INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Asclepios

Analysis and Simulation of Biomedical Images

Sophia Antipolis

THEME BIO

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2. Overall Objectives

2.1. Overall Objectives

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

This evolution is supported by a constantly increasing number of biomedical devices providing *in vivo* measurements of structures and processes inside the human body, at scales varying from the organ to the cellular and even molecular level. Among all these measurements, biomedical images of various forms play 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.

3. Scientific Foundations

3.1. Introduction

Tremendous progress has been made in the automated analysis of biomedical images during the past two decades [118]. 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 [108], [104]. Regarding the target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [103], in N. Ayache's article [113] and in the more recent synthesis [118]. The scientific journals *Medical Image Analysis* [106], *Transactions on Medical Imaging* [107], and *Computer Assisted Surgery* [105] 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'2005 (Medical Image Computing and Computer Assisted Intervention) [100], [101] or ISBI'2004 (Int. Symp. on Biomedical Imaging) [102].

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 [119], [142]. 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 [146], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [112], Ultrasound or Nuclear Medicine images [120].

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 (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, multi-photon confocal microscopy, Optical Coherent Tomography, 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 [129].

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 [148].

[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.

[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.

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 [137] and to the Mouse Brain Atlas Project [110]. 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] [133].

Studying the variability of biological shapes is an old problem (cf. the remarkable book "On Shape and Growth" by D'Arcy Thompson [144]). Significant efforts have been made since that time to develop a theory for statistical shape analysis (one can refer to [117] for a good synthesis, and to the special issue of Neuroimage [143] 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 [131]: 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 [136], [127], [115], [138], [121]). 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. [139], [132] and the development of new data assimilation methods coping with massive numbers of measurements and unknowns.

[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.

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 [130]). 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 [126], [127]). 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. MedINRIA

Keywords: *DTI*, *Log Euclidian*, *MRI*, *f-MRI*, *fiber tracking*, *image processing*, *medical imaging*, *registration*.

Participants: Nicolas Toussaint, Pierre Fillard.

MedINRIA (Medical Image Analysis Platform from Asclepios[6]) is a platform containing a set of softwares, called modules, developed by the Asclepios team. It aims at providing state-of-the-art algorithms dedicated to medical image processing and visualization for clinicians. Efforts have been made to simplify the user interface, while keeping high-level algorithms. Each application is called a module, and can be loaded dynamically from a single main window. The platform uses ITK[7] for image processing, VTK[8] for visualization, and wxWidgets[9] for the user interface. MedINRIA is freely available from the Asclepios website for Microsoft windows XP, Linux Fedora Core 3.

Two different modules are currently available:

- DTI Track module: The DTI Track module provides all necessary tools for in-deep DT-MRI analysis and fiber tracking. From diffusion tensor field estimation, to scalar coefficient computation (ADC/FA), tensor smoothing, and fiber bundle extraction. This module uses Log-Euclidean metrics to process tensors, see Fig. 1, which are protected by a patent[10].
- Tensor Viewer module: The Tensor Viewer is complementary to DTI Track. It allows 3D tensor field visualization and geometry correction (flip among an axis). Tensor fields are displayed slice by slice, in three possible orientations (axial, sagittal and coronal). Various primitives are available for visualization : arrows, cubes, spheres, superquadrics, etc.

Several modules are underway, and will be plugged in MedINRIA. A registration module that will provide manual and semi-automatic registration will be ready very soon. See Fig. 2.

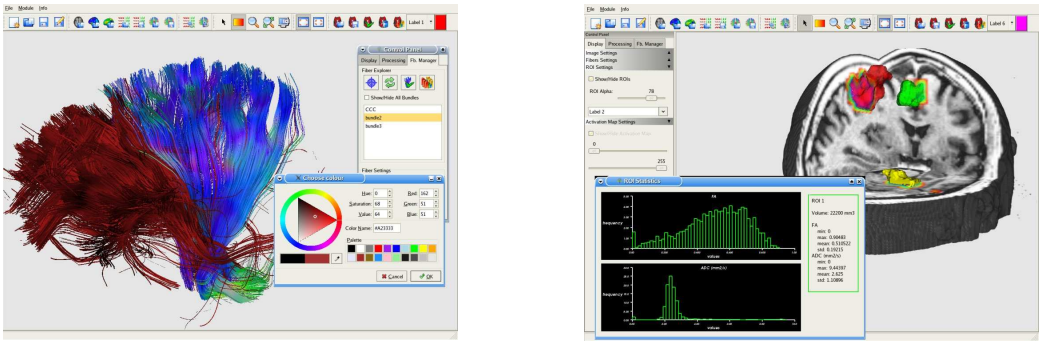


Figure 1. left: Screenshot of the DTI Track module, showing a set of brain extracted fiber bundles, and a panel to set some visualization parameters such as their color. right: Screenshot of the DTI Track module, showing a MRI-T1 image of the brain displayed in volume rendering mode. A set of activated regions (f-MRI) are shown as colored isosurfaces, and a window summarizing some tensor-derived coefficient of these regions.

