INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Asclepios

Analysis and Simulation of Biomedical Images

Sophia Antipolis - Méditerranée

Theme : Computational Medicine and Neurosciences

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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, M. Sermesant, I. Strobant, A. Cortell were strongly involved in the organization of the FIMH'2009 conference (Functional Imaging and Modeling of the Heart). The conference gathered together 120 experts from 15 countries between 3 to 5 June 2009 in Nice.
- Our research results were presented during several prestigious invited lectures (including the French Academy of Sciences, the Isaac Newton Institute (Cambridge UK), the SPIE Medical Imaging Conference, etc.).
- The team members received several honors and distinctions, including the PhD awards of Jonathan Boisvert and Pierre Fillard.

3. Scientific Foundations

3.1. Introduction

Tremendous progress has been made in the automated analysis of biomedical images during the past two decades [93]. 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 [87], [83]. Regarding the target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [81], in N. Ayache's article [90] and in the more recent syntheses [69] [93]. The scientific journals *Medical Image Analysis* [79], *Transactions on Medical Imaging* [82], and *Computer Assisted Surgery* [86] 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'2009 (Medical Image Computing and Computer Assisted Intervention) [84], [85] or ISBI'2009 (Int. Symp. on Biomedical Imaging) [80].

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], [111]. 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 [117], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [89], Ultrasound or Nuclear Medicine images [95].

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.

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

[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.

[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.

(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 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 level. 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 [119].

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 [108] and to the Mouse Brain Atlas Project [88]. 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, the discovery of structural differences between healthy and diseased populations, and the detection and classification of pathologies from structural anomalies[5] [104].

Studying the variability of biological shapes is an old problem (cf. the remarkable book "On Shape and Growth" by D'Arcy Thompson [113]). 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 [112] 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 [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 less 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 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 [107], [98], [91], [109], [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 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. [110], [103]) 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:

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

These different levels of modeling are closely related to each other, and several physiological systems may interact together (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 [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

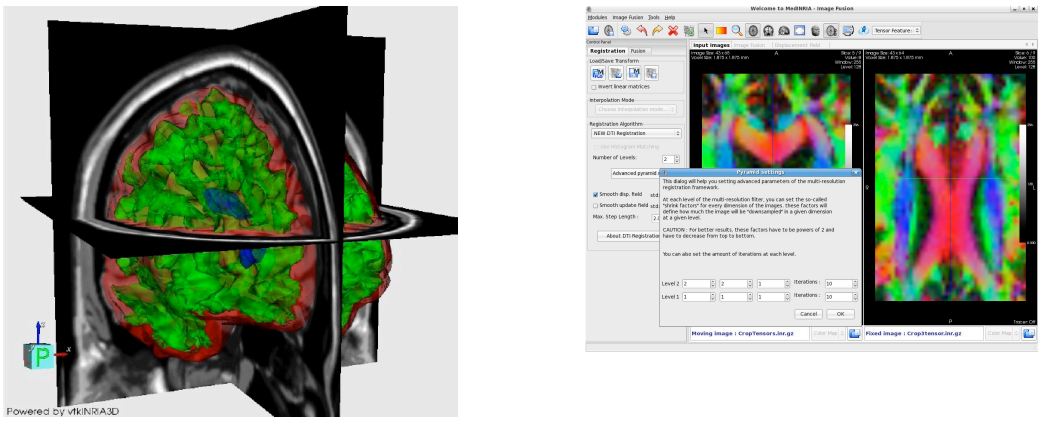
4.1. vtkINRIA3D

Participants: Nicolas Toussaint [Correspondant], Tommaso Mansi.

http://www.inria.fr/sophia/asclepios/software/vtkINRIA3D

vtkINRIA3D is an open source set of C++ libraries [115], extending the Visualization ToolKit VTK (http://www.vtk.org). It was initiated to gather the developement efforts in terms of data visualization and synchronization.

In particular, an ITK-based framework for image registration is proposed. The contribution in this framework is to gather different ITK state-of-the-art image registration methods in a single "console". Furthermore, we propose to store the successive registrations between input images in order to easily go back and force in the global alignement process.



a- vtkINRIA3D b- MedINRIA

Figure 1. (a) vtkINRIA3D also provides developer-friendly API for synchronizing data. In this figure, segmentation results are shown as overlying the input MRI image. (b) MedINRIA: the visual comparison between tensor field is done by extracting features from the tensor fields such as the Color Fractional Anisotropy (FA) maps as shown here.

4.2. MedINRIA

Participants: Olivier Clatz [Correspondant], Florence Dru, Maxime Sermesant, Julien Wintz, Aurélie Canale.

http://www.inria.fr/sophia/asclepios/software/MedINRIA

MedINRIA is a free collection of softwares developed within the Asclepios research project [116]. It aims at providing to clinicians state-of-the-art algorithms dedicated to medical image processing and visualization in a friendly user interface. MedINRIA is freely available.

Most recent release of MedINRIA (1.9 - Oct 2009) includes rigid and non-rigid registration of structural images, non-rigid registration of diffusion tensor images [44], diffusion tensor estimation and visualization, fiber tracking. It also includes Q-Balls image estimation and visualization algorithms developed in the Odyssee project team.

MedINRIA has undergone a major refactoring in 2009, including a new kernel (DTK), a change of GUI toolkit, a new mechanism for plugins, multiple script language management and new design of the interface. The new version of MedINRIA (II) is expected in 2010.

4.3. CardioViz3D

Participants: Maxime Sermesant [Correspondant], Jean-Marc Peyrat, Tommaso Mansi, Hervé Delingette.

http://www.inria.fr/sophia/asclepios/software/CardioViz3D

CardioViz3D is a freely available platform dedicated to dynamic cardiac simulation and processing [114]. It uses advanced and interactive frameworks to provide researchers and clinicians with adapted tools for pre-processing dynamic cardiac data, from the segmentation of the myocardium to the delineation of pathological regions, resulting in a patient-specific anatomical and geometrical model of the heart. Moreover, simulation results can be intuitively evaluated and compared to initial clinical data.

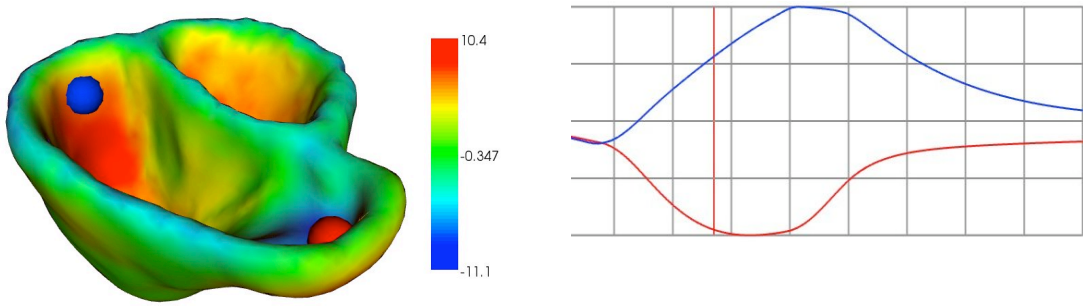


Figure 2. CardioViz3D allows to follow the evolution of scalar information at a specific location in the myocardium. Left: The vertex displacements (in mm) along the surface normal (with respect to a rest position) is shown. Two landmarks have been placed respectively in the healthy part (in blue) and the dyskinetic area (in red) of the right ventricle (patient with a RV overload). Right: Graphs representing the evolution of the displacement among the sequence for both landmark locations, showing a significant difference of curve patterns.

4.4. Isis

Participants: Daniel Barbeau [Correspondant], Grégoire Malandain, David Rey.

Isis is a software designed to strictly do volume reconstruction from Histological cross sections. It uses in-house algorithms developped at Asclepios as well as the Insight Toolkit from Kitware.

Histological observations provide direct 2D observations of the anatomical structures and allow for visualisation at a higher resolution than CT or MRI. Isis makes the reconstruction of 3D anatomical volumes from serial slices easier for both clinicians and researchers. Clinicians can perform an automatic registration of the whole stack of images, control the quality of the reconstruction and correct the errors locally or globally. Researchers have access to finer controls to the registration algorithms and could process images before registration. The output of Isis is a volume image and the geometrical transformations between each image.

The work concerning Isis at the end of 2007 and during 2008 covers the definition of its use cases, its functional and technical specifications.

4.5. Simulation Open Framework Architecture (SOFA)

Participants: Stéphanie Marchesseau, Erik Pernod, Tobias Heimann, Hervé Delingette [Correspondant].

Web site: http://www.sofa-framework.org/ Gforge link: http://gforge.inria.fr/projects/sofa/

SOFA is an Open Source framework for the real-time simulation of deformable structures, particularly for medical simulation and planning. Three INRIA research teams are currently contributing to development of the SOFA platforms: the project team Alcove in Lille, Asclepios in Sophia-Antipolis and Evasion in Grenoble. The simulation group of the CIMIT (affiliated to MIT / Harvard / Massachussets General Hospital) has also strongly supported its development. This international open source platform is mostly intended for the research community to help the development of new algorithms, but it can also be used as a prototyping tool thanks to its modular architecture.

The involvement of the Asclepios team has been mostly focused on a new design that allows each SOFA component to cope with topological changes. Indeed, when simulating the surgical resection or suturing of an organ, it is necessary to update the data structure associated with the mesh of the organ but also the sparse matrices used in the computation of the mass and stiffness of the material. Propagating those topological changes to all components in a modular and generic way is a challenging task but provides a significant added value to all SOFA users.

An additional objective includes the definition of scalar fields (like pressure, electric potential fields) on surface or volumetric meshes in order to implement physiological models. Our mid-term goal is to develop in SOFA a real-time simulator of radiofrequency ablation involving haptic devices which is suitable to train cardialogist for this endovascular procedure.

4.6. Symmetric Log-Domain Diffeomorphic Image Registration Software

Participants: Florence Dru [Correspondant], Tom Vercauteren.

This work has been done in collaboration with Mauna Kea Technologies, Paris, France.

