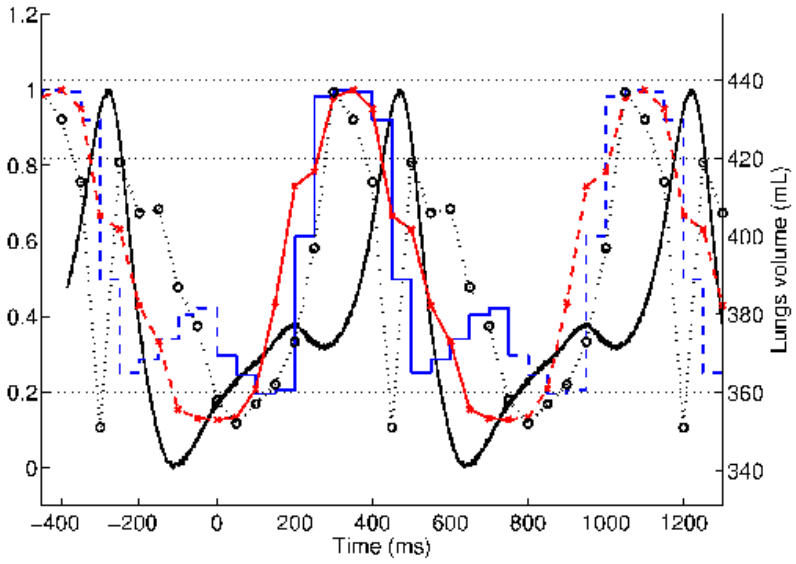

Figure 3. ***Comparison between pressure signal and image-based measures computed on 4D-SPECT and 4D-CT.*** *Normalized average pressure signal (continuous black curve); normalised histogram $h_{4D-SPECT}(n)$ computed on the 4D-SPECT image (blue staircase); normalised histogram $h_{4D-CT}(n)$ of motion phase computed on the 4D-CT image (red curve with cross-shaped markers); and lung volume (mL) measured on the 4D-CT image (black dotted curve with circle-shaped markers).*

In order to perform statistics on transformations for computational anatomy purposes, we investigate alternative theoretical structures to the right- (or left-) invariant Riemannian setting usually used.

- In order to define a notion of a mean which is consistent with Lie group operations we propose in [58] to replace the Riemannian metric by an affine connection structure on the group. We show that the canonical Cartan connections of a connected Lie group provides group geodesics including one-parameter subgroups which are completely consistent with the composition and inversion. To extend statistical operations to such a non-metric structure, we propose an implicit definition as an exponential barycenter (there is no Fréchet mean like in Riemannian Manifolds) and a linearly convergent iterative fixed point algorithm to reach it. This results into naturally bi-invariant means which are unique when the dispersion of the data is small enough. In some cases including rotations and rigid-body transformations, there is even a global existence and uniqueness theorem which is similar to the Riemannian case.
- In [15], we investigate the canonical Cartan connections and their associated parallel transport for diffeomorphisms, which justifies the use of one-parameter subgroups (the flow of stationary velocity fields or SVF) for diffeomorphic image registration. In particular, we derive closed-forms for different parallel transports and we compare SVF and LDDMM approaches with experiments on longitudinal and inter-subject registration.
- In [34], we analyses with practical expriments what kind of parallel transport is needed to reorient the deformation characteristics along the time sequences of the cardiac motion. Contrarily to the case of the brain, inter-subject transformations to normalize the heart between different subjects are of the same order than deformations along the sequence.

5.3.2. Statistical Analysis of Longitudinal Transformations in the LDDMM framework

Participants: Stanley Durrleman [Correspondant], Xavier Pennec, Alain Trouvé [CMLA, ENS Cachan], Nicholas Ayache, José Braga [UMR 5288 CNRS-Université Toulouse Paul Sabatier].

Lie groups, transformations, mean value, non-linear registration

The work initiated the previous years with the PhD of S. Durrleman on the spatio-temporal modeling of shapes was applied with J. Braga to quantify ontogenetic differences between bonobo (Pan paniscus) and chimpanzee (Pan troglodytes) endocrania, using dental development as a timeline. We perform a temporal surface regression that estimates typical endocranial ontogenetic trajectories separately for bonobos and chimpanzees which highlights non-linear patterns of endocranial ontogenetic change and significant differences between species at local anatomical levels rather than considering the endocranium as a uniform entity. The decomposition of the spatio-temporal inter-species difference into a morphological deformation (accounting for size and shape differences independently of age) and a time warp (accounting for changes in the dynamics of development) indicates that juvenile bonobos develop much slower than juvenile chimpanzees, suggesting that inter-specific ontogenetic shifts do not only concern endocranial volume increase, but also the rate of shape changes over time. Our method provides, for the first time, a quantitative estimation of inter-specific ontogenetic shifts that appear to differentiate non-linearly. This work was pusblished in the journal of human evolution [10].

5.3.3. The Kernel Bundle Framework for Diffeomorphic Image Registration

Participants: Xavier Pennec [Correspondant], Stefan Sommer [Computer Science Dpt, University of Copenhagen, DK], François Lauze [Computer Science Dpt, University of Copenhagen, DK], Mads Nielsen [Computer Science Dpt, University of Copenhagen, DK].

This work in collaboration with the Computer Science Department of the University of Copenhagen (DK) was initiated during the 6 month visit of S. Sommer at Asclepios in 2010-2011 and was continued remotely since then.

non-rigid registration algorithm, statistics, deformations, shapes, locally affine deformations, sparsity

In order to detect small-scale deformations during longitudinal registration while allowing large-scale deformation needed for inter-subject normalization, we wish to model deformation at multiple scales and represent the deformation at the relevant scales only. We combined in [49], [27] a sparsity prior with the multi-scale Kernel Bundle framework, resulting in an algorithm allowing compact representation of deformation across scales.

In [28], we further extend the framework by introducing higher-order momentum distributions in the LDDMM registration framework. While the zeroth order moments previously used in LDDMM only describe local displacement, the first-order momenta that are proposed here represent a basis that allows local description of affine transformations. Beyond the careful mathematical construction, we show the implications for sparse image registration and we provide examples of how the parametrization enables registration with a very low number of parameters.

5.3.4. *Spectral Correspondances in Non-linear Image Registration*

Participants: Xavier Pennec [Correspondant], Hervé Lombaert, Nicholas Ayache, Leo Grady [SCR, Princeton, US], Farida Cheriet [Saint-Justine Hospital, Montreal, CA].

This work was performed in collaboration with Saint-Justine Hospital in Montreal (CA) and Siemens Corporate Research in Princeton (US).

non-rigid registration algorithm

The demons algorithm was enhanced to include spectral feature correspondences between the images [38]. This feature proves to drastically enhance the robustness of the registration algorithm, which turns out to have a major impact on the construction of atlases. This work was awarded the best paper award at the Medical Computer Vision Workshop [39] and was protected by a patent filling in the US [63]

5.3.5. *Longitudinal Analysis of Brain Atrophy in Alzheimer's Disease*

Participants: Marco Lorenzi [Correspondant], Xavier Pennec, Nicholas Ayache, Giovanni B. Frisoni [IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy].

This work is done in collaboration with LENITEM, IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy.

Alzheimer's Disease, non-rigid registration algorithm, longitudinal analysis.

The accurate analysis of the longitudinal structural changes in the brain plays a central role in the study of Alzheimer's disease (AD), for diagnostic purposes and for the assessment of the drugs efficacy in clinical trials. The goal of this project is to provide robust and effective instruments based on non-rigid registration of serial MR images for the modeling and the quantification of the brain atrophy evolution in AD. In 2012, our main scientific developments were the following:

- We developed a framework for the consistent definition of anatomical regions of longitudinal brain atrophy, and for the robust quantification of longitudinal regional percentage volume loss. The framework is based on the analysis of the flux associated to longitudinal deformations (see Figure 4), and was successfully applied to large public dataset of brain images (ADNI - http://adni.loni.ucla.edu/). The work was accepted for oral podium presentation at the MICCAI conference 2012 [41].
- We applied the flux analysis for the quantification of the longitudinal hippocampal and ventricular atrophy in AD. The proposed framework was presented at the NIBAD MICCAI Challenge 2012 [42] , and compared favorably with state-of-art methods in terms of accuracy and stability when applied on the challenge dataset.
- We proposed in [40] a model of the morphological changes in Alzheimer's based on the disentangling of the normal aging component from the pathological atrophy. The model was promoted and presented to the neuroscience community during international scientific conferences [72], [71].