4.2. Baladin

Keywords: *Multimodal image registration.*

Participant: Grégoire Malandain [Correspondant].

[6] http://www-sop.inria.fr/asclepios/software/MedINRIA
[7] http://www.itk.org
[8] http://www.vtk.org
[9] http://www.wxwidgets.org
[10] Patent Filing Number: 0503483

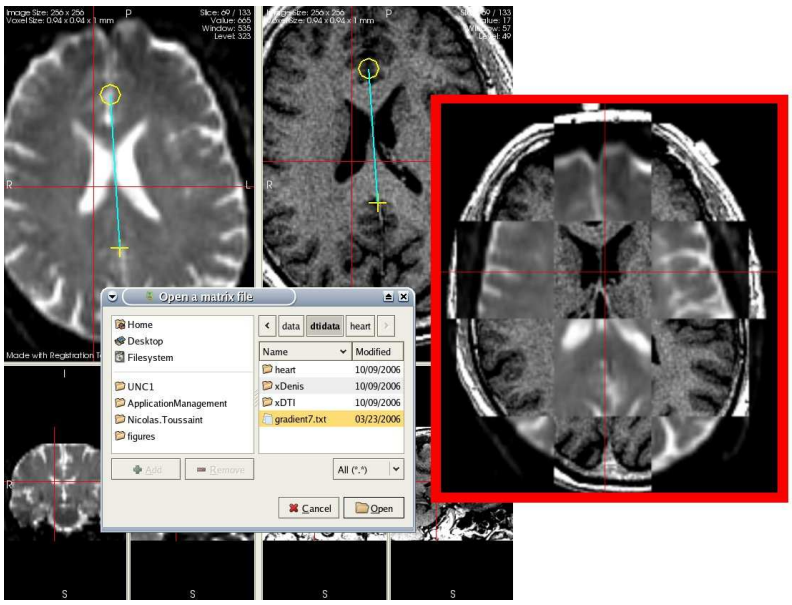


Figure 2. Screenshot of the future registration module showing a manual rigid registration of a DT-MRI baseline image (left) on a T1 image (right). The registration can be visually evaluated with a grid mixing the two images (red square on the right).

This software allows to register 3-D multimodal medical images with rigid or affine transformations. It is based on the computation of correspondences obtained by registering small sub-images (or blocks) with a local similarity measure (correlation coefficient). As a result, it yields the computed transformation and resampled images.

4.3. smDeform

Participant: Hervé Delingette [Correspondant].

smDeform is a software that allows the interactive segmentation of medical images based on deformable simplex meshes. With such a software, the user can define local and global constraint on the mesh deformation based on a priori knowledge about the shape and appearance of the anatomical structure to be segmented.

4.4. simuDeform

Participant: Hervé Delingette [Correspondant].

simuDeform allows the real-time simulation of soft tissue deformation, especially in the context of surgery simulatiom. This software can handle haptic devices for force-feedback interaction and includes different types of soft tissue models (tensor-mass, non-linear elastic, precomputed elastic) suitable for simulating the deformation and cutting of volumetric materials (parenchymatous organs like the liver or the brain).

4.5. Medical Image Processing Software (MIPS)

Participant: Hervé Delingette [Correspondant].

This library is an effort to gather and capitalize all software developments of the team. It includes mainly YAV++ but also a number of other softwares (EpidaureLib, Baladin, CrestMatch, Demons, Pasha, Yasmina, etc). MIPS is composed of several librairies and executables that allows the visualisation and manipulation of 3-D images and meshes.

4.6. Yasmina

Keywords: *Multimodal image registration*.

Participant: Grégoire Malandain [Correspondant].

This software allows to register 3-D multimodal medical images with rigid or affine transformations. It is based on the minimisation (or maximisation) of global iconic similarity measures (e.g. mutual information, correlation ratio, etc).

4.7. Pasha

Participant: Xavier Pennec [Correspondant].

This software allows advanced nonlinear registration of 3-D images, using both iconic and geometric criteria.

4.8. Runa

Participant: Xavier Pennec [Correspondant].

This software allows advanced nonlinear registration of 3-D images, with a parallel implementation.

4.9. Prospect

Participant: Xavier Pennec [Correspondant].

This software is designed for protein matching, and is based on geometric hashing.