An open-source ITK implementation of the symmetric log-domain diffeomorphic demons algorithm has been provided [77]. This algorithm generalizes Thirion's demons and the diffeomorphic demons algorithm. The main practical advantages of the symmetric demons [118] with respect to the other demons variants is that is provides the inverse of the spatial transformation at no additional computational cost and ensures that the registration of image A to image B provides the inverse of the registration from image B to image A. The algorithm works completely in the log-domain, i.e. it uses a stationary velocity field to encode the spatial transformation as its exponential. Within the Insight Toolkit (ITK), the classical demons algorithm is implemented as part of the finite difference solver framework. The provided code reuses and extends this generic framework. The source code is composed of a set of reusable ITK filters and classes. A program that allows the user to run different variants of the demons algorithm has also been made available.

4.7. Other softwares

Baladin, MIPS, Pasha, Prospect, Runa, smDeform, simuDeform, and Yasmina have been described in previous activity reports.

5. New Results

5.1. Medical Image Analysis

5.1.1. Estimation of 3D Myocardium Strain from Clinical Cine MRI Using Incompressible Demons

Participants: Tommaso Mansi [Correspondant], Xavier Pennec, Jean-Marc Peyrat, Hervé Delingette, Maxime Sermesant, Nicholas Ayache.

This work has been performed in close collaboration with J. Blanc, MD, and Y. Boudjemline, MD, (AP-HP Necker-Enfants Malades, Paris, France).

The purpose of this research is to include prior knowledge in an efficient non-linear registration algorithm to estimate 3D myocardium strain from standard clinical cardiac cine MRI. The motivation is to have an algorithm that can extract function information for direct clinical applications. The idea consists in constraining diffeomorphic demons, an efficient non-linear registration method previously developed in the team, to provide volume preserving deformations as myocardium is known to be almost incompressible during the cardiac cycle. The incompressibility constraint is expressed in the tangential space of diffeomorphic deformations, which consists in a linear divergence-free constraint on velocities. Elastic-like regularisation is integrated to simulate myocardium visco-elasticity, and a Jacobian-preserving framework is implemented to improve the recovery of incompressible deformations. First results have shown promising results on normal and pathological subjects, when compared with tagged MRI or 2D ultra-sound speckle tracking (see figure 3).

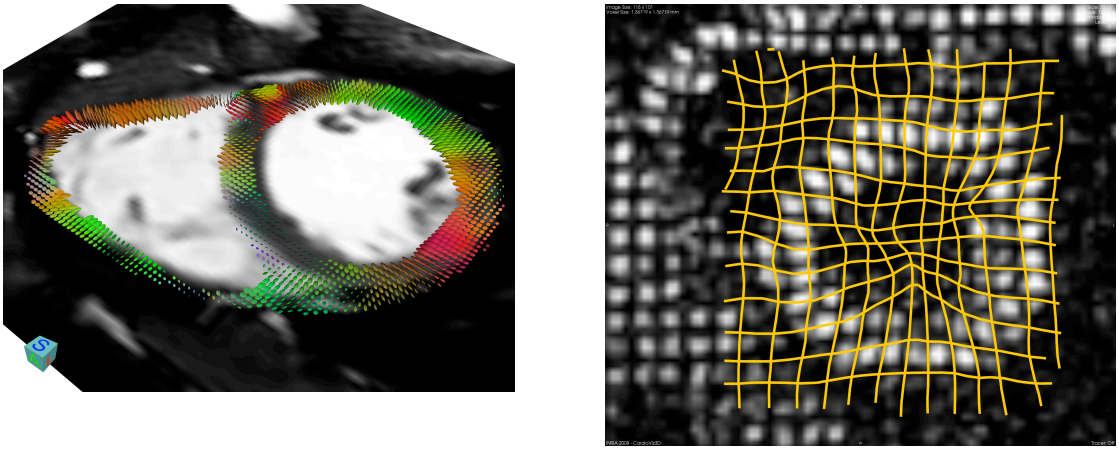


Figure 3. (Left) Strain tensors estimated from cardiac gated cine MRI. (Right) Qualitative validation of myocardium deformation recovery from cine MRI. The grid has been deformed using cine MRI information only and overlaid onto the corresponding tag image, demonstrating promising correlation.

5.1.2. Regional shape and appearance modeling for deformable model-based image segmentation

Participants: François Chung [Correspondant], Tobias Heimann, Hervé Delingette.

This work is supported by the EU Marie Curie project 3D Anatomical Human (MRTN-CT-2006-035763).

Within the framework of the 3D Anatomical Human project, INRIA is leading the workpackage WT2 which consists in providing algorithms that efficiently extract lower limb structures and motion from static and dynamic medical images [67], [73]. Our current focus is the appearance description around regions of interest (*e.g.* lower limb structures, liver, ...) for model-based image segmentation. Instead of relying on Principal Component Analysis such as in Statistical Appearance Models, we propose a method based on Multimodal Prior Appearance Models that does not rely on an accurate pointwise registration [49]. Our method is built upon the Expectation-Maximization algorithm with regularized covariance matrices and includes spatial regularization. The number of appearance regions is determined by a novel model order selection criterion. The prior is described on a reference mesh where each vertex has a probability to belong to several intensity profile classes (see some priors on figure 4). This prior's objective is to determine optimal external forces that will guide the deformable model in segmentation approaches.

5.1.3. Analysis and simulation of the heart function from multimodal cardiac images

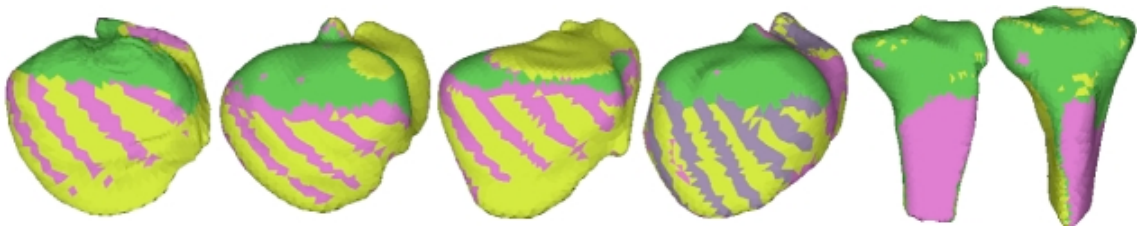


Figure 4. EM classification of outward profiles performed on 4 livers and 2 tibias.

Participants: Adityo Prakosa [Correspondant], Hervé Delingette, Maxime Sermesant, Tommaso Mansi, Pascal Cathier [Philips Medical Systems], Patrick Etyngier [Philips Medical Systems], Pascal Allain [Philips Medical Systems], Eric Saloux [CHU Caen], Nicholas Ayache, Nicolas Villain [Philips Medical Systems].

This work is done in collaboration with the MEDISYS group of Philips HealthCare, Suresnes, France, and with the University Hospital of Caen, Normandy, France.

In Cardiac Resynchronization Therapy (CRT), used on patients suffering from cardiac motion asynchrony, the selection of patients and the placement of pacemaker electrodes play a crucial role and must be improved since currently 30% of the patients with pacemaker show no benefit from this therapy. We propose to analyze multimodal cardiac images, that are widely available, in order to obtain cardiac mechanical activation times and strains. To this end, we are evaluating the strain estimation based on the incompressible diffeomorphic demons algorithm [59] from volumetric echocardiographics image sequences. Echocardiography myocardium tracking and obtained radial and longitudinal strain are shown in figure 5.

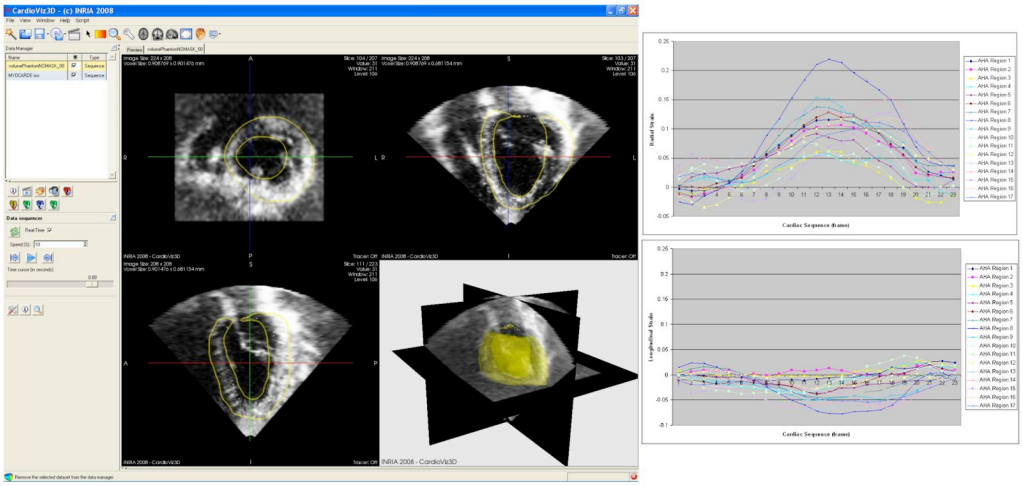


Figure 5. Strain estimation from ultrasound images.

5.1.4. Automatic detection and segmentation of lesions in medical images

Participants: Ezequiel Geremia [Correspondant], Nicholas Ayache, Olivier Clatz, Antonio Criminisi [Microsoft Research Cambridge UK], Hervé Delingette, Bjoern Menze.

Our method aims to automatically detect and segment various types of lesions in 3D MRI scans. The random decision forest framework provides us with a fast discriminative voxel-wise classifier. In conjuction with a random feature generator, this approach allows a better understanding of relevant features and especially of context based features.

5.1.5. Building generic atlases for radiotherapy planning of the head and neck region

Participants: Liliane Ramus [Correspondant], Grégoire Malandain.

This work is done in collaboration with DOSIsoft S.A., Cachan and Université Catholique de Louvain.

In the context of atlas building for the head and neck region, we proposed a novel method based on kappa statistics to estimate an average segmentation from a database of manual segmentations [61]. We also proposed another method to perform this task from a database of manual segmentations with missing contours. Both methods enable to overcome the over-segmentation obtained with the STAPLE algorithm, as illustrated on Fig. 6. We also proposed several approaches to design patient-specific atlases, taking into account clinical information such as the localization and stage of the tumor as well as image criteria.