These scientific advances were also included along with the previous ones in the PhD manuscript [1].

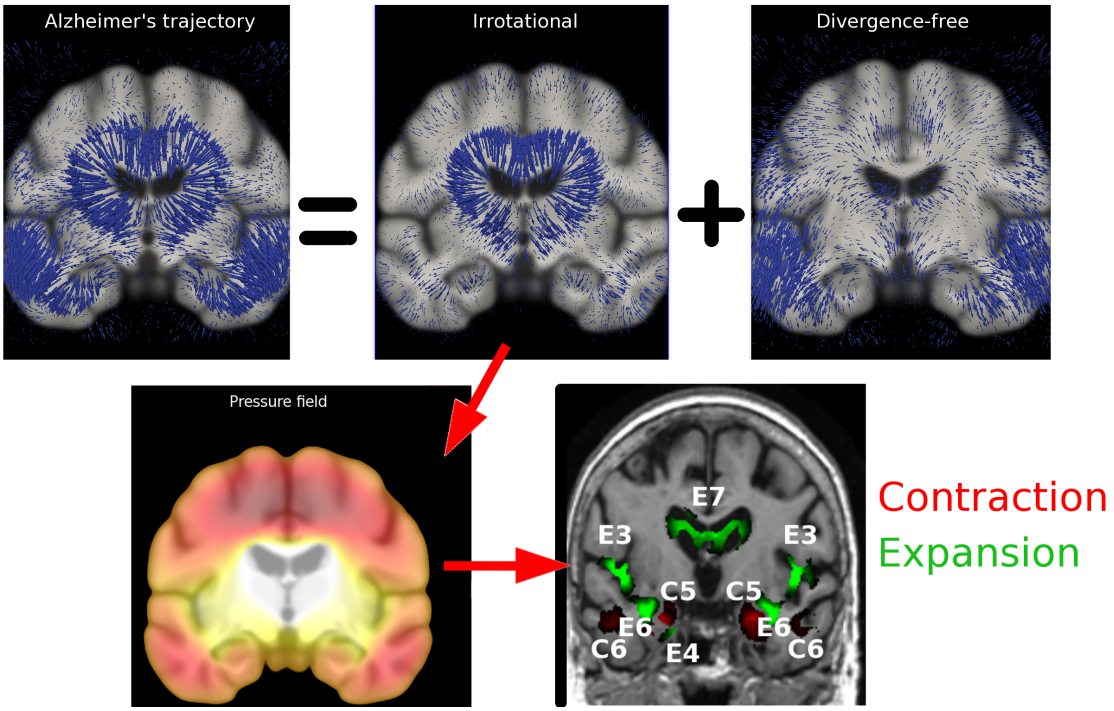

Figure 4. Flux analysis of the longitudinal morphological changes in Alzheimer's disease. The irrotational component associated to the longitudinal deformation encodes the volume loss and gain (top figure). This component is parameterized by a pressure potential (bottom left) which is used to determine the areas of significant flux of the deformation (matter expansion and contraction) in patients affected by Alzheimer's disease (bottom right).

5.3.6. Statistical Modelling of Cardiac Growth, Deformation and Blood Flow from Medical Images

Participants: Kristin McLeod [Correspondant], Adityo Prakosa, Christof Seiler, Maxime Sermesant, Xavier Pennec.

This work was partially funded by the EU project Care4me ITEA2.

Image registration, Demons algorithm, LDDMM, reduced models, CFD, polyaffine, cardiac motion tracking

This work involves developing reduced models of cardiac motion, blood flow and growth.

- Extending the 2011 motion tracking challenge [44], the iLogDemons registration algorithm was applied this year to a data-set of synthetic echocardiography sequences with a training set (provided with ground truth) and testing set to quantitavely compare this algorithms with other cardiac motion tracking algorithms [46].
- A reduced order model of cardiac motion based on a polyaffine log-demons registration was developed to represent the motion along the cardiac cycle with a smaller number of parameters compared to previously proposed methods. The method was applied to a data-set of 10 volunteers and the results were presented at the 2012 STACOM workshop at the MICCAI conference [45].
- The analysis of a statistical model for reduced blood flow simulations in the pulmonary artery proposed in the 2010 STACOM workshop is currently being extended to a journal version with an improved method and a larger data-set.
- The statistical modeling of the right ventricle growth in a population of Tetralogy of Fallot patients was extended to a full bi-ventricular growth model on different data [56]. Results confirm the previous findings which were shown to be useful in providing insights for patient treatment [13] (see Figure 5).

5.3.7. Trees on Geometrical Deformations to Model the Statistical Variability of Organs in Medical Images

Participants: Christof Seiler [Correspondant], Xavier Pennec, Mauricio Reyes [Institute for Surgical Technology and Biomechanics, University of Bern, Switzerland].

This work is performed in the context of the joint PhD of Christof Seiler at the Institute for Surgical Technology and Biomechanics, University of Bern, Switzerland and Asclepios Inria [3].

Parametrization of diffeomorphisms, Shape statistics, Multiscale and hierarchical trees, Log-Euclidean polyaffine transformations, Polyaffine registration, Log-Demons registration, Generative statistical model, Bayesian registration, Mandibles, Femurs

Intersubject anatomical deformations between patients can be found on coarse and fine scales. Each level of granularity has specific regions of interest in clinical applications. The challenge is to connect geometrical deformations to clinical regions across scales.

- We presented this connection by introducing structured diffeomorphic registration [25]. At the core of our method is the parametrization of geometrical deformations with trees of locally affine transformations describing intersubject variability across scales (see Figure 6).
- The methodology of [25] was successfully applied to mandible implant design [32] and in a clinical journal paper on allograft selection [22].
- We statistically modeled the deformation parameters in a population by formulating a generative statistical model [48]. This model allowed us to incorporate deformation statistics as a prior in a Bayesian setting and it enabled us to extend the classical sequential coarse to fine registration to a simultaneous optimization of all scales.
- We explored cell shape statistics to classify stem cells [24].
- We investigated the benefits of considering patient metadata and morphometric measures to enhance bone surface shape prediction [6].

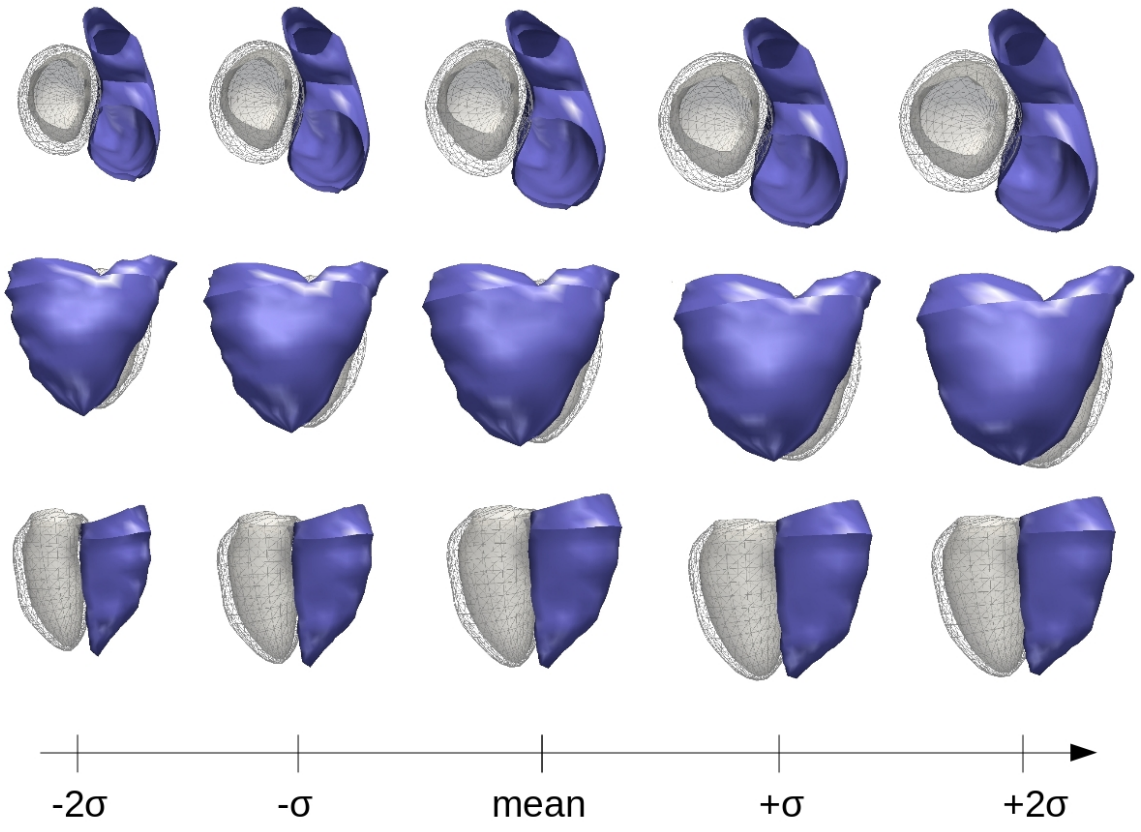

Figure 5. Mean growth model computed from a population of 13 repaired Tetralogy of Fallot patients. Both ventricles grow as body surface area (BSA) increases.