5. New Results

5.1. Introduction

Current research activities are focused on:

- Medical Image Analysis
- Biological Image Analysis
- Computational Anatomy
- Computational Physiology
- Clinical and Biological Validation

5.2. Medical Image Analysis

5.2.1. Segmentation of anatomical structures of the lower abdomen for radiotherapy planning

Keywords: *deformable models*, *lower abdomen*, *radiotherapy planning*, *segmentation*, *simplex meshes*.

Participants: María Jimena Costa, Nicholas Ayache, Hervé Delingette, Grégoire Malandain.

This work is performed in the framework of the European project MAESTRO (Methods and Advanced Equipment for Simulation and Treatment in Radio Oncology), in collaboration with DOSIsoft SA, Cachan.

5.2.1.1. Objective

We are interested in the automatic delineation of anatomical structures of the lower abdomen in the frame of dose calculation for conformational radiotherapy. We approach the segmentation issue as a process of fitting a series of 3D deformable templates to the contours of anatomical structures.

5.2.1.2. Materials

- *Deformable models*: Many deformable surface representations have been proposed for model–based segmentation of medical images. Among existing representations, we use the discrete simplex meshes for their simple geometry and their ability to define shape constraints in a computationally efficient manner.
- *Images*: For our study, we rely on a database of tomodensitometric (CT) images of male patients' lower abdomens, and first apply this method to the segmentation of the bladder, which is one of the structures of interest.

  The bladders in our database images are very heterogeneous: while some of them present an homogeneous intensity that is quite similar to that of the background, others show both high and low intensity zones due to the presence, to a smaller or greater degree, of a contrast agent. Since we need a fully automatic segmentation algorithm, we must be able to determine what type of bladder is present in each image and follow the necessary (and often different) steps in each of the cases.

5.2.1.3. Outline of the method

1. Initially, we perform some preliminary treatments (see [69] for more details) and compute a series of parameter values that describe the structure of interest for each patient. We determine whether the image shows the presence of a contrast agent or not, and whether the bladder's intensity is homogeneous or not.
2. A binary approximation of the structure is then computed in order to guide the preliminary stages of deformation (both local and global) of a simplex mesh. The model undergoes several deformations, guided by regularizing forces and also by image-derived forces, so that it can adjust to the structure's boundaries. Further details can be found at [116].
3. The parameter values are then refined and used in a more precise step in the mesh deformation process. If the bladder was found to be non–homogeneous, the mesh is divided into zones that respond to different forces, in order to account for these intensity inhomogeneities.
4. It is now the image itself, and not the initial binary approximation, together with a histogram based force that we have devised to this end, that guide the model's last deformation stage.

If needed, the final automatic result may be manually improved by an expert.

5.2.1.4. Validation

In order to validate the approach, we use a set of CT images that have been segmented by medical experts. These handmade contours act as "ground truth", allowing for an objective evaluation of the performance of the algorithm.

5.2.1.5. Work in progress

We are now working on the joint segmentation of the bladder and the prostate by the competitive, simultaneous deformation of two simplex meshes.

5.2.2. Log-Euclidean Polyaffine Transformations

Keywords: *Log-Euclidean*, *Non-rigid registration*, *locally linear deformations*, *polyaffine*, *polyrigid*.

Participants: Vincent Arsigny, Olivier Commowick, Xavier Pennec, Nicholas Ayache.

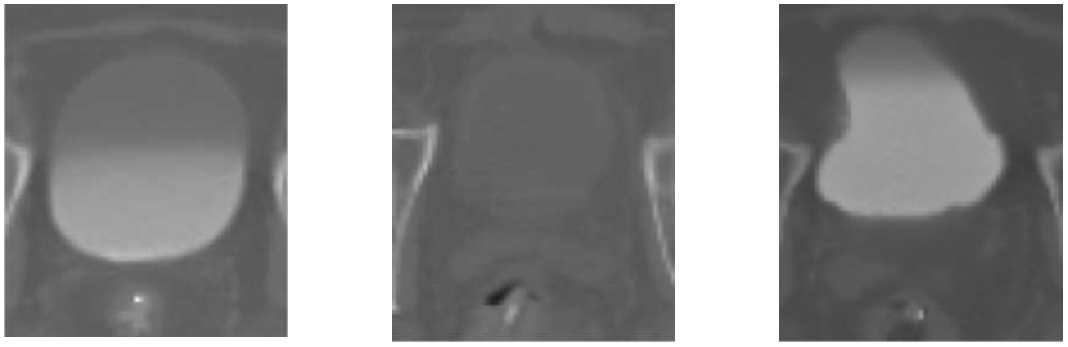


Figure 3. Inter–patient bladder variability: (in–)homogeneity, presence or absence of contrast agent, overall intensity.