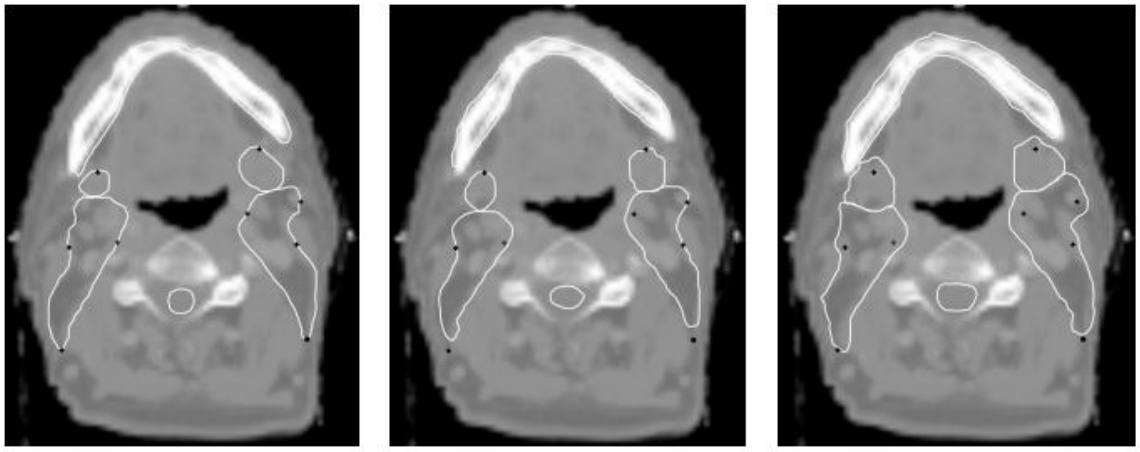


Figure 6. Atlas-based segmentation results using the atlas obtained with our method (middle column) and the atlas obtained with STAPLE (right column), compared with the manual contours (left column). Black landmarks were attached to the manual contours of the lymph node levels II and the submandibular glands to draw the comparison.

5.1.6. Building patient-adapted atlases for radiotherapy planning of the head and neck region

Participants: Olivier Commowiick [Childrens hospital, Boston], Grégoire Malandain [Correspondant].

This work is done in collaboration with DOSIsoft S.A., Cachan and Université Catholique de Louvain.

Because of the high inter-subject anatomical variability, using one single generic atlas to segment every subject in the whole population is perhaps unrealistic. We studied here the building of a patient-specific atlas made of pieces of already segmented images. For each region of interest, the most similar image is retrieved among a database, and then all images are fused to generate a virtual image that is further used as atlas to segment the patient at hand [50].

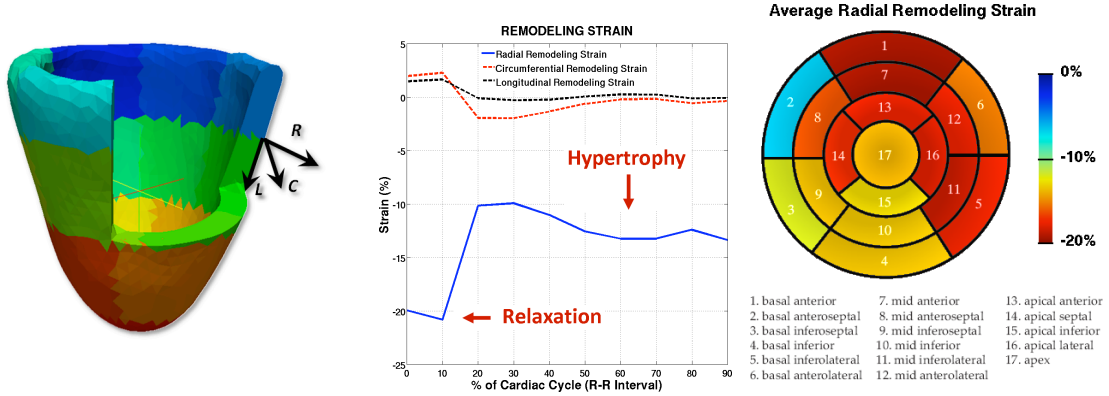
5.1.7. Spatiotemporal Registration of 4D Time-Series of Cardiac Images

Participants: Jean-Marc Peyrat, Hervé Delingette, Maxime Sermesant, Chenyang Xu [Siemens SCR], Nicholas Ayache.

This work was partially funded by Siemens Corporate Research (NJ, USA) and Microsoft Research (Cambridge, UK).

We propose a novel spatiotemporal registration framework for 4D cardiac CT sequences where the temporal registration aims at mapping corresponding physiological events and where the spatial registration aims at mapping corresponding trajectories of points. By introducing *trajectory constraints*, the 4D spatial registration problem can be simplified into a 3D multichannel registration problem solved with an extension of the *Diffeomorphic Demons* [42] to vector-valued images, called *Multichannel Diffeomorphic Demons*.

A thorough evaluation and comparison with other competing methods was performed on real patient data and synthetic data simulated from a physiologically realistic electromechanical cardiac model [24]. Results showed that the proposed method was the best compromise between registration accuracy, spatial and temporal smoothness of intersequence spatial transformations, and computation times. Moreover, we proposed a new prospective example of application with the spatiotemporal registration of 4D cardiac CT sequences of the same patient before and after radiofrequency ablation (RFA) in case of atrial fibrillation (AF). The intersequence spatial transformations over a cardiac cycle provide a new analysis and quantification of the regression of left ventricular hypertrophy and its impact on the cardiac function. All results were published in a journal article [39] and a PhD thesis [27].



(a) Radial, circumferential and longitudinal components of strain

(b) Remodeling strain

(c) Bull's eye view of average radial remodeling strain

Figure 7. (a) The strain of intersequence trasnformations can be decomposed into radial, circumferential and longitudinal components in the pseudo-prolate coordinate system. - (b) Radial remodeling strain of intersequence transformations can be used to measure regression of hypertrophy and recovery of relaxation at end of diastole. - (c) Bull's eye view of average radial remodeling strain for regional analysis of therapy effect.

5.1.8. Atlas-based Registration of Brain Images with Tumors

Participants: Hans Lamecker [Correspondant], Marco Lorenzi, Tommaso Mansi, Xavier Pennec.

This project was funded by the European Commission (FP6 - IST-2004-027749: Health-e-Child)

A patient specific simulation of the tumor growth requires the accurate localisation of the tumour and a model of the fibers around it. A standard approach is to register a diffusion tensor atlas to the patient image. Such pediatric DTI atlases could be available through a collaboration with UNC Chapel Hill (USA). One of the difficulties of this approach is to compute (efficiently, accurately and in a robust manner) deformations in the presence of the tumour where there is clearly no correspondence between the atlas and the image. We started developing an efficient atlas-based registration algorithm integrating spatially adaptive confidence weights, first for the special case of binary masks (tumor vs. no tumor). First results demonstrated the feasability (see Fig. 8).

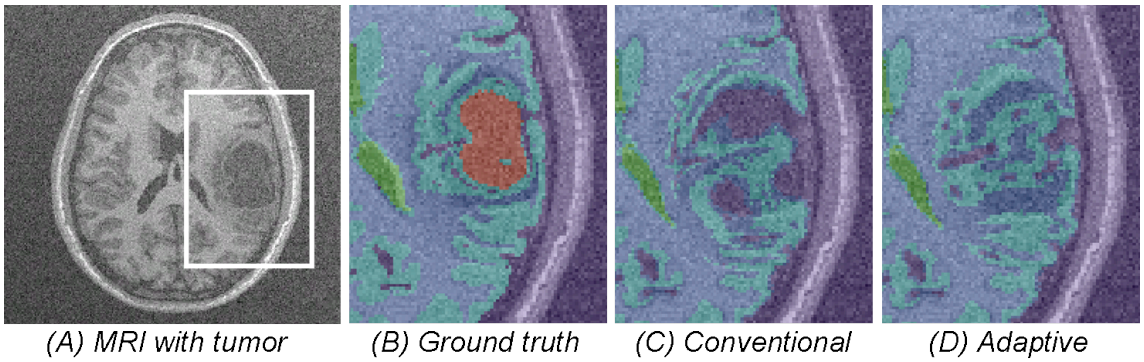


Figure 8. Atlas-based registration of MRI data (A) with simulated tumor (SCI institute, Univ. Utah, USA). Hence, a ground truth segmentation is known (B). The conventional registration approach yields a significantly worse segmentation (C) than our new approach using spatially adaptive regularisation (D).

5.2. Biological Image Analysis

5.2.1. Content-based Image Retrieval for the Early Diagnosis of Gastrointestinal Cancer based on Optical Biopsies

Participants: Barbara André [Correspondant], Tom Vercauteren [Mauna Kea Technologies], Nicholas Ayache.

In vivo pathology from endomicroscopy videos can be a challenge for many physicians. To ease this task, we propose a content-based video retrieval method providing, given a query video, relevant similar videos from an expert-annotated database (see Fig. 9). Our main contribution consists in revisiting the Bag of Visual Words method by weighting the contributions of the dense local regions according to the registration results of mosaicing. We perform a leave-one-patient-out k-nearest neighbors classification and show a significantly better accuracy (e.g. around 94% for 9 neighbors) when compared to using the video images independently. Less neighbors are needed to classify the queries and our signature summation technique reduces retrieval runtime [46], [47].