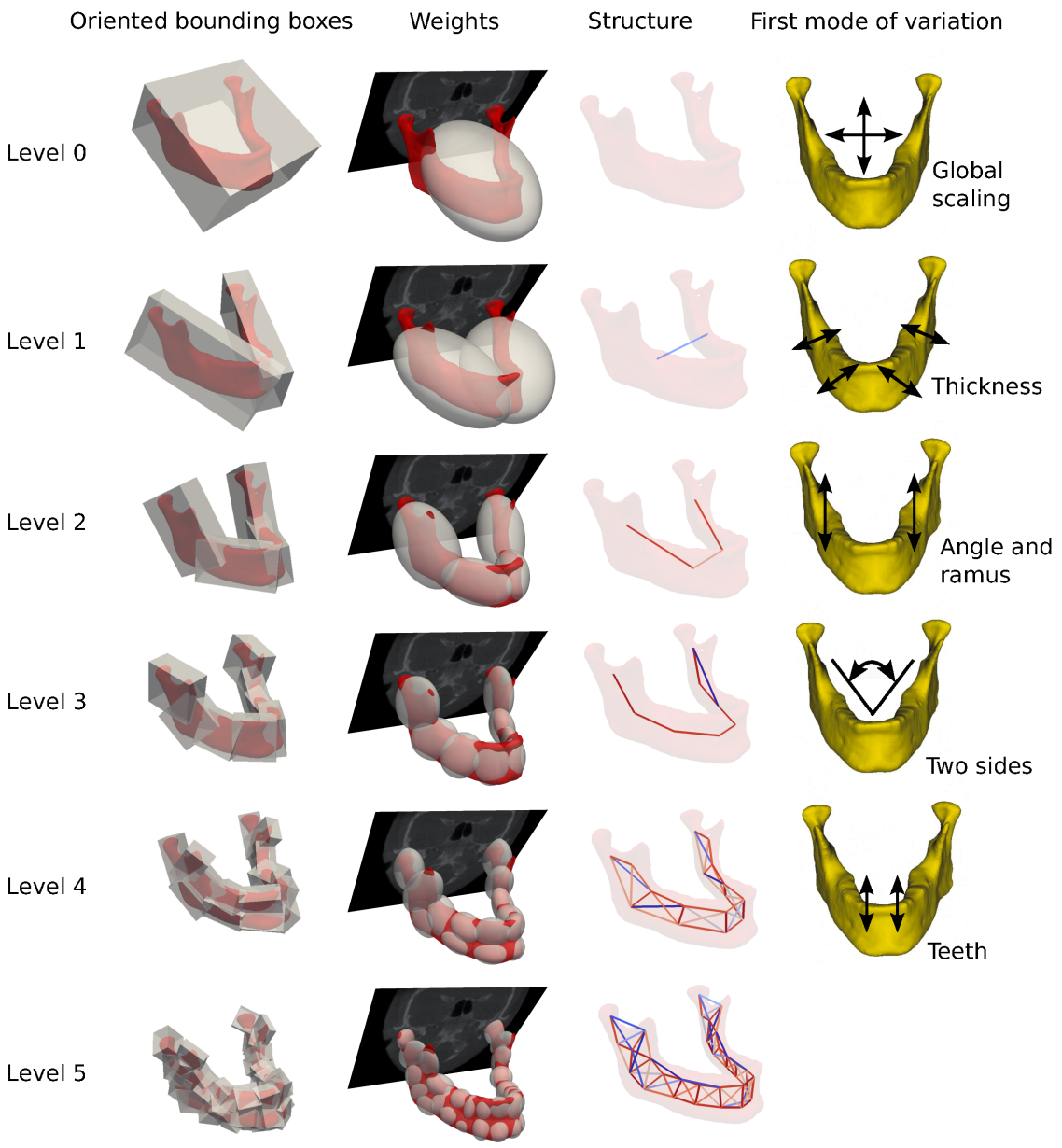

Figure 6. The red mandible is the surface extracted from the template image. Column 1: Oriented bounding boxes computed using the algorithm presented in [25]. Column 2: Ellipsoids representing Gaussian weights derived from the oriented bounding boxes. Column 3: Structure given by the weights with correlations between regions ranging from low (blue=0:4) to high (red=1). Column 4: First PCA mode at each level showing the residual variation.

5.3.8. Evaluation of iLogDemons Algorithm for Cardiac Motion Tracking in Synthetic Ultrasound Sequence

Participants: Adityo Prakosa [Correspondant], Kristin McLeod, Maxime Sermesant, Xavier Pennec.

This work was partially funded by the European Research Council (ERC) through the support of the MedYMA advanced grant 291080 and the European project euHeart.

synthetic echocardiography, iLogDemons, cardiac motion tracking

- The LogDemons and iLogDemons non-linear registration algorithms were evaluated on a dataset of synthetic cardiac ultrasound sequences [33], [46]. With these synthetic sequences, it is possible to quantify the performance of these registration algorithms since the ground truth motion was given. Therefore the LogDemons/ iLogDemons can be evaluated objectively (see Figure 7).

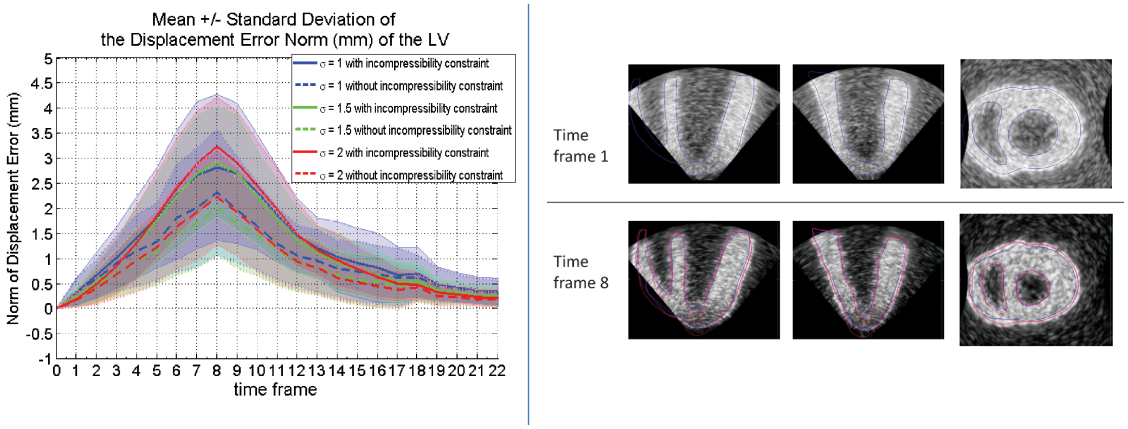

Figure 7. ***Registration Error and Motion Tracking Result*** *The error quantification for different registration parameter (left) and the myocardium tracking result during the maximum contraction (right): ground truth, LogDemons and iLogDemons estimation are shown in blue, purple and red respectively.*

5.3.9. Simulation of Atrophy in Alzheimer's disease

Participants: Arnaud Le Carvennec [Correspondant], Sebastien Ourselin [UCL], Nick Fox [UCL], Xavier Pennec [Inria], Nicholas Ayache [Inria].

Thesis in collaboration between Asclepios team at Inria and Center for Medical Image Computing (CMIC)-Dementia Research Center (DRC) at University College London (UCL).

Simulation, Alzheimer's disease, registration

- Evaluation of registration algorithm using multi-channel images.
- Simulation of atrophy based on registration.

5.4. Computational Physiology

5.4.1. Tumor Growth Modeling

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

This work was funded by Care4me, EU program.

DTI, MRI, simulation, clinical, tumor, brain, glioma

We aim at developing image analysis methods and biophysical models in order to guide the planning of therapies (surgical removal and radiotherapy) for brain cancer (glioma) patients. Our work is focused on those objectives :

- Predicting the location of glioma recurrence after a resection surgery [50].
- Determining the best description 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.
- Comparing tumor growth speeds on 3 patient cases. This is a work in progress and the objective is to reach 30 patients when the work is complete.