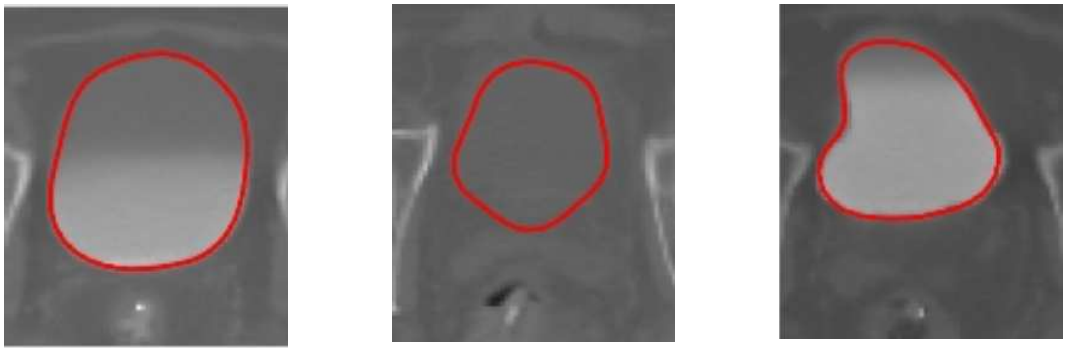


Figure 4. Fully automatic 3D segmentation of the bladders shown in previous figure. If needed, an expert may manually improve these results.

In 2003, we introduced a novel kind of geometrical transformations, named polyrigid and polyaffine. These transformations efficiently code for locally rigid or affine deformations with a small number of intuitive parameters. They can describe compactly large rigid or affine movements, unlike most free-form deformation classes. Very flexible, this tool can be readily adapted to a large variety of situations, simply by tuning the number of rigid or affine components and the number of parameters describing their regions of influence [111].

This year, we presented a novel framework, called *Log-Euclidean polyaffine*, which drastically simplifies our previous framework and guarantees strong invariance properties. In particular, the inverse of a (Log-Euclidean) polyaffine transformation is polyaffine, and the (Log-Euclidean) polyaffine fusion of affine components is invariant with respect to a change of coordinate system. The nice mathematical properties of these transformations allow to compute them very efficiently as well as their inverses on regular grids. Details about the theory and the efficient numerical algorithms are available in [91]. Results were presented at the international workshop of Biomedical image Registration WBIR'06 [59], and used to design efficient non-linear registration algorithms such as [69] (see also Section 5.2.3).

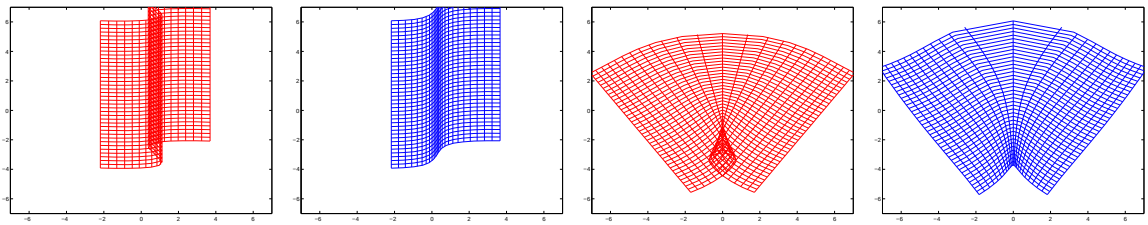


Figure 5. Guaranteeing invertibility with polyaffine fusion. In red: regular grid deformed by the fusion of two affine transformations, using the direct averaging of displacements. In blue: regular grid deformed by the infinitesimal fusion of the transformations in the polyaffine framework. Left: two translations are fused. Right: two rotations of opposite angles are fused. Note how the regions of overlap disappear when infinitesimal fusion is used.

5.2.3. Locally Affine Registration Framework for the Registration of Anatomical Structures

Keywords: *Non-rigid registration*, *affine transformation regularization*, *atlas-based segmentation*, *poly-affine*.

Participants: Olivier Commowick, Vincent Arsigny, Jimena Costa, Nicholas Ayache, Grégoire Malandain.

In collaboration with DOSIsoft SA, Cachan, Centre Antoine Lacassagne, Nice and Institut Gustave Roussy, Villejuif.