5.2.2. Pre-clinical molecular imaging

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

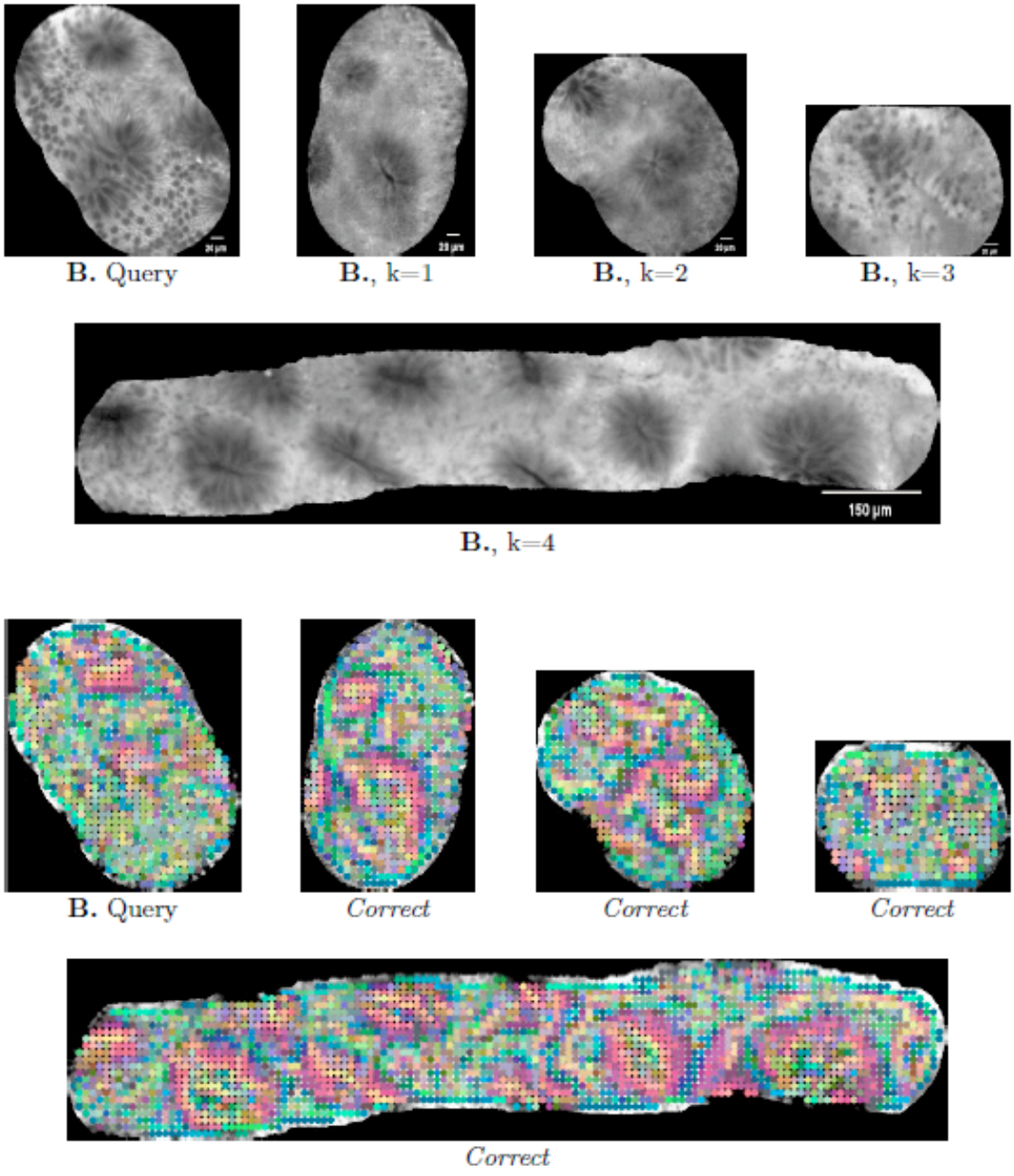


Figure 9. Typical mosaic retrieval results provided by our method from one benign query. ***B.*** *indicates Benign and* ***N.*** *Neoplastic. From left to right on each row: the queried mosaic, and its k-NNs on the top layer, and their respective colored visual words on the bottom layer. FOV of the mosaics: from 260 microns to 1300 microns.*

The aim of this project is to track and to quantify the cancer growth in mice with a coupled SPECT/CT imaging device. The collaboration with the Transporter in Imagery and Oncologic Radiotherapy team (TIRO, UNSA) allow a hand-in-hand work, from the planning of the experiment and manipulation of the animal to the study of the evolution of the disease through the acquisition of SPECT and CT images. Among others, the respiratory motion will be studied as metastasis can appear in organs surrounding the diaphragm (see Fi. 10), since this motion can lead to blurred acquisitions.

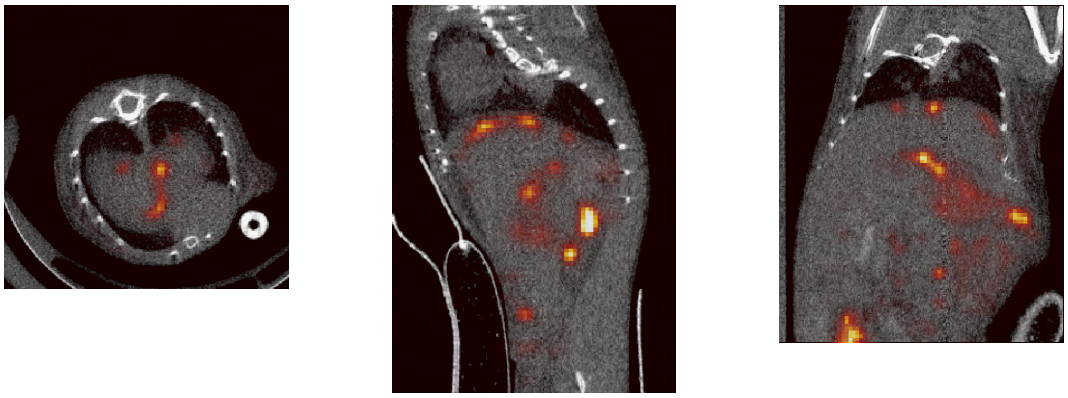


Figure 10. Tranverse, sagittal and coronal slices of a SCID mouse depicting the fusion of a CT image with SPECT data acquired with GE eXplore speCZT CT 120: hot spots reveal liver metastasis from adenocarcinoma of the colon.

5.2.3. Microscopy image reconstruction and automatic lineage tracking of the growing meristem cells

Participants: Romain Fernandez [Correspondant], Grégoire Malandain, Christophe Godin [EPI Virtuals Plants], Jean-Luc Verdeil [Cirad], Jan Traas [INRA/ENS Lyon], Pradeep Das [ENS Lyon].

We studied the tracking of meristem cells using time-lapse confocal microscopy acquisition on early stages flowers of Arabidopsis shoot apical meristems. We designed a reconstruction method (MARS) and a tracking algorithm (ALT) in order to map the segmentations of the same meristem at different times, based on a network flow representation in order to solve the cell assignment problem (see results in Fig. 11). We validated the MARS-ALT pipeline on a four-steps timecourse of an early stage floral bud. The validation by biologists showed the efficiency of the segmentation algorithm on the reconstructed images (near to 96% of well-identified cells) and of the lineaging algorithm (100% of well-identified lineages in the easiest case and 90% in the hardest).

5.3. Computational Anatomy

5.3.1. Statistical Model of the Right Ventricle in Tetralogy of Fallot for Prediction of Cardiac Remodelling

Participants: Tommaso Mansi [Correspondant], Stanley Durrleman, Xavier Pennec, Maxime Sermesant, Nicholas Ayache.

This work has been performed within the Health-e-Child consortium, in close collaboration with several people outside from the lab. In particular I. Voigt (Siemens AG, Erlangen, Germany), B. Bernhardt (McGill University, Montreal Neurological Institute, Montreal, Canada), Dr. A. M. Taylor (Great Ormond Street Hospital, London, UK) and Dr Y. Boudjemline (AP-HP Necker-Enfants Malades, Paris, France).

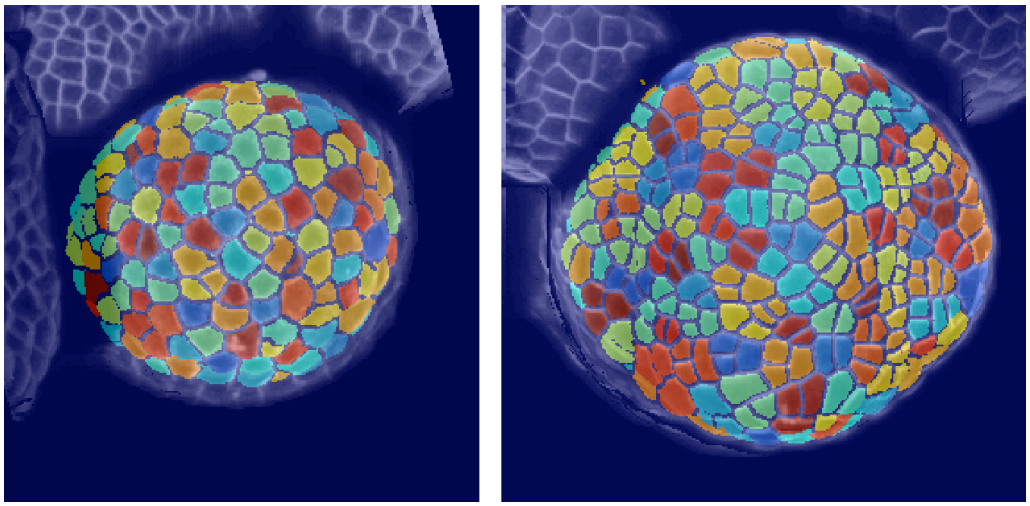


Figure 11. The Automated Lineage Tracking algorithm identifies succesfully most of the descendances (image on the right) of the mother cells (image on the left) of a full Arabidopsis floral bud, despite the 24 hours between the two acquisitions and the big amount of deformations and divisions. The colormap is randomly generated in order to validate visually the detected lineages by comparing the colors on both images.

Understanding and modelling cardiac growth and remodelling is crucial to predict the pathophysiology of patients suffering from repaired tetralogy of Fallot and, therefore, to decide the timing for therapy. In this work, we propose a statistical approach to model cardiac growth in these patients and to exhibit anatomical features that are related to the pathology. From a population of 18 patients (mean age 15 ± 3), we created an average model of the right ventricle anatomy at end diastole by using the unbiased currents-based template estimation method proposed in [32]. Deformation modes are computed to exhibit the variabilities in right ventricle anatomy. Variabilities correlated with body surface area (a continuous clinical index highly correlated with age) and with regurgitation severity are selected using ad-hoc statistical analyses. A generative model of right ventricle growth is obtained from the selected deformation modes. Visual inspection of relevant deformation modes showed realistic patterns according to cardiologists involved in the project. Moreover, the generative statistical model of right ventricle growth has been successfully tested on two new patients. Their body surface area could be predicted by using right ventricle shape only.

5.3.2. Brain morphometry for Alzheimer's disease

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

The work started in October 2009 is actually focused on the definition of a workflow for the robust evaluation of Alzheimer's disease brain changes in datasets of longitudinal structural MRIs.

This will help in the early diagnosis of the disease and in the clinical trials to monitor the effect of new drugs, reducing costs and invasiveness of measurements. Finding surrogate markers to evaluate the progression of Alzheimer's disease is of fundamental importance and currently several measures based on specific functional images are available, but they are expensive and require the injection of mulecular markers.

Several possible algorithms for deformations mapping were investigated, with a particular emphasis on the Symmetric Diffeomorphic Demons. In particular, we are investigating improved measurement of local volume changes.