5.4.2. Generation of Synthetic but Visually Realistic Time Series of Cardiac Images Combining a Biophysical Model and Clinical Images

Participants: Adityo Prakosa [Correspondant], Maxime Sermesant, Hervé Delingette, Stéphanie Marchesseau, Eric Saloux [CHU Caen], Pascal Allain [Philips Healthcare], Nicolas Villain [Philips Healthcare], Nicholas Ayache.

This work was done in collaboration with Medisys, Philips Healthcare Suresnes, France, and the Cardiology Department of CHU Caen, France. This work was partially supported by the European Research Council through the ERC Advanced Grant MedYMA on Biophysical Modelling and Analysis of Dynamic Medical Images and the European project euHeart.

synthetic 4D cardiac sequences, cardiac electromechanical model, non-rigid registration

- A pipeline to create visually realistic synthetic 4D cardiac sequence using the cardiac motion simulated by an electromechanical model is developed. This pipeline combines the simulated myocardium displacement field with the estimated myocardium displacement field from a registration method. This combined displacement field is then used to warp the original images in order to create the synthetic cardiac sequence.
- In [20],we proposed a new approach based on Stationary Velocity Fields to combine the two motions (see Figure 8). We also proposed a new method that diffuses displacement fields in order to maintain the continuity between the simulation and the real image with minimal texture distortion. Thanks to the detailed interplay between image processing and biophysical modeling, we can fully use a complete sequence in order to generate several new ones. This method also gives better realism compared to traditional methods based on the deformation of an end-diastolic image, since the generated synthetic sequence will also contain the motion of surrounding tissues such as the motion of the mitral valve.
- The new synthetic images are similar to the original ones except for the motion of the heart which is modified to follow the motion provided by a biophysical model. The parameters of the biophysical model can be modified to create variations around this motion. This pipeline has been applied to generate different synthetic sequences from different imaging modalities. It is generic and can be used with a different biophysical model or a different image registration algorithm, and it can be extended to other organs.
- As these synthetic 4D cardiac sequences have kinematic ground truth information, those sequences represent in themselves a valuable resource to benchmark motion tracking methods or to train machine-learning algorithm.

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 funded by the ADT Sofa and is conducted in collaboration with project teams Shacra and Evasion.

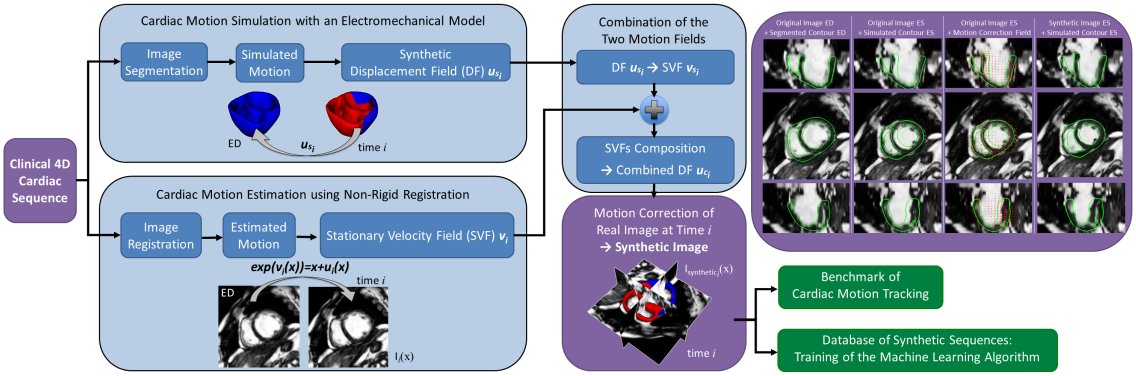

Figure 8. ***Synthetic 4D Cardiac Sequence Generation Pipeline*** *A clinical 4D sequence is used as an input to create a synthetic 4D sequence in which the myocardium motion follows a prescribed simulated displacement field. The combined simulated and registration motion are used to correct the motion of the real clinical images in order to create the synthetic cardiac sequence.*

Cardiac electrophysiology simulation, real-time, GPU computing, patient-specific study

Cardiac arrhythmia is a very frequent pathology related to an abnormal electrical activity in the myocardium. This work aims at developing a training simulator for interventional radiology and thermo-ablation of these arrhythmias.

- The latest improvements lead on electrophysiology simulation (see Figure 9) using GPU computing allowed us to reach real-time performance[52]. The issue of fast electrophysiology was a major bottleneck in the development of our simulator.

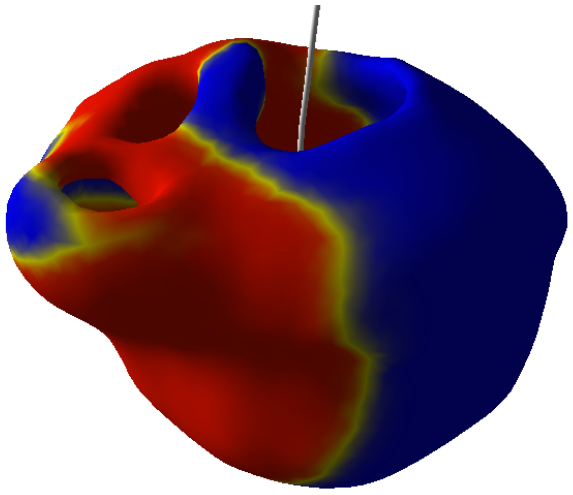

Figure 9. Cardiac electrophysiology computed on a patient-specific geometry

Coupling between the cardiac electrophysiology model with cardiac mechanical models has been achieved, thus leading to an interactive framework. Moreover, the electrophysiology simulation has been also coupled with a navigation simulation.

- In the context of his work on cardiac electrophysiology, we initiated two different collaborations. Joint work has been performed with the team CARMEN from Inria Bordeaux on bidomain modeling for cardiac electrophysiology. This exchange targeted the implementation in SOFA of these models. Secondly, a collaboration with the MACS team in Saclay has been initiated to personalize the cardiac electrophysiology model based on the Verdandi library.

5.4.4. Personalized model of the heart for cardiac therapy planning

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

An award has been won for this work at the MICCAI 2012 Conference. It was partially funded by the European Community's euHeart project under grant agreement 224495 and by the ERC advanced Grant MedYMA 291080.

Cardiac simulation, sensitivity analysis, calibration algorithm, specificity study

- We implemented the full Bestel-Clement-Sorine electromechanical model of the heart in SOFA [55], [52].
- We ran a complete sensitivity analysis to check its behaviour for healthy and pathological cases [16].
- A new calibration algorithm was proposed [16] in order to initialize global mechanical parameters from the volume and pressure curves, before further personalization (see Figure 10).
- The application of this new method on 6 healthy and 2 pathological cases allowed to draw preliminary conclusions on specific parameters to a given pathology [43], [17].
- The model has also been used to create synthetic images in [20] and for the data of the STACOM 2012 challenge [33].

5.4.5. Image-based glioma modeling for radiotherapy planning

Participants: Bjoern Menze [Correspondant], Ender Konukoglu [MSR Cambridge], Jan Unkelbach [Harvard MGH].

- Implemented the generative tumor segmentation model together with the E. Konukoglu's tumor infiltration model for evaluation at the MGH Department of Radiation Oncology.
- Integrated tumor infiltration model with radiation therapy model.

5.4.6. 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 the PhD of Rocio Cabrera Lozoya in collaboration with the IHU 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 (see Figure 11).
- Prediction validation with acquired clinical data

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

Participants: Chloe Audigier [Correspondant], Herve Delingette, Tommaso Mansi [Siemens Corporate Research], Nicholas Ayache.