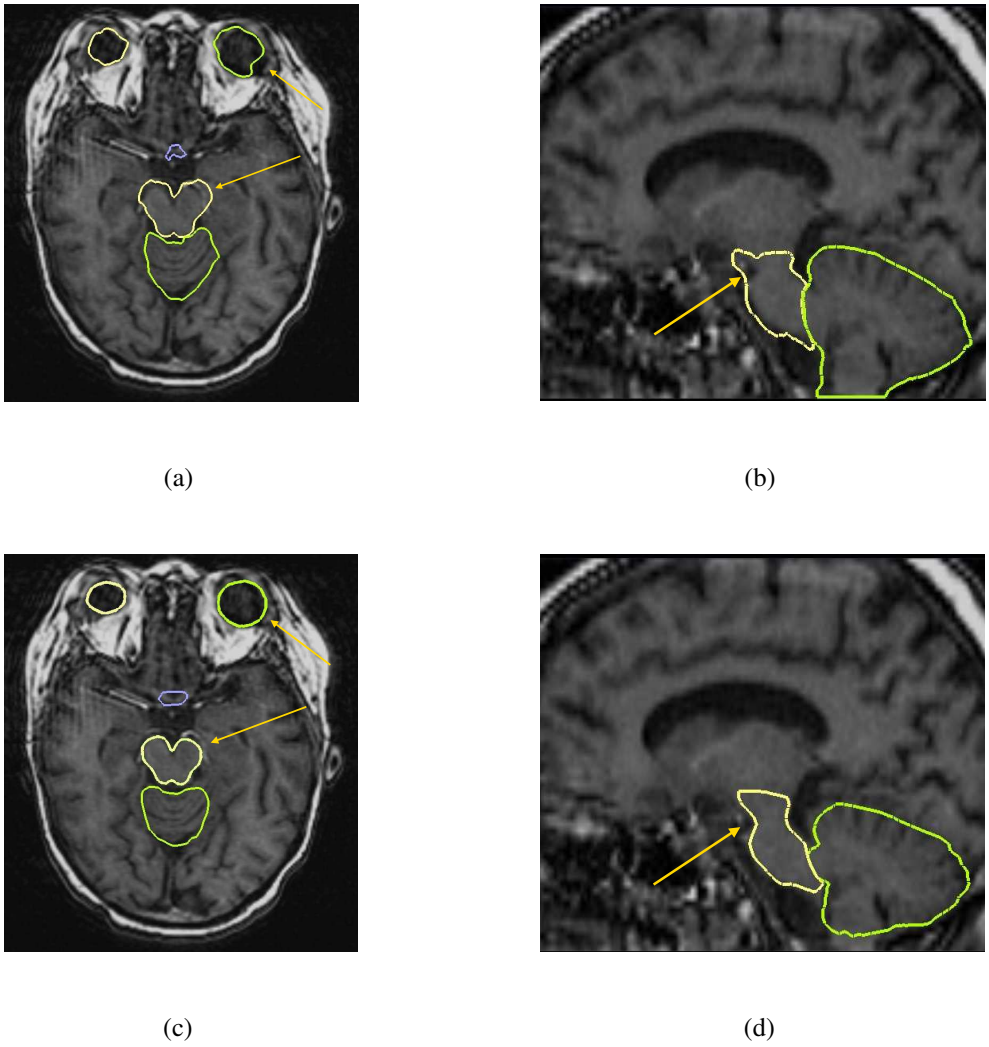
The planning of conformal radiotherapy requires accurate localizations of the tumor and the critical structures. In existing planning systems, the segmentation of brain structures is manual. An automatic segmentation algorithm of all the critical structures in a patient image is then an invaluable tool for radiotherapy.

In order to segment all these structures in a specific patient image, we use an anatomical atlas containing labels of the structures of the brain. The atlas was manually labeled from an artificial MR image (obtained from the BrainWeb). The first step of the general segmentation method is an affine matching between the atlas and the patient MRI (usually T1). The recovered transformation is then refined using non-rigid registration, and applied to the atlas labelization in order to obtain a segmentation of the patient image.

The transformations obtained using dense registration algorithms such as [141] are however often noisy, leading to irregular contours. These do not reflect the shapes expected for the structures. To overcome this problem, we have introduced in [69] a locally affine registration framework allowing to use an *a priori* on the structures we want to register. This is done by using a transformation parameterized by local affine transformations defined on regions. Thanks to the use of a Log-Euclidean regularization and of the

fast polyaffine framework [91], we ensure a smooth and invertible transformation, while using an efficient optimization scheme.

Thanks to this method, we obtain results that are much smoother than with a classical dense registration method (see images (c) and (d) on figure 6). The structures have indeed shapes corresponding to the ones expected by the clinicians. The algorithm is also much more robust to local perturbations in the images (see the eyes on figure 6). Finally, this work is currently being validated in clinical conditions at Institut Gustave Roussy [81], [80].