5.3.3. Statistical regularization of DTI registration

Participants: Andrew Sweet [Correspondant], Xavier Pennec.

In 2008, methods were created to perform efficient non-parameteric registration of diffusion tensor (DT) images using an exact finite strain differential [44]. In this work, we have already adapted these methods to perform the same type of registration in the 'log-domain' with symmetric demons forces, as was done in [118] for scalar images. Initial results (see Fig. 12) suggest that DT registration exhibits the same benefits from these adaptations as those observed for scalar images. Additionally, these should allow us to easily calculate reliable deformation statistics over a population of diffusion tensor images registered to a general anatomical template. The ultimate goal of the project is to incorporate these statistics back into the regularization scheme, so that we can improve performance and generate smoother deformation fields.

Figure 12. A moving DT image (left) is registered to a fixed DT image (left-center) using the existing DT-REFinD method [44] and produces a warped DT image (right-center) that is registered to the fixed image, while still retaining the white matter structures of the moving image. Performing this in the log-domain produces very similar output (right), but allows us to easily calculate deformation statistics. Images use the classic DTI color encoding: red defines the left-right, green defines the posterior-anterior and blue defines the inferior-superior axes.

5.4. Computational Physiology

5.4.1. Personalisation of Cardiac Electrophysiology Model for simulation of Patient-Specific Ventricular Tachycardia (VT)

Participants: Jatin Relan [Correspondant], Hervé Delingette, Maxime Sermesant, Nicholas Ayache.

This work is funded by the FP7 European Project euHeart.

Modeling of the cardiac electrophysiology has been an important research interest for the last few decades, but in order to translate this work to the clinics, there is an important need for personalisation of such models, i.e. estimation of the model parameters that best fit the simulation to the clinical data. In this work, we propose a method to personalize a 3D simplified ionic monodomain electrophysiology model, the Mitchell-Schaeffer (MS) model. The personalization is performed using the 2D epicardial depolarization and repolarization maps obtained *ex-vivo* from optical imaging of porcine healthy heart. The model parameters are estimated by matching the simulated and experimental conduction velocities, Action Potential Duration (APD) and APD Restitution (see Fig. 13). APD restitution is defined as the relationship of the succeeding APD with the preceeding diastolic interval (DI). After personalisation of the model, we evaluate the prediction ability of the model for different epi- and endocardial pacing scenarios [62]. This personalisation strategy could also be applied to clinical data where the 2D optical data can be replaced by 2D endo- or epicardial electro-anatomical mapping of the patient. The model is also used to simulate clinical VT-Stim Protocol to induce VT in patients, which is used to plan ablation lines in radio-frequency ablation therapy [63], [64].

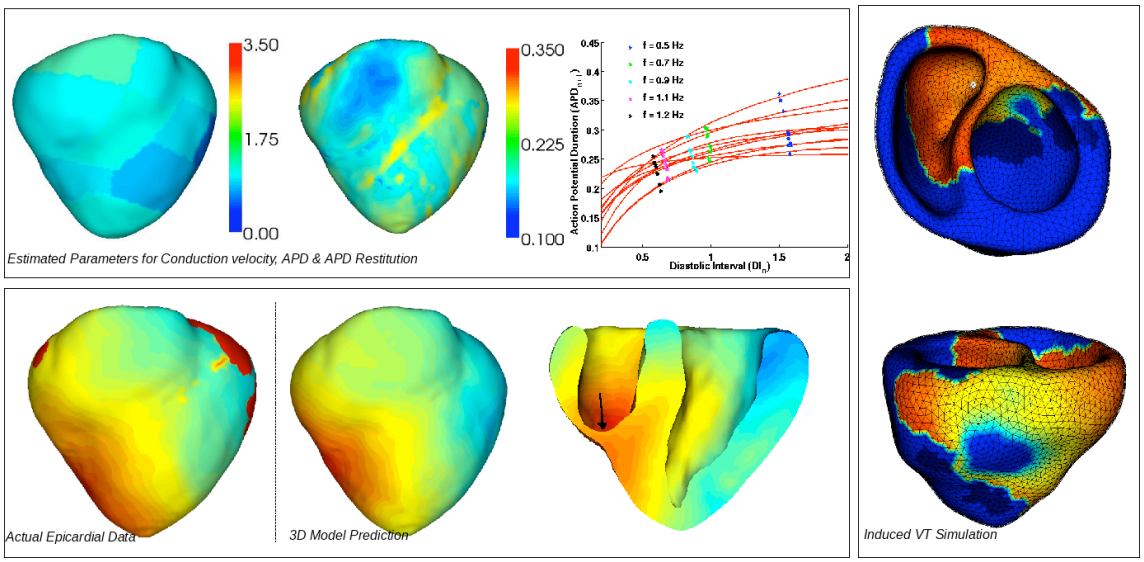
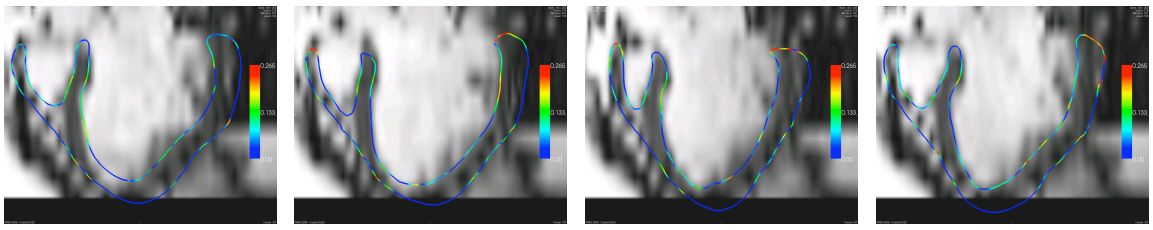


Figure 13. Estimated parameters of MS model used for prediction of cardiac electrophysiology for different pacing scenario i.e. Right Ventricle Endocardium, and simulation of clinical VT-Stim protocol for induction of VT [62].

5.4.2. Data assimilation for the estimation of the mechanical parameters of the heart model.

Participants: Florence Billet [Correspondant], Maxime Sermesant, Hervé Delingette, Nicholas Ayache.

In this work, we build a patient-specific model by coupling an electromechanical model [24] and cine-MRI data. To achieve this personnalisation, we have to estimate both the state (*i.e* the position and the velocity) and the parameters of the electromechanical model. Thus, we first estimated the state of the heart by using a proactive deformable model [48] (see Fig. 14). Second, we used variational assimilation methods to estimate some mechanical parameters of the heart.



(a) $t = 0.01$s (b) $t = 0.337$s (c) $t = 0.574$s (d) $t = 0.921$s

Figure 14. Short axis (top) and long axis (bottom) views at different times of the cardiac cycle. Contours of the mesh estimated with the proactive deformable model are surimposed with the images. Colors correspond to the intensity of the image forces applied on the heart surfaces [48].

5.4.3. Biomechanical modeling of the knee joint

Participants: Tobias Heimann [Correspondant], Francois Chung, Olivier Clatz, Hervé Delingette.

Within the EU project 3D Anatomical Human, our goal is the construction of subject-specific models of the knee joint to predict exact movement patterns for the lower limbs. To this end, we developed a highly efficient finite element model for ligament tissue, which features realistic anisotropic behavior and non-linear stress-strain response [54]. The collagen fiber directions required for this model are estimated automatically from ligament geometry. Using this material model and segmentations from MRI data, we implemented an interactive simulation of a subject-specific joint in the Open Source software SOFA (see Fig. 15). Current work focuses on improving collision detection and response by employing implicit surface descriptions.

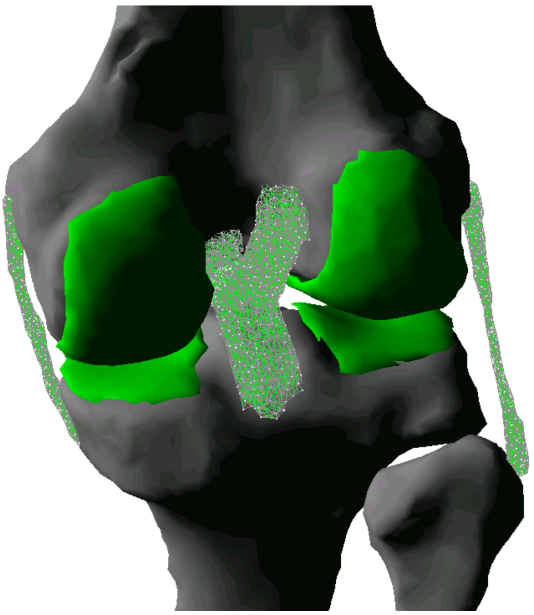


Figure 15. 3D finite element model of a subject-specific knee joint with cruciate and collateral ligaments.

5.4.4. Biomechanical Liver Modeling

Participants: Stéphanie Marchesseau, Erik Pernod, Tobias Heimann, Hervé Delingette [Correspondant].

In the context of the Passport European project, a realistic biomechanical model of the liver has been developed based on the SOFA platform. This model relies on visco-elasticity for large displacements (non-linear elasticity) and also a poro-elastic behavior to cope with the blood motion within the hepatic parenchyma. Specific attention has been paid to the optimized formulation of hyperelastic materials on a linear tetrahedral FEM mesh. To this end, we chose to isolate in the strain energy the terms involving the infinitesimal volume change J in order to optimize the assembly of the nodal forces and stiffness matrices. Furthermore, we have described the visco-elasticity of the liver using Prony series where parameters have been estimated from rheological experiments performed at the University of Strasbourg.

Comparison with analytical curves and other FEM software confirmed the accuracy of the visco-elastic formulation model. Additional work needs to be done in order to combine poro-elasticity with the visco-elastic model of the liver and to build a realistic patient specific liver model suitable for real-time surgery simulation.

5.4.5. Adaptive Tetrahedral Meshing for Personalized Cardiac Simulations

Participants: Hans Lamecker [Correspondant], Tommaso Mansi, Jatin Relan, Hervé Delingette.

This project was funded by the European Commission (FP7 - ICT-2007-224495: euHeart)

Personalized simulation for therapy planning in the clinical routine requires fast and accurate computations. The aim of this project was to analyze the meshing requirements for finite-element simulations of ventricular tachycardia and Tetralogy of Fallot. We have evaluated and benchmarked a variety of existing meshing software systems. Based on the insights gained from this study, we have developed a pipeline for generating high-quality, adaptive meshes (Fig. 16). The results indicate how to construct computationally efficient meshes in electrophysiological and electromechanical cardiac simulations [57].