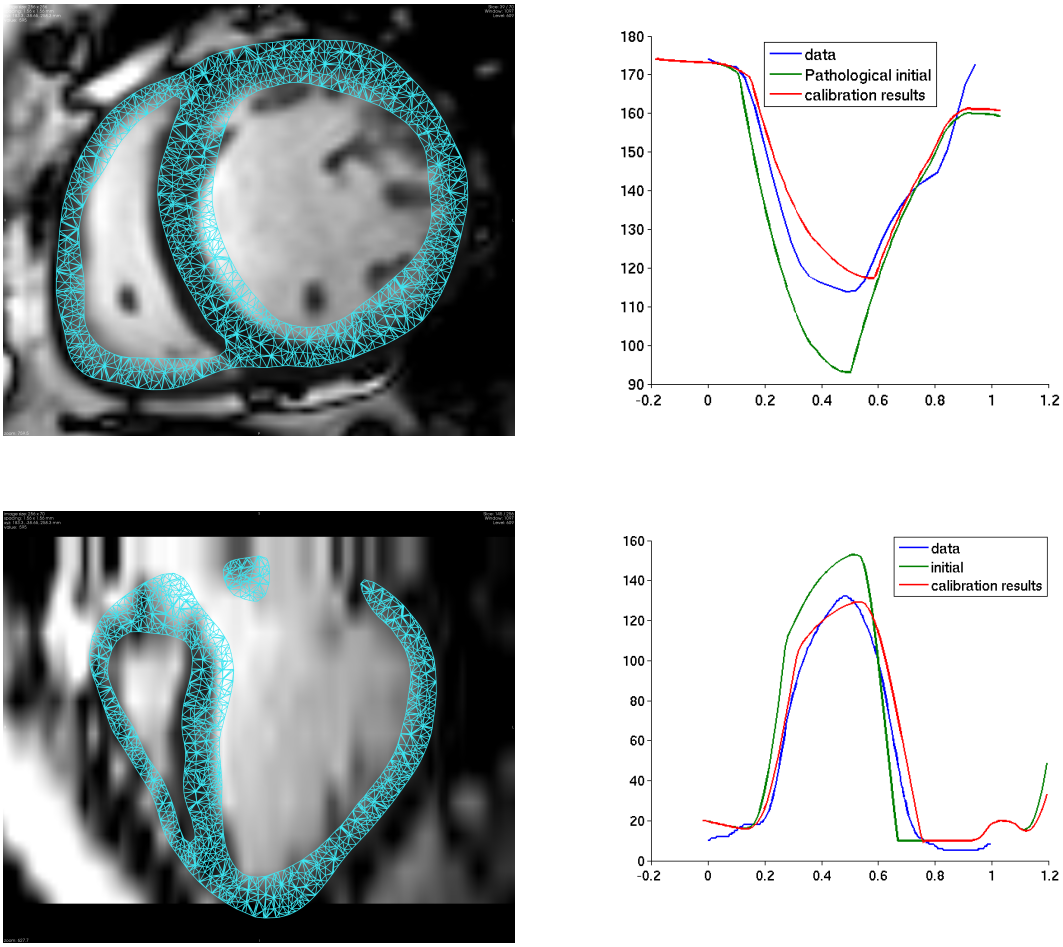

Figure 10. Results of the calibration algorithm fro one pathological case. (Left) Simulated mesh after calibration compared to the images (at end-diastole). (Right) Resulting volume and pressure curves.

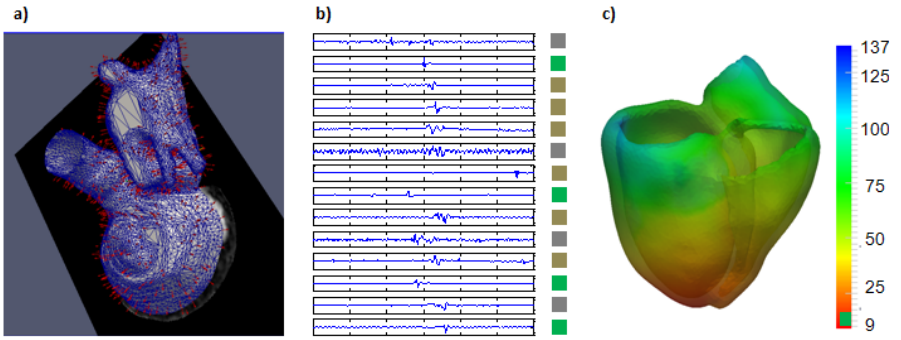

Figure 11. a) MRI Feature Extraction b) EP Signal Feature Extraction c) EP Model Personalization

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

Therapy planning, radio-frequecy ablation, Liver

The objective of this work is to develop a computational framework for patient-specific planning of radiofrequency ablation:

- A patient-specific detailed anatomical model of the liver is estimated from standard CT image and meshed to generate a tetrahedral volume mesh.
- A porous media model is used to compute the patient-specific blood flow in the hepatic circulatory system.
- Bio-heat equations have been implement in SOFA to model the heat propagation in biological tissues.
- A cell death model is included to account for the cellular necrosis.

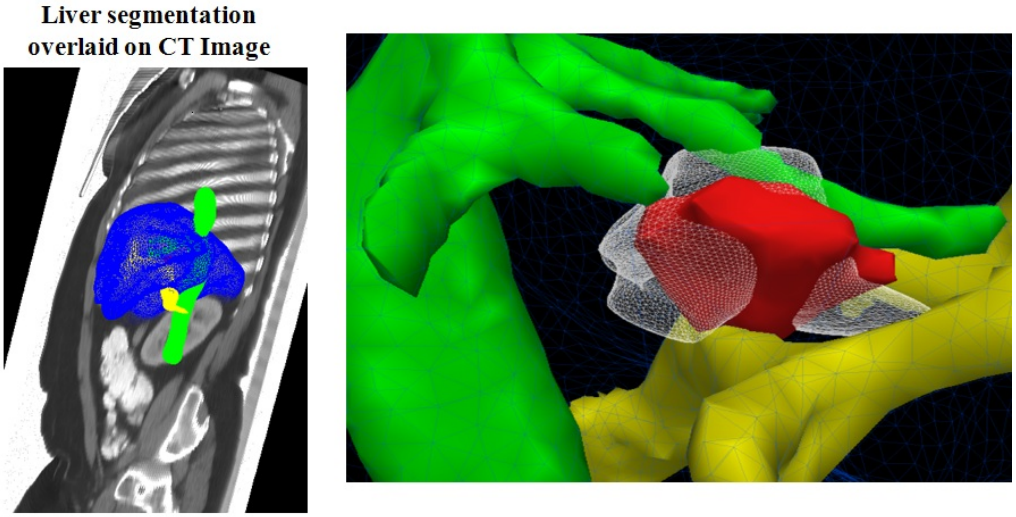

Figure 12. (Left) Anatomical model of the liver estimated from standard clinical CT image. (Right) The predicted necrosis computed with our model compares qualitatively well with the necrosis region observed on a post-operative MRI scan.

5.4.8. Tumor Growth Simulation for the creation of a database of virtual patients

Participants: Nicolas Cordier [Correspondant], Nicholas Ayache, Hervé Delingette, Bjoern Menze, Ezequiel Geremia.

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, Tumor simulation.

- Synthesizing multi-channel MR images with healthy and glial tumors.
- Creating a database of synthetic images for training and validating of brain tumor segmentation algorithms.

5.4.9. Learning approach for the Mechanical personalization of cardiac models

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

This work was partly funded by Microsoft Research through its PhD Scholarship Programme and by the ERC Advanced Grant MedYMA.

Inverse problem, machine learning, patient-specific, current, kinematics

- A machine-learning framework for the mechanical personalization of the Bestel-Clement-Sorine model of the heart from patient-specific kinematics
- The computational burden is moved to an offline stage, where the inter-subject variability in motion is captured via the statistical analysis of training samples
- Towards a probabilistic framework for the personalization and therapy planning problems, to better account for significant and diverse uncertainty sources
- Published at the MICCAI 2012 Workshop on Medical Computer Vision[37]

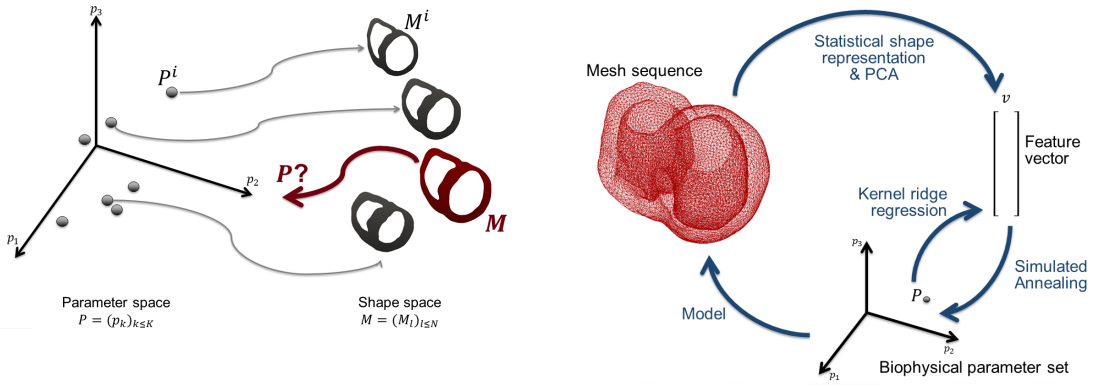

Figure 13.