(a) (b)

(c) (d)

Figure 6. Comparative results of the atlas-based segmentation. From left to right: Registration using : (a), (b) a dense registration algorithm (axial and sagittal views) and using (c), (d) our locally affine framework (axial and sagittal views).

5.2.4. Evaluation of Atlas Construction Strategies for Head and Neck Atlas Construction

Keywords: *Non-rigid registration*, *atlas*, *head and neck*, *quantitative evaluation*.

Participants: Olivier Commowick, Grégoire Malandain.

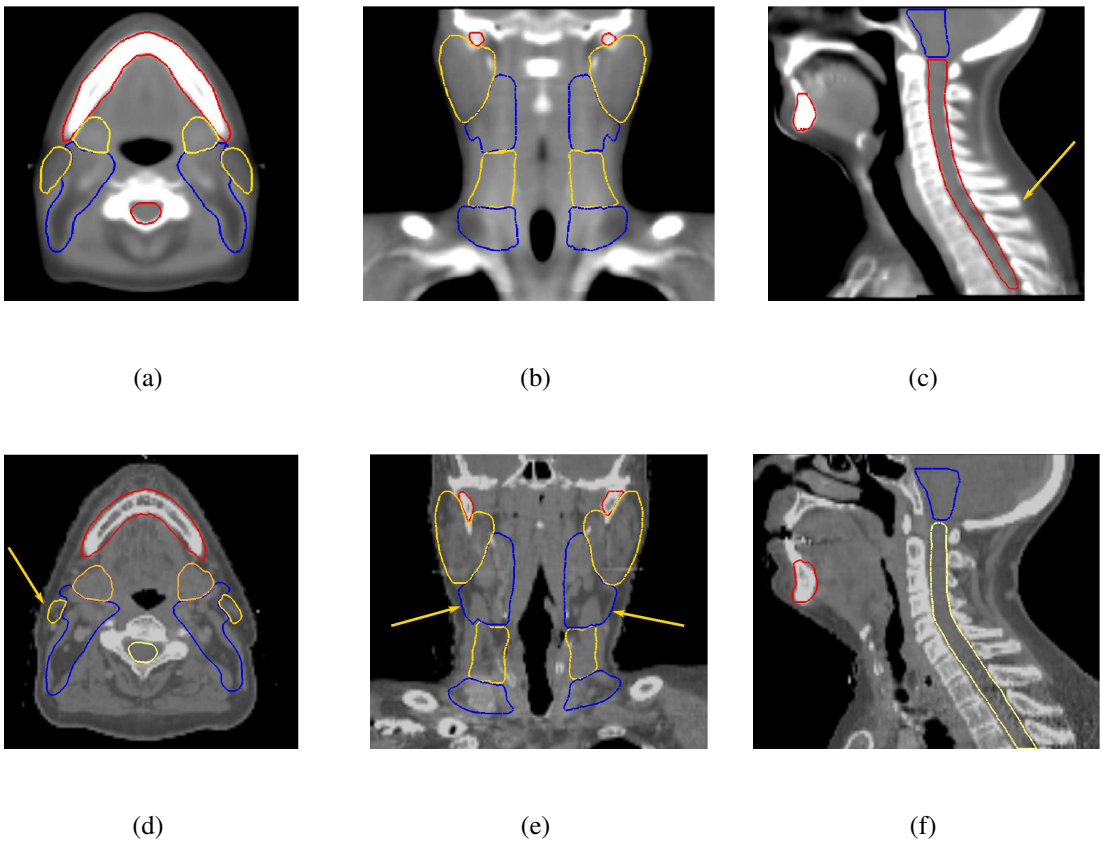
In collaboration with DOSIsoft SA, Cachan and Université Catholique de Louvain

Atlas-based segmentation has been shown to be very efficient to delineate brain structures. A major localization of cancers is the head and neck region (7 % of all cancers). It would then be of great interest to use an anatomical atlas of this area to help the clinicians with the therapy planning.

However, on this part of the body, using an atlas built from one single image as for the brain does not seem adequate, since the structures to be delineated are not clearly defined. Using only one image may then introduce an undesirable bias. Building an atlas from a set of segmented images address this issue, but it will then depend on the choice of the registration method used to fuse the images.

Since the atlas is designed to delineate structures, we have presented in [70] a framework based on the evaluation of the automatic delineations obtained from the constructed atlas. This allows us to evaluate both the registration method used to build the atlas, and the one used to deform it on an individual image. This is obtained by first leaving one image out of the dataset used to build the atlas. Then, using the manual delineations of this image and the automatic segmentations obtained by the atlas registration, we can compute quantitative measures (sensitivity and specificity) of the atlas quality.