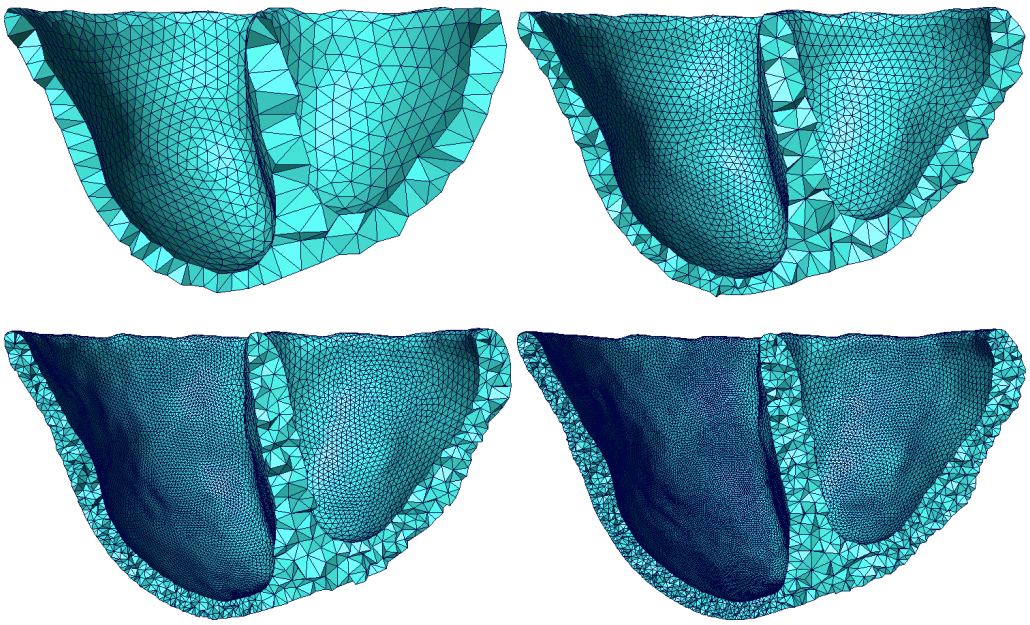


Figure 16. Four meshes with varying number of layers in the myocardium wall for studying discretization effects in electromechanical simulations.

5.4.6. Interactive Medical Simulation based on the SOFA Platform

Keywords: *Manifold triangulation*, *edge swapping*, *incision*, *manifold tetraedrisation*, *point snapping*, *resection*.

Participants: Erik Pernod [Correspondant], Hervé Delingette.

SOFA is a software platform developed jointly with mainly the Alcove and Evasion project teams. Several developments have been performed in order to improve the topological description of meshes in SOFA. For instance, manifold triangulations and tetrahedrisations have been implemented as specialization of generic triangulations classes. Furthermore, the handling of topological changes has be extended to cope with manifold triangulation by avoiding the removal or additional of triangles when it violates the manifold constraint.

In addition, the method for interactively cutting triangular meshes has been much improved by allowing the incision path to go through existing vertices and edges in order to minimize the number of created triangles. The creation of several connected components during the simulation of incision is now possible.

The support of several input and output file formats has been improved and streamlined by defining mesh loaders factory in SOFA. For instance, this allows us to import in SOFA all meshes and anatomical information (e.g. fiber orientation) used in our proprietary platform MIPS. Finally, in order to simulate the propagation of electrical potentials in the heart, we have developed a software module that implements reaction-diffusion partial differential equations on a triangular or tetrahedral mesh.

6. Contracts and Grants with Industry

6.1. European Marie Curie RTN project 3D Anatomical Human

Participants: François Chung, Olivier Clatz, Hervé Delingette [correspondant], Tobias Heimann.

The Research Training Network 3D Anatomical Human (MRTN-CT-2006-035763 , http://3dah.miralab.unige.ch/) is a European project aiming at developing realistic functional three-dimensional models for the human musculoskeletal system, the methodology being demonstrated on the lower limb. François Chung has been hired as ESR (Early Staged Researcher) and Tobias Heimann as ER (Experienced Researcher). In this context, INRIA has collaborated with UCL (UK) and University of Geneva for the acquisition and segmentation of the MR images of the lower limbs and with Istituti Ortopedici Rizzoli (Italy) and EPFL (Switzerland) for the biomechanical modeling of the knee. Other research groups include the Vrije Universiteit Brussel (Belgium), Aalborg University (Denmark) and CRS4 (Italy). Within this project, a plenary meeting has been organized in Sophia-Antipolis on Oct 19-20 2009. Also in 2009, Asclepios has hosted several students for a few weeks from research groups involved in this Marie-Curie project : M. Chen from University College London, A. Sansholm and N. Pronost from EPFL and J. Schmid from University of Geneva.

6.2. Virtual Physiological Human Network of Excellence

Participants: Nicholas Ayache, Olivier Clatz, Hervé Delingette, Florence Dru [Correspondant], Maxime Sermesant.

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.

During the first year of the VPH NoE, several deliverables were submitted by INRIA to the project coordinators and to the commission, regarding the horizontal data fusion task:

- A document presenting software requirements for a mesh to mesh or mesh to image manual fusion tool. The purpose of this document is to explain the purpose and features of this fusion tool, how it works and the constraints under which it must operate.
- A software for automatic image fusion has been made available. This software handles rigid and affine transforms and is based on ITK open-source components.
- A report presenting the assessment of the rigid fusion process for two algorithms belonging to two main classes of fusion approaches: geometric and iconic. This assessment described in this document is a first step towards designing more robust, accurate and faster algorithms. It also provides an evaluation framework that could be used to assess performance of other fusion algorithms.
- In the framework of collaboration between VPH-NoE partners, and through interaction between the Toolkit team and the exemplar projects, an use case presenting how horizontal data fusion can be used at different steps of a tumour growth modelling workflow has been written.

6.3. PASSPORT

Participants: Stéphanie Marchesseau, Hervé Delingette [Correspondant].

The PASSPORT project (Ref 223894, http://www.passport-liver.eu/) is a 3-year (2008-2011) STREPS European project which aims at developing patient-specific models of the liver. Those models should integrate anatomical, functional, mechanical, appearance, and biological descriptions of the liver. More precisely, it is expected to simulate the liver deformation due to breathing as well as the liver regeneration after hepatectomy.

INRIA is involved in this project through the teams Alcove, Evasion and Asclepios and around the software platform SOFA which will serve as the integration plartform for the project. IRCAD (Strasbourg) is the project leader which also gathers TUM (Munich, Germany), UCL (London, UK), ETH (Zurich, Switzerland), ICL (London, UK), INSERM (Paris), ULP (Strasbourg), IZBI (Leipzig, Germany).

One plenary meeting has been organized in 2009 in Strasbourg. We have collaborated with the Fluid Mechanics department of the University of Strasbourg in order to build a realistic biomechanichal model of the liver and integrate it in the SOFA platform.

6.4. EuHeart

Participants: Nicholas Ayache, Florence Billet, Hervé Delingette [Correspondant], Tommaso Mansi, Adityo Prakosa, Ken Wong, Jatin Relan, Maxime Sermesant.

The EuHeart project (Ref 224495, http://www.euheart.eu/) is a 4-year (2008-2012) 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. This project is lead by Philips Research and also involves two other Inria teams (Macs and Reo) as well as Univ. of Oxford (UK), Univ. of Auckland (New Zealand), Univ. of Pompeu Fabra (Barcelone, Spain), Univ. of Karlsruhe (Germany), King's College London (UK), Univ. of Sheffield (UK), Amsterdam Medical Center (The Netherlands). One plenary and three topical meetings in WP6 have been organized in 2009. The general assembly of EuHeart has also been organized in Sophia-Antipolis on Sept 3rd and 4th 2009.

6.5. Health-e-Child

Participants: Xavier Pennec [Correspondant], Nicholas Ayache, Stanley Durrleman, Ender Konukoglu, Hans Lamecker, Tommaso Mansi, Maxime Sermesant.

The European project Health-e-Child (IST 027749, http://www.health-e-child.org/), coordinated by Siemens, Germany, aims to create an IT platform to share pediatric knowledge and clinical data based on grid technologies. The project currently brings together eight European countries and intends to integrate heterogeneous biomedical data from three clinical specialities (cardiology, neurology and rheumatology) coming from three pediatric hospitals in Europe (Hôpital Necker in Paris, France, Giannina Gaslini institute in Genoa, Italy, and Great Ormond Street Hospital in London, Great-Britain). This integration should lead to a better understanding of the pathologies studied, and, in the long term, provide real tools to help pediatricians make the right decisions. In this project, the role of the Asclepios team is to model the congenital heart pathologies of the right ventricle and the grown of brain tumors. A description of the work done is available at http://www-sop.inria.fr/asclepios/projects/hec/.

6.6. Cooperative Advanced REsearch for Medical Efficiency (Care4Me)

Participants: Grégoire Malandain [Correspondant], Nicholas Ayache, Hervé Delingette, Xavier Pennec, Maxime Sermesant.

The ITEA2 European project Cooperative Advanced REsearch for Medical Efficiency (Care4Me) aims to increase 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 disease), 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.

6.7. Microsoft Research Award

Participants: Nicholas Ayache [Correspondant], Grégoire Malandain, Olivier Clatz, Hervé Delingette, Xavier Pennec, Maxime Sermesant.

This European prize funded by Microsoft Research and awarded jointly by the Royal Society (UK) and the Académie des Sciences (FR) allows us to co-fund some basic research efforts on the development of personalized models of brain tumors, cardiac function, and brain anatomy; The grant was awarded for a period of 18 months, starting in Nov. 2008.

6.8. CIFRE PhD Fellowships

6.8.1. Dosisoft

The work of Liliane Ramus, *Digital anatomical atlases for radiotherapy planning*, is supported by a PhD fellowship from the Dosisoft company.

6.8.2. Mauna Kea Technologies

The work of Barbara André, *Smart Atlas for the Early Diagnosis of Gastrointestinal Cancers from Optical Biopsy Images*, is supported by a PhD fellowship from the Mauna Kea Technologies company.