5.4.10. Brain Tumor Growth Modeling

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

Gliomas simulations, reaction-diffusion, brain tumors

- In collaboration with the MC2 research team in Bordeaux, we developed a tumor growth model based on different types of cell : necrotic, proliferative and quiescent cells (see Figure 14). It is also based on the underlying vascularization of the brain.
- We studied the impact of the vascularization angiogenesis factor and degradation factor.

5.4.11. Modeling of atrophy of the brain in Alzheimer's Disease

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

Alzheimer's Disease (AD), modeling atrophy, biomechanical model

- The idea is to have a model which produces deformation of the brain when a known distribution of local volume change (atrophy) is prescribed to the model. The study is to understand how brain deformation evolve in time with respect to temporal and spatial variation of atrophy.
- During the masters internship period a simple model was tested in 2D square and 3D cube where high atrophy regions acted as sinks for the displacement field [70] (see Figure 15).

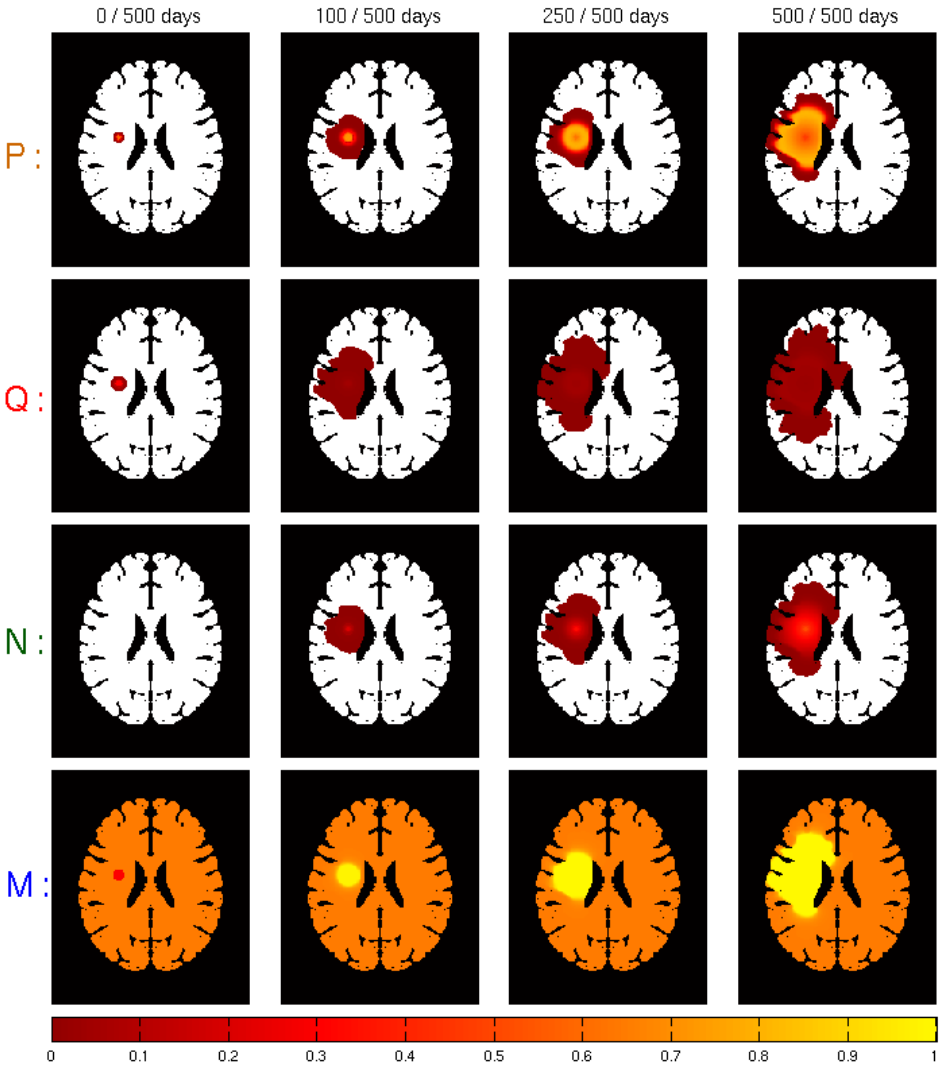

Figure 14. Results of a glioma simulation at day 0, 50, 250 and 500. The proliferative cells are on the first row, the quiescent cells on the second row, the necrotic cells on the third one and the vascularization is on the fourth row.

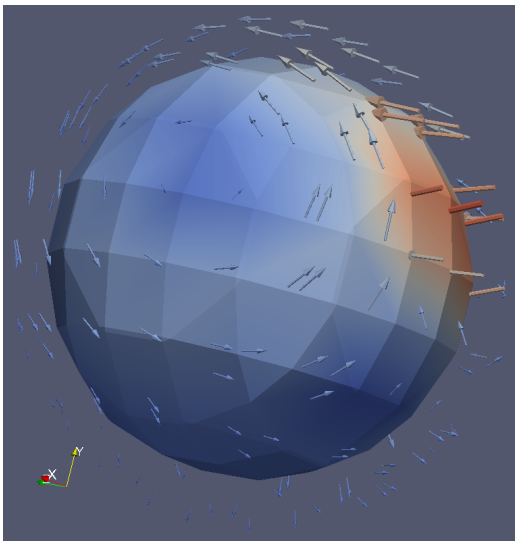

Figure 15. Displacement field in 3D when high atrophy is prescribed in the center of a cube.

6. Bilateral Contracts and Grants with Industry

6.1. Inria - Mauna Kea Technologies I-Lab SIWA

Participants: Nicholas Ayache, Xavier Pennec, Irina Vidal Migallon, Marzieh Kohandani Tafreshi, Barbara André [Mauna Kea technologies], Tom Vercauteren [Mauna Kea technologies], Julien Dauguet [Mauna Kea technologies].

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 the 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.

The opening ceremony of the I-Lab SIWA took place on Friday, November 16, 2012 in the presence of Michel Cosnard (CEO of Inria) and Gérard Giraudon (head of Inria-SAM Center). Keynotes lectures by Asclepios members were given by Xavier Pennec and the two engineers dedicated to this project: Irina Vidal Migallon and Marzhieh Kohandani Tafreshi. For more information, visit: https://lisa.sophia.inria.fr/siwa-loasis-numerique-dinria-et-de-mauna-kea-706.html

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. National initiatives

6.4.1. ANR KaraMetria

Participants: Xavier Pennec [correspondant], Vikash Gupta, Marco Lorenzi.

KaraMetria is the concatenation of Kara ("head", "brain" in ancient Greek), and Metria ("measure"). This ANR-funded project (2010-2012, http://sites.google.com/site/karametria/) aims at: developing an extensible image registration framework able to map anatomical descriptors (such as sulcal lines or white matter fibers) of the brain shape from one subject to another : providing all necessary statistical tools to compare a subject with a group or compare groups of subjects based on the aforementioned registration framework ; and identifying biomarkers of certain brain pathologies and psychiatric disorders. In particular, we target the study of a population of depressive teenagers. This project is led in collaboration with the LNAO at CEA, the MAP5 laboratory from the University Paris Descartes, and the INSERM U797 unit.

6.4.2. Consulting for Industry

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

6.4.3. 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.

7. Partnerships and Cooperations

7.1. European Initiatives

7.1.1. FP7 Projects

7.1.1.1. VPH NOE

Participants: Benoît Bleuzé [correspondant], Olivier Clatz, Maxime Sermesant, 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 more 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 into the new version of MedInria (2.x).