Thanks to this method, we have developed an anatomical atlas of the head and neck region, illustrated on figure 7, images (a), (b) and (c). We obtain good segmentation results (see images (d), (e), (f) in figure 7 for a qualitative view) thanks to the use of a constrained transformation (locally affine) followed by a dense registration method.



(a) (b) (c)

(d) (e) (f)

Figure 7. Segmentation of the head and neck region using an anatomical atlas. From top to bottom: Head and Neck atlas built from a dataset of manually segmented images (axial, coronal and sagittal views), and automatic segmentations obtained on a patient left out of the atlas construction dataset.

5.2.5. Evaluation of skull-stripping methods and atrophy measurements on magnetic resonance images

Keywords: *Atrophy*, *Multiple Sclerosis*, *Skull-Stripping*.

Participants: Jean-Christophe Souplet, Christine Lebrun [Neurology, Pasteur Hospital, Nice], Nicholas Ayache, Grégoire Malandain.

This work finds a direct application in the Qualicore project (evaluation of cognitive troubles and quality of life of multiple sclerosis patients) and is performed in close collaboration with Christine Lebrun (Neurology Department), at Pasteur Hospital, Nice.

Our previous work aimed at detecting lesion in MRI images [29]. However, the lesion load is not correlated to the pathology evolution, and the cerebral atrophy seems to be a better indicator. We have therefore developed tools to measure this atrophy independently in the cortex, the cerebellum and the brain stem. Our method relies on the previous classification results into Gray Matter (GM), White Matter (WM), Cerebro Spinal Fluid (CSF) and lesions [29]. It has appeared that the classification step as well as the atrophy measurements, are very sensitive to a preliminary step, called skull stripping, which aimed at isolating the brain in the image. Using the Staple probabilistic framework [147], a comparative study of five skull stripping methods has been done in the case of relapsing remitting multiple sclerosis [140]. Methods were run on 30 sets of MRI sequences (T1, T2 FSE, PD). From these five segmentations, the Staple algorithm was used to give a probabilistic reference segmentation for each set. This segmentation was visually validated by an expert and compared with manual delineation when possible.

The Staple framework allowed to assess any segmentation method, by its sensitivity and its specificity. All methods and method combinations have been tested. A method combination binary segmentation was obtained by an automatic optimized thresholding of the corresponding Staple probabilistic segmentation.

The (sensitivity-specificity) measurement ranges from (0.838-0.763) to (0.985-0.993) for all methods and combination of methods. Considering additional information (average execution time, software installation facility, robustness...), the best segmentation is a combination of only three methods with (0.980-0.951). This new method has been tested and validated by an expert on all database sets.

Thanks to [69] and morphological operations, the last step was to divide the mask given by this skull stripping method in three regions of interest : cortex, cerebellum and brain stem.

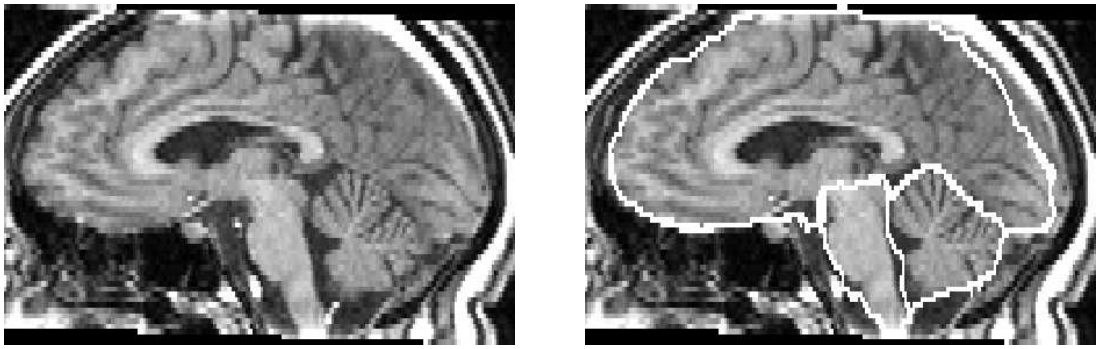


Figure 8. Left: T1 weighted MRI of a multiple sclerosis patient, Right: Three regions of interest (cortex, cerebellum, brain stem) in the skull stripping mask delineation on this image

Using the previous classification results, we compute brain atrophy. Future works will study the sensitivity of this measure and compare atrophy measurements obtained on the study database subjects with atrophy measurements available in the literature.