6.9. Other contracts

The contracts Cancéropôle PACA CPER Telius, Maestro[6], Miniara, Philips, and Siemens are described in our previous activity reports.

7. Other Grants and Activities

7.1. Regional initiatives

7.1.1. Regional PhD fellowships

Ender Konukoglu is partially supported by a Région Provence-Alpes Côte d'Azur PhD fellowship.

7.2. National initiatives

7.2.1. INRIA Large Collaborative Effort CARDIOSENSE3D

Participants: Hervé Delingette [coordinator], Nicholas Ayache, Maxime Sermesant, Florence Billet, Tommaso Mansi, Adityo Prakosa, Nicolas Toussaint, Damien Lepiller, Jatin Relan, Jean-Marc Peyrat.

[6] http://www.maestro-research.org/

The action CARDIOSENSE3D is a 4-year large initiative action (2005-2009) on the topic of cardiac simulation. This action gathers the expertise of four INRIA research teams (Asclepios, Macs, Reo and Sisyphe) on this multi-disciplinary research topic. CardioSense3D has three main objectives:

1. to build a cardiac simulator that couples four different physiological phenomena,
2. to estimate patient specific parameters and state variables from observations (images, electrophysiology mappings) of the cardiac activity,
3. to build several applications to solve clinical problems related to the diagnosis or therapy of cardiac pathologies.

H. Delingette is in charge of the coordination of this action. More information can be found at the following web site http://www.inria.fr/CardioSense3D/

7.2.2. ANR TechLog NeuroLOG

Participants: Xavier Pennec [correspondant], Andrew Sweet, Pascal Girard, Grégoire Malandain.

The ARN TLOG NeuroLOG (2007-2010, neurolog.polytech.unice.fr): project adresses software technologies for the integration of processes, data and knowledge in neurological medical imaging: management and access of partly structured data, heterogeneous and distributed in an open environment; access control and protection of private medical data; control of workflows implied in complex computing process on grid infrastructures; extraction and quantification of relevant parameters for three different pathologies: Multiple sclerosis, Brain Vascular Stroke and Brain tumors.

This is a multi-disciplinary project which associates partners in software technologies (I3S at Sophia-Antipolis, LRI in Orsay), databases (Business Objects, LaRIA, Visages at IRISA-Rennes) and medical imaging (Visages at IRISA-Rennes, Visioscopie, U594, IFR49, Asclepios at INRIA-Sophia).

7.2.3. INRIA Cooperative Research Initiative 3DMorphine

Participants: Xavier Pennec [coordinator], Stanley Durrleman.

The aim of this two-year Collaborative Research Initiative is to devise, implement, validate and apply new mathematical and computational methods for the automated morphometric analysis of extant and extinct hominid cranial virtual endocasts. The particular interest of the Asclepios team is on the morphometric analysis of endocasts on different populations of subjects, including: modern humans, fossil pre-humans and humans (such as South African australopithecines, European Cro-Magnons and Neandertals), and the closest extant relatives of modern humans (i.e. chimps and bonobos).

The action is led by S. Prima from the Visages team at INRIA, Rennes, France. Other participants include the ICAR team at CNRS, Montpellier, France, the lab of paleoanthropology and anatomical imaging at the Université Paul Sabatier, Toulouse, France and the lab of general histology, neuroanatomy and neuropathology at the Université Libre de Bruxelles, Belgium.

7.2.4. Other Initiatives

The ATP CIRAD Meristem Grant and QUALICORE are described in our previous activity report.

7.2.5. Consulting for Industry

- Nicholas Ayache is scientific consultant for the company Mauna Kea Technologies (Paris).
- Grégoire Malandain is a member of the technical council of the company Dosisoft (Paris), a subsidiary from the Gustave Roussy Institute and the Curie Institute (Paris).

7.2.6. Collaboration with national hospitals

Here we provide a list of research centers in national hospitals with whom we collaborate in common research projects.

7.2.6.1. IRCAD, hôpitaux de Strasbourg

Pr. Marescaux and L. Soler : hepatic surgery simulation segmentation of abdominal structures from CT scan images and augmented reality for guidance in hepatic surgery [105], [106].

7.2.6.2. Centre anti-cancer Antoine Lacassagne, Hôpital Pasteur, Nice

Dr. Bondiau participates in our research on atlas registration for radiotherapy planning and on tumour growth simulation.

7.2.6.3. CHU de Nice, Hôpital Pasteur

We continue our collaboration with Dr. C. Lebrun-Frenay of the neurology department, and with Dr. Chanalet of the radiology department, within the framework of a study on the temporal evolution of MS lesion load [45], [28].

7.2.6.4. CHU de Nice, Hôpital L'Archet

We continue our collaboration with Pr. Dellamonica and Dr. Vassallo of the infectiology department on the study of cognitive impairment in HIV patients.

7.2.7. Collaboration with international hospitals

7.2.7.1. 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. The XMR facility within this hospital is a unique possibility to validate and exploit the cardiovascular modelling work.

7.3. Foreign Associated Team: CompuTumor

Participants: Nicholas Ayache, Olivier Clatz [Correspondant], Pierre Fillard, Polina Golland [CSAIL, MIT], Ender Konukoglu, Xavier Pennec, Tom Vercauteren, Simon Warfield [CRL, Harvard Medical School], William Wells [CSAIL, MIT], Boon Thye Thomas Yeo [CSAIL, MIT].

The CompuTumor associated team has been funded early 2007. This project is dedicated to the study of brain tumor models and their integration with medical images to better assist diagnosis and therapy. The project strongly relies on the current collaborations between INRIA and world leading teams with complementary technical and clinical expertise in Boston and Nice.

In 2008, the work on DTI processing was continued and extended [120], [121]. New algorithms were developped to assess the growth of slowly evolving tumors [99]. Ongoing work aims at coupling models and images to infer quantitative tumor paramters that could be used for therapy planning.

8. Dissemination

8.1. Promotion 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**[7]. This scientific journal was created in 1996 and is published by Elsevier. Its impact factor in 2003 was 4.4, it was 3.2 in 2004, 3.14 in 2005, 3.26 in 2006, 3.5 in 2007 and 3.6 in 2008.

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).

N. Ayache is associated editor of **IEEE Transactions on Medical Imaging**[8].

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

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

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).

G. Malandain is a member of the editorial board of the journal *International Journal on Computer Vision* (Kluwer).

X. Pennec is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier) and of the *International Journal on Computer Vision* (Kluwer).

8.1.2. Participation in the organization of conferences

N. Ayache, H. Delingette, M. Sermesant, I. Strobant, A. Cortell were strongly involved in the organization of the FIMH'2009 conference (Functional Imaging and Modeling of the Heart). The conference gathered together 120 experts from 15 countries between 3 to 5 June 2009 in Nice. More precisely N. Ayache was Conference Chair, H. Delingette Program Chair, M. Sermesant Publication Chair, I. Strobant (Web Site Chair), A. Cortell (Local Organization Chair). Proceedings were published by Springer Verlag (500 pages, cf. http://www-sop.inria.fr/asclepios/events/FIMH09/) [74].

H. Delingette was the program chair of the conference Functional Imaging and Modeling of the Heart (FIMH'09) organized in Nice, a member of the scientific review committee of International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'09), the International Symposium on Biomedical Imaging (ISBI'09) and the Conference on Information Processing in Medical Images (IPMI) 2009, a program committee member of the International Conference on Computer Graphics Theory and Applications (GRAPP'09), the conference on Virtual Reality Interactions and Physical Simulation (VRIPHYS'09), the workshop on 3D Physiological Human (3DPH'09), the 5th International Symposium on Visual Computing (ISVC'09).

G. Malandain was a member of the program committee of the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'09), and a member of the review committees of the International Symposium on Biomedical Imaging (ISBI'09), MICCAI workshop on Medical Image Analysis on Multiple Sclerosis (MIAMS'09), and the ateliers de travail sur le traitement et l'analyse de l'information (TAIMA'2009).

X. Pennec was Workshop co-chair and a member of the program committee of International Conference on Medical Image Computing and Computer Assisted Intervention MICCAI'09, track chair at the Medical Physics and Biomedical Engineering World Congress 2009, member of the program committee of Information Processing in Medical Images (IPMI) 2009, the 13th IMA conference on Mathematics of Surfaces 2009, the Probabilistic Models for Medical Image Analysis PMMIA 2009) MICCAI workshop.

M. Sermesant was a member of the program committee of the Functional Imaging and Modelling of the Heart conference and of the MICCAI 2009 Workshop on Cardiovascular Interventional Imaging and Biophysical Modelling.

8.1.3. Scientific animation

Nicholas Ayache is member of the scientific council of the Institute for Technologies of INSERM. He is also a member of the "comité sectoriel du département Biologie-Santé of the "Agence Nationale pour la Recherche (ANR)", and a member of the "Comité de la Recherche Biomédicale en Santé Publique (CRBSP)" of the Nice hospitals from beginning of 2008.

G. Malandain is deputy scientific director of INRIA in charge of the Computational Sciences for Biology, Medicine and the Environment domain. He is also chairing the local experimentation and software development committee (CDT).

G. Malandain was an evaluator for the Axa Research Fund, and for Paris 13 university.

O. Clatz is a member of the scientific committee and evaluator for the research cluster ISLE of Rhônes-Alpes.

X. Pennec was an evaluator for the French research evaluation agency (AERES), for the Natural Sciences and Engineering Research Council of Canada (NSERC), for the (US) Air Force Office of Scientific Research (AFSOR), for the ARED and DEFIS program of the French Research Agency (ANR) and for the research council of the University of Liege (Belgium). He was also a member of the Jury of the Gilles Kahn SPECIF PhD award, member of the Jury of the Chair of Numerical Medicine between INRIA and the University of Nice.

H. Delingette was 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 an austrian competence center in the COMET program, for several project proposals submitted to the french research agency ANR.

M. Sermesant is a member of the INRIA-INSERM reflexion group on "modelling living systems". He is an evaluator for the Biotechnology and Biological Sciences Research Council (BBSRC), and the National Institute for Health Research (NIHR), EPSRC United Kingdom, and New Zealand and Netherlands Research councils. He is 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).

8.2. University teaching

École Centrale de Paris. H. Delingette, G. Malandain and X. Pennec are co-responsible of 2 modules on medical imaging (formation and analysis of medical images) (45 hours of lectures). These 2 modules are common to the Master MVA of ENS Cachan "Mathematiques, Vision et Apprentissage".