7.1.1.2. EUHEART

Title: euHeart
Type: COOPERATION (ICT)
Defi: Virtual Physiological Man
Instrument: Integrated Project (IP)
Duration: June 2008 - May 2012
Coordinator: Philips Technologie GmbH Forschungslaboratorien (Germany)
Others partners: Philips Technologie GmbH (DE), The University of Oxford (UK), Universitat Pompeu Fabra (SP), The University of Sheffield (UK), Inria, French National Research Institute in Informatics and Mathematics (FR), King's College London (UK), Academisch Medisch Centrum bij de Universiteit van Amsterdam (NL), Universität Karlsruhe (TH) (DE), Institut National de la Santé et de la Recherche Médicale, INSERM (FR), Philips Medical Systems Nederland BV (NL), Berlin Heart GmbH (DE), HemoLab BV (NL), Universitätsklinikum Heidelberg (DE), Volcano Europe SA / NV (BE), Hospital Clínico San Carlos de Madrid (SP), Philips Ibérica S.A. (SP)
See also: http://www.euheart.eu/
Abstract: The euHeart project (Ref 224495), is a 4-year integrated European project which aims at developing personalized, and clinically validated multi-physics, multi-level models of the heart and great vessels. Those models need to be tightly integrated with signal and image processing tools in order to assist clinical decision making and to help reducing morbidity and mortality rates associated with cardiovascular diseases. Asclepios is leading a workpackage on radiofrequency ablation for which electromechanical models of the heart are used to improve the planning of radiofrequency ablation lines for patient suffering from atrial fibrillation and ventricular tachycardia. The research performed in this project is partially described in section 5.4.3 and 5.4.4.

7.1.1.3. MedYMA

Title: Biophysical Modeling & Analysis of Dynamic Medical Images
Type: IDEAS ()
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 to capture 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 on their principled biophysical and statistical foundations, these new models will bring a 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 the 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.

7.1.2. 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: Sept. 2009 - Sept. 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 are 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 the hospital information systems using a new system architecture. In this project, the role of the Asclepios team is to develop atlas of the ageing brain and the beating heart, and to model tumor growth.

7.2. International Initiatives

7.2.1. Inria Associate Teams

Title: Analysis of structural MR and DTI in neonates

Inria principal investigator: Pierre Fillard [Parietal]

Asclepios investigator: Xavier Pennec

International Partner (Institution - Laboratory - Researcher):

University of Pennsylvania (United States) - Penn Image Computing and Science Laboratory - Caroline Brun

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 of premature versus 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 between 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 hundreds of premature and normal neonates MR scans. This joint collaboration is consequently a unique chance of addressing key questions pertaining to neonatal and premature development. It will make it possible to elaborate new tools to analyze neonate MR images while tremendously increasing our knowledge of neuroanatomy at such an early stage in life.

7.2.1.1. COMPUTUMOR

Title: Computational Brain Tumor

Inria principal investigator: Olivier Clatz

International Partner:

Institution: Massachusetts Institute of Technology (United States)

Laboratory: Computer Science and Artificial Intelligence Laboratory (CSAIL)

International Partner:

Institution: German Cancer Research Center (United States)

Laboratory: DKFZ Heidelberg diffusion group

Duration: 2007 - 2012

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

The CompuTumor associated team has been funded early 2007 and renewed in 2009. The CompuTumor project is dedicated to the study of brain tumor models and their coupling with medical images to better assist diagnosis and therapy. The project strongly enhance the current collaborations between Inria and a group of world leading teams with complementary technical and clinical expertise on these topics in Boston and Nice. More specifically, the project aims at (a) proposing new medical image processing method that could be used to better analize tumor images, (b) developping new brain tumor models in order to personalise these models with patient data. Microsoft Research has been also recently involved in the collaboration on lesion segmentation. Our most recent activity is described in sections 5.1.1 and 5.4.1 and also on the website of the associated team : http://www-sop.inria.fr/asclepios/projects/boston/.

7.2.2. Inria International Partners

7.2.2.1. Collaboration with international hospitals

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

Maxime Sermesant is a part-time lecturer in the Interdisciplinary Medical Imaging Group, Division of Imaging Sciences, St Thomas' Hospital, King's College London lead by Pr Reza Razavi. The XMR facility within this hospital is a unique possibility to validate and exploit the cardiovascular modelling work.

7.2.2.1.2. Children Hospital, Boston

A collaboration with Dr Simon Warfield, director of the Computational Radiology Laboratory has been active for several years, especially on the issue of atlas-based image segmentation and registration.

7.2.2.1.3. Other International Hospitals

Collaborations with several other European hospitals have been established through the European projects Passport and euHeart.

7.3. International Research Visitors

7.3.1. Visits of International Scientists

- **Marc Niethammer** (Assoc. Prof. at the Biomedical Research Imaging Center (BRIC), Univ. North Carolina Chapel Hill). Hosted by the Inria-Microsoft common research lab. *Control methods in diffeomorphic non linear registration for longitudinal image analysis*. September to November.

8. Dissemination

8.1. Animation of the scientific community

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* [6]. This scientific journal was created in 1996 and is published by Elsevier.

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).

I. Strobant is editorial assistant for *IEEE Transactions on Medical Image Analysis*, (since october 2001)

N. Ayache is associated editor of *IEEE Transactions on Medical Imaging* [7].

N. Ayache is a member of the editorial board of the following journals: new SIAM Journal on Imaging Sciences, *Medical Image Technology* (Japanese journal) and *Journal of Computer Assisted Surgery* (Wiley).

X. Pennec is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier), of the *International Journal on Computer Vision* (Springer) and of the SIAM Journal on Imaging Sciences (SIIMS).

8.1.2. Participation in the organization of conferences

The MICCAI 2012 conference gathered a record number of more than 1200 participants in the Acropolis Center in Nice, from the 1st to the 5th of October 2012. It was chaired by Nicholas Ayache. 32 satellites events, coordinated by Xavier Pennec, were held on the 1st and the 5th of October, while the main conference, whose scientific program was under the responsability of Hervé Delingette, took place from teh 2nd to the 4th of October. Agnès Cortell was in charge of the local organisation, with the help of M. Barret, G. Malandain, M. Sermesant, I. Strobant and the MCI company. Inria services, especially O. Carron, M. Oricelli, along with the students helped in the organisation too.

N. Ayache was the chair of the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2012) in Nice.

H. Delingette was the program chair and a member of the local organization committee of International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'12) which involved selecting 256 papers from 780 submissions, and organize the 7 oral sessions and the 18 poster sessions. He was also member of the program committees of the International Symposium on Biomedical Imaging (ISBI'12), the conference on Virtual Reality Interactions and Physical Simulation (VRIPHYS'12).

X. Pennec was workshop/challenges and tutorial chair (and a member of the local organization committee) of the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2012) in Nice. This involved in particular the coordination of 32 MICCAI satellite events with 140 organizers and 975 participants. He was also a member of the program committees of: Int. Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'2012); IEEE Workshop on Mathematical Methods in Biomedical Image Analysis (MMBIA 2012); Workshop on Biomedical Image Registration (WBIR 2012); Workshop on computational diffusion MRI (CDMRI'12).

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

M. Sermesant was a member of the program committee of International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'12), and was a co-organisator of the MICCAI 2012 Workshop on Statistical Atlases and Computational Models of the Heart and the VPH Network of Excellence 2nd workshop on medical imaging software.

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 in Fukuoka, Japan in February 2012 to evaluate a national program on "Computational Anatomy" funded by the MEXT.

Xavier Pennec is a member of the Doctoral follow-up Commitee (CSD) at Inria Sophia Antipolis since 2010. In 2012, he was elected member of the MICCAI Society boards of Directors for the period 2012-2016, and was an evaluator for the EU STREP PredictAD (neuroimaging in Alzheimer's disease), for 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 applications (Comité Nice). He was an evaluator for the integrated European project ARTREAT, for the Research Foundation Flanders (FWO), for several project proposals submitted to the French research agency ANR, to the Medicen Paris Innovative cluster.

M. Sermesant acted as an evaluator for the ANR, the CNRS and the Dutch and UK Research Councils. He is a member of the 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 2012).

8.2. Teaching

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

Master IFI - Computational Biology, Univ. Nice-Sophia-Antipolis. X. Pennec is responsible of 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 3 h course.

8.3. PhD Theses and Internships

8.3.1. PhD defended in 2012

1. Hervé Lombaert, *Atlas Construction for Measuring the Variability of Complex Anatomical Structures*, Ecole Polytechnique de Montréal. June, 2012.
2. Marco Lorenzi, *Deformation-based morphometry of the brain for the development of surrogate markers in Alzheimer's disease*. University of Nice-Sophia Antipolis, December 2012. In collaboration with G.B. Frisoni, IRCCS Fatebenefratelli, Brescia, Italy.
3. Jatin Relan, *Planning of radiofrequency ablation of the heart using electromechanical models personnalized from cardiac images and electrophysiological signals*, Ecole des Mines de Paris. June, 2012.
4. Christof Seiler, *Trees on Geometrical Deformations to Model the Statistical Variability of Organs in Medical Images*. Joint PhD (co-tutelle) of University of Nice Sophia Antipolis and University of Bern. September 2012.