5.3. Biological Image Analysis

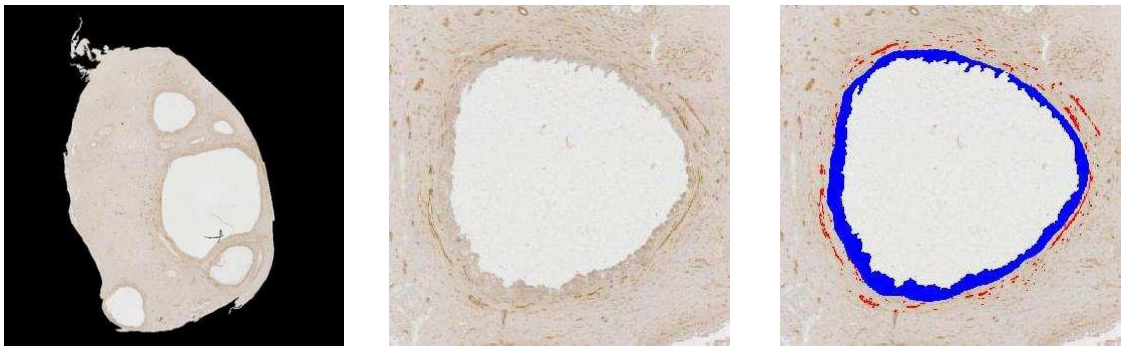
5.3.1. Imaging Study of the Ovarian Function from Histological Images

Keywords: *3D Reconstruction*, *Histology*, *Registration*, *Segmentation*.

Participants: Johan Debayle, Grégoire Malandain.

This work takes place in the Cooperative Research Initiative (CRI) named REGulation of Ovulation (REGLO).

This CRI aims to study the follicular development in mammals, and proposes mathematical models that allow to follow the granulosa cell population, and then to predict the outcome of the follicular development (ovulation or degeneration) with respect to the hormonal environment.
To study the ovarian function, we have to extract, from ovary images (in ewe), quantitative parameters that will allow to better understand and assess those mathematical models. These parameters will be either morphological: temporal evolution of the follicle volume, vascular density around follicles; or functional: vascular perfusion, following the imaging modalities. At this time, we have histological images (after staining procedures) which give access to microscopic reference images.
So, we have to reconstruct 3-D volumes from those histological sections and then to extract quantitative parameters from those images.



(a) histological section (b) zoom on a selected follicle (c) extraction of the parameters

Figure 9. After registration and 3D reconstruction from the histological sections [a], the granulosa cells and the vascularization [c] (superimposed in blue and red respectively) of each selected follicle [b] are extracted.

After the 3-D reconstruction, we have to segment the granulosa cells and the vascularization (Fig. 9) of each follicle within the ovary to be studied. Those regions are segmented by thresholding and/or model deformation. Quantitative parameters are then computed and discussed with the biologists involved in the REGLO project, before validation of the results.

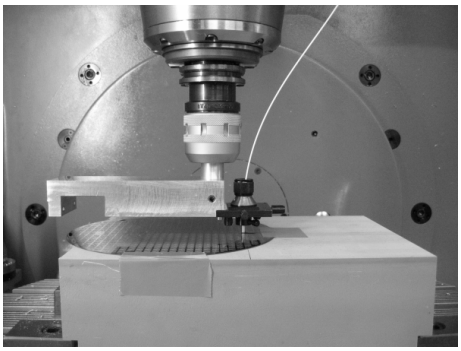
5.3.2. Mosaicing of Confocal Microscopic In Vivo Soft Tissue Video Sequences

Keywords: *In Vivo fibered confocal microscopy*, *Mosaicing*, *multi-image registration*.

Participants: Tom Vercauteren, Xavier Pennec, Aymeric Perchant [MKT], Grégoire Malandain, Nicholas Ayache.

This work is done in collaboration with Mauna Kea Technologies, Paris, France, www.maunakeatech.com.

Fibered confocal microscopy (FCM) is a potential tool for *in vivo* and *in situ* optical biopsy. FCM is based on the principle of confocal microscopy which is the ability to reject light from out-of-focus planes and provide a clear in-focus image of a thin section within the sample. This optical sectioning property is what makes the confocal microscope ideal for imaging thick biological samples.



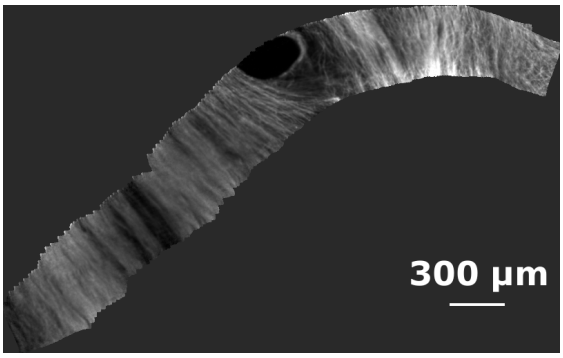