Master PENSUM, ENS Lyon / Univ. Nice-Sophia-Antipolis. X. Pennec is responsible of a 21h module on Mathematics for Medical Image processing.

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 (6h) and Gregoire Malandain (3h).

Master Génie biomédical, université de Nice Sophia-Antipolis. G. Malandain is responsible of one module of 48 hours (24 hours of lectures + 24 hours of practical work) with the participation of Liliane Ramus.

Master IMA, université Pierre et Marie Curie. G. Malandain gave a 3 h course.

Diplôme Inter Universitaire - Radiothérapie externe Haute Technicité. G. Malandain gave a 3 h course.

Enseignement post-universitaire: imagerie en radiothérapie externe. G. Malandain gave a 3 h course.

Grégoire Malandain gave a tutorial presentation at the winter school "Hot Topics in Molecular Imaging - TOPIM" organized by the European Society for Molecular Imaging.

Applied Mathematics Master, Ecole des Ponts et Chaussées O. Clatz gave a 3h lecture.

Hervé Delingette gave a tutorial presentation on Cardiac electrophysiology and brain tumor growth at the School CEA-INRIA-EDF at INRIA Rocquencourt. He gave also a tutorial presentation on image segmentation during the training session organised during the plenary meeting of the 3D Anatomical Human project in Sophia-Antipolis.

8.3. PhD Theses and Internships

8.3.1. PhD defended in 2009

1. Ender Konukoglu. Modeling Glioma Growth and Personalizing Growth Models in Medical Images. PhD Thesis, Université Nice Sophia-Antipolis, February 2009.

2. Jean-Marc Peyrat. Comparison of Cardiac Anatomy and Function: Statistics on Fibre Architecture from DT-MRI and Registration of 4D CT Images. PhD Thesis, Nice Sophia Antipolis University, November 2009.
3. Jean-Christophe Souplet, *Évaluation de l'atrophie et de la charge lésionnelle sur des séquences IRM de patients atteints de sclérose en plaques*, Nice-Sophia Antipolis University, January 21, 2009. Committee: Christian Barillot (president and reviewer), Jean-Paul Armspach (reviewer), Grégoire Malandain (supervisor), Sébastien Ourselin (referee), Christine Lebrun (invited).

8.3.2. Current PhDs

1. Barbara André, *Smart Atlas for the Early Diagnosis of Gastrointestinal Cancers from Optical Biopsy Images*, École des Mines de Paris. Cifre collaboration with Mauna Kea Technologies.
2. Florence Billet, *Analyse de la fonction cardiaque à l'aide d'un modèle électromécanique du coeur*, Nice-Sophia-Antipolis University. Cardiosense3D.
3. Marine Breuilly, *Tracking and quantification of tumour processes in rodents with SPECT imaging* , Nice-Sophia-Antipolis University.
4. François Chung, *Regional shape and appearance modelling for deformable model-based image segmentation*, École des Mines de Paris.
5. Stanley Durrleman, *Joint modeling of the brain growth and of the population variability. Application to pediatric brain imaging.* Nice-Sophia Antipolis University. In collaboration with A. Trouvé, CMLA, ENS.
6. Romain Fernandez, *3D segmentation and reconstruction of rice's root meristem from multiphoton microscopic images*, Montpellier university. In collaboration with C. Godin, Virtual Plants.
7. Ezequiel Geremia, *Multi-scale computational models of brain tumors for medical image analysis*, Nice-Sophia Antipolis University.
8. Heike Hufnagel, *Statistical shape analysis of normal and pathological organs within the abdomen*, University of Hamburg. PhD in collaboration with Prof. Dr. Heinz Handels, Institut für Medizinische Informatik, University of Hamburg.
9. Yonni Levy, *Advanced Guidance in interventional cardiology* , École des Mines de Paris.
10. Marco Lorenzi, *Imaging Biomarkers in Alzheimer's Disease* , Nice-Sophia Antipolis University.
11. Tommaso Mansi *Modelling of pediatric cardiac pathologies*. École des Mines de Paris.
12. Nicolas Toussaint, *In vivo cardiac DTI* , KCL, London.
13. Adityo Prakosa, *Analysis and Simulation of the heart function from multimodal cardiac images*, Nice-Sophia Antipolis University.
14. Liliane Ramus, *Digital anatomical atlases for radiotherapy planning*, Nice-Sophia Antipolis University. Cifre collaboration with Dosisoft.
15. Jatin Relan, *Planning of radiofrequency ablation of the heart using electromechanical models personnalized from cardiac images and electrophysiological signals*, Ecole des Mines.

8.3.3. Participation to thesis committees

N. Ayache participated as chair of the PhD committee of X. Hubert (Centrale Paris & Neurospin), as a committee member to the PhD defense of Thomas Yeo (at MIT, USA) and F. Benmansour (Paris Dauphine), as a supervisor or co-supervisor to the committee of E. Konukoglu and J.M. Peyrat (Sophia-Antipolis), as a committee member to the Habilitation of B. Thirion (Neurospin).

Hervé Delingette participated as co-supervisor to the PhD thesis of J-M. Peyrat (Nice University) as reviewer to the Phd thesis committee of J. Laforet (Montpellier II University), O. Somphone (Paris-Dauphine University), E. Arbabi (EPFL, Switzerland), J. Abi-Nahed (Impérial College London).

Grégoire Malandain participated as chair to the PhD thesis committees of S. Stoma (Montpellier university) and L. Provot (Nancy I university), as reviewer to the PhD thesis committee of J. Anquez (Télécom ParisTech) and to the Habilitation committee of F. Richard (Paris 5 university) as referee to the medecine thesis committee of M. Cohen (Nice university), to the PhD thesis committees of A. Isambert (Paris XI university) and O. Nempont (Télécom ParisTech), and as supervisor to the PhD thesis committee of J.-C. Souplet (Nice Sophia-Antipolis university).

Xavier Pennec participated as referee to the PhD thesis committees of Manik Bhattacharjee (University Paris XI Orsay), Guillaume Auzias (University Paris XI Orsay), Matthieu Perrot (Ecole normale supérieure, Cachan) and Mickaël Péchaud (Ecole Normale Supérieure, Cachan).

Maxime Sermesant participated as invited member to the PhD thesis committee of Jean-Marc Peyrat.

8.4. Participation to workshops, conferences, seminars, invitations

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:
  - a Keynote at the SPIE Medical Imaging conference in Orlando (USA) on Feb 9, 2009, on the anniversary date of Gilles Kahn death, and dedicated the talk to honor his memory.
  - a Lecture at the "Cercle des industriels" of the Academy of Sciences (Paris) 3 March, 2009
  - a Keynote at ETSI (Sophia-Antipolis) for the ERCIM organization on April 2, 2009.
  - a Keynote at the Fondation Sophia Antipolis for the cycle of conferences "La Science à Sophia" on April 6, 2009;
  - a Keynote at the Academy of Sciences (Paris) for the "Challenges of the 21st Century" on May 12, 2009
  - a Keynote at the Isaac Newton Institute of Cambridge (UK) for the "Cardiac Physiome Project", on July 23, 2009
  - 4 invited lectures at the international summer school "Molecular and Medical Image Analysis and BioInformatics" in Lipary (Italy) between 11 and 18 July 2009.
- **Olivier Clatz** gave an invited lecture at the "Imaging and Measurements in Biomechanics and Medical Engineering" workshop in Talence and at the "Imaging and Measurements in Biomechanics and Medical Engineering" workshop in Paris.
- **Hervé Delingette** gave an invited lecture at the INRIA Visiting Committee on December 18th, at the conference ICT Bio 2008 at Brussels le 24 octobre 2008, at the Miccai workshop on 3D analysis of cardiac structure and function on Sept. 10th in New-York (USA), at the ENS Cachan symposium on physiopathology modeling on June 16th 2008, at the GID conference in Ibiza (Spain) on May 8th 2008.
- **Grégoire Malandain** gave invited plenary talks at: ESTRO Conference on Physics and Radiation Technology for Clinical Radiotherapy, and Journée Thématique GDR CNRS-INSERM STIC Santé "Volumes cibles biologiques en Radiothérapie".

  He also gave an invited seminar at Telecom ParisTech.
- **Xavier Pennec** gave invited talks at the trimestrial colloquium of the Jean Kuntzmann Laboratory, Grenoble, June 11 2009 and at the Systems and Modeling Seminar Series, Montefiore Institute, University of Liège, April 3, 2009.
- **Maxime Sermesant** gave an invited lecture at the Isaac Newton Institute of Cambridge (UK) for the "Cardiac Physiome Project", on July 23, 2009 and at the ETH Zurich on December 1, 2009.
- **Hervé Delingette** gave a keynote presentation at the conference SIMBIO-M on July 2nd in Juan-les-Pins, an invited presentation at the Isaac Newton Institute of Cambridge (UK) for the "Cardiac Physiome Project", on July 23, 2009, an invited presentation at the Physiome tutorial organized with the Miccai conference on Sept. 24th, an invited lecture at the 9th workshop on Automatic Differentiation in Sophia-Antipolis on Nov. 26th.

8.5. Nominations and prizes

- **Nicholas Ayache** received the following distinctions and awards:
  - he was elected a member of the "College of Fellows" of the American Institute for Medical and Biological Engineering (AIMBE), and received this distinction during an official ceremony at the National Academy of Sciences on Feb 12, 2009, in Washington DC.
  - he was elected a "Fellow of the MICCAI society" for his scientific contributions and support to this scientific organization in September 2009, London.
- **Grégoire Malandain** has been nominated deputy scientific director of INRIA in charge of the "Computational Sciences for Biology, Medicine and the Environment domain" in november 2009.
- **Pierre Fillard** was awarded a special mention for best PhD in Biomedical Engineering from the SFGBM-IEEE France Section, at the RITS days, March 18-20 2009 in Lille.
- **Jonathan Boisvert** was awarded the 2009 prize for the best PhD thesis co-supervised between France and Quebec. His PhD was conducted through a collaboration between the Asclepios project-team, the University of Montreal, and the Sainte-Justine Hospital in Montreal. The topic was the construction from medical images of statistical and geometrical models of scoliosis in children. The PhD was supervised by N. Ayache and X. Pennec (Asclepios), and F. Cheriet (Univ. Montreal).

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