5. Nicolas Toussaint, *In vivo cardiac DTI*, King's College London, London. July 2012.

8.3.2. Current PhDs

1. Chloé Audigier, *Modeling radio-frequency ablation for the planing 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. Marine Breuilly, *Tracking and quantification of tumour processes in rodents with SPECT imaging* , Nice Sophia-Antipolis University. Started in November 2009
4. 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.
5. Nicolas Cordier, *Simulation and Analysis and Simulation of Brain Tumors Images*, University of Lille. Started in February 2012.
6. Ezequiel Geremia, *Multi-scale computational models of brain tumors for medical image analysis*, Nice Sophia-Antipolis University. Started in December 2008.
7. Vikash Gupta, *Diffusion tensor imaging of the brain: towards quantitative clinical tools*, Nice Sophia-Antipolis University. Started in November 2011.
8. Mehdi Hadj-Hamou, *Biophysical modeling of the anatomical evolution of the brain*, Nice Sophia-Antipolis University. Started in September 2012.
9. Bishesh Khanal, *Modeling the atrophy of the brain in Alzheimer's disease*, Nice Sophia-Antipolis University. Started in November 2012.
10. Arnaud Le Carvennec, *Registration and simulation of atrophy in Alzheimer's disease using MRI images*, University College London. Started in September 2011.
11. Loic Le Folgoc, *Biophysical Personalization of Cardiac Models based on Machine Learning*, Nice Sophia-Antipolis University. Started in June 2012.
12. Stéphanie Marchesseau, *Simulation of patient-specific cardiac models for therapy planning*, Ecole des Mines de Paris. Started in November 2009.
13. Jan Margeta, *Indexation of time-series 4D cardiac MR images*, Ecole des Mines de Paris. Started in March 2011.
14. Kristin Mc Leod, *Modeling of Cardiac Growth and Deformation from Medical Images*, Nice-Sophia Antipolis University. Started in Octobere 2010. .
15. Adityo Prakosa, *Analysis and Simulation of the heart function from multimodal cardiac images*, Nice-Sophia Antipolis University. Started in November 2008.
16. 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.
17. Hugo Talbot, *Simulation of Radiofrequency ablation of cardiac cells*, University of Lille. Started in September 2010.
18. Anant Vemuri, *Augmented reality for image-guided surgery*, Nice-Sophia Antipolis University. Started in 2012.

8.3.3. Master Student

1. Sonia Durand, *Generation of personalized volumetric meshes of cardiac ventricles*, Ecole Centrale de Lyon. From April to September 2012
2. Bishesh Khanal, *Modeling the atrophy of the brain in Alzheimer's disease*, Master Computational Biology and Biomedicine, University Nice-Sophia Antipolis. From April to September 2012

3. Matthieu Lê, *Enhancement of a pathophysiological model of brain tumor growth to take into account anatomical and metabolic information coming from MR images. Application to the simulation of tumor growth for better planning of therapeutic intervention*, Ecole Centrale de Paris. From May to December 2012.
4. Andreas Mieritz, *Interaction Segmentation of Medical Images*, DTU, Denmark. Started in September 2012.

8.3.4. Internship of Medical Doctor Student

1. Nicolas Bronsard, *Study of the 3D variability of the lower spine*, University Hospital of Nice-Sophia Antipolis.

8.3.5. Participation to thesis committees

N. Ayache participated as co-supervisor to the PhD thesis of Jatin Relan (École des Mines de Paris) and Marco Lorenzi (University of Nice-Sophia Antipolis).

Hervé Delingette participated as co-supervisor to the PhD thesis of Jatin Relan (École des Mines de Paris), as reviewer to the PhD thesis committee of C. Casta (Lyon University), G. Bousquet (Grenoble University), C. Conte (Marseille University).

Xavier Pennec participated as president to the PhD thesis committee of N. Duchateau (U. Pompeu Fabra, Barcelona, SP) and as co-supervisor to the PhD thesis of Christof Seiler (University of Nice Sophia Antipolis and University of Bern) and Marco Lorenzi (University of Nice-Sophia Antipolis).

Maxime Sermesant participated as co-supervisor to the PhD thesis committee of Jatin Relan (École des Mines de Paris).

8.3.6. Invited Lectures

We only give here the invited participations. Please refer to general references for the regular participation to conferences with a submission process.

- **Nicholas Ayache** gave the following invited lectures:
  - at the *Moroccan Academy of Sciences*, Rabat, Morocco on February 15, 2012
  - at the *3rd International Symposium on Computational Anatomy*, Fukuoka, Japan on March 4, 2012
  - at the *Scientific Council of Inria* for the ERC MedYMA project, Inria, France, on March 23, 2012
  - at the *Annual Guest Lecture of the Oxford Biomedical Imaging Festival*, Oxford, UK on October 25, 2012
  - at *Microsoft Research Cambridge*, Cambridge, UK on November 7, 2012
  - at the *Let's Imagine the Future symposium*, Rennes, France on November 9, 2012
  - at the *Ecole Centrale de Paris*, France on November 13, 2012
  - at the *Surgery for life innovation conference*, IHU de Strasbourg, France on December 21, 2012
- **Hervé Delingette** gave an invited lecture at the CardioStim 2012 Modeling session in Nice.
- **Xavier Pennec** gave invited lectures:
  - at the Workshop on Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces, Sonderborg, DK, October 8-12, 2012;
  - at the MICCAI workshop and challenge on Statistical Atlases and Computational Models of the Heart: Imaging and Modelling Challenges (STACOM 2012), Nice, October 5, 2012;
  - at the Premières rencontres Technologies de l'Information et de la Communication pour la santé mentale, 21 et 22 octobre 2011, Nice et Monaco.
  - at the PENN Image Computing and Science Lab (PICSL), Philadelphia, May 23, 2012;
  - at the Minisymposium on 4D Medical Imaging, SIAM Imaging Science Conf., Philadelphia, May 20-22, 2012.
- **Maxime Sermesant** was invited to organise a cardiac modelling session at the Cardiostim 2012 clinical conference. He was also an invited lecturer at the ISCAT 2012 conference: 9th International Symposium on Catheter Ablation Techniques and the DD21 conference on Domain Decomposition.

8.3.7. Nominations and Prizes

- **Nicholas Ayache** was awarded an ERC grant in Oct 2011, to start in April 2012 with the collaboration of H. Delingette, X. Pennec and M. Sermesant.
- **Nicholas Ayache** was elected CSO (Chief Scientific Officer) of the IHU of Strasbourg (Institut Hospitalo Universitaire) on January 1, 2012. More informations on: http://www.ihu-strasbourg.eu/Bienvenue.html
- **Caroline Brun**, collaborator of X. Pennec during her PhD, won the Young Scientist Publication Impact Award 2012 of the MICCAI Society (Oct 2012) for the paper "A tensor-based morphometry study of genetic influences on brain structure using a new fluid registration method", published at MICCAI 2008 by C. Brun, N. Leporé, X. Pennec, Y.Y. Chou, A.D. Lee, M. Barysheva, G.I. de Zubicaray, M. Meredith, K. McMahon, M.J. Wright, A.W. Toga, and P.M. Thompson.
- **Hervé Lombaert** won the MCV 2012 best paper award at the MICCAI workshop on Medical Computer Vision (Oct. 2012) for the paper "Groupwise Spectral Log-Demons Framework for Atlas Construction" by H. Lombaert, L. Grady, X. Pennec, J.-M. Peyrat, N. Ayache, F. Cheriet.
- **Stéphanie Marchesseau** received the Young Investigator award at the MICCAI 2012 conference held in Nice (Oct. 2012) for her paper [43] .
- **Hervé Lombaert** has received a prize from the research fund of Québec FRQ (http://www.frq.gouv.qc.ca) as the "star research student" of the month January 2013 for his paper [14] .

9. Bibliography

Publications of the year

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[2] J. RELAN. *Personalised Electrophysiological Models of Ventricular Tachycardia for Radio Frequency Ablation Therapy Planning*, Ecole Nationale Supérieure des Mines de Paris, June 2012, http://www.inria.fr/sophia/asclepios/Publications/Jatin.Relan/JatinRELAN-Thesis-Manuscript_compressed_final.pdf.

[3] C. SEILER. *Trees on Geometrical Deformations to Model the Statistical Variability of Organs in Medical Images*, University of Nice Sophia Antipolis and University of Bern, September 2012, http://www.inria.fr/sophia/asclepios/Publications/Christof.Seiler/Seiler_PhDThesis.pdf.

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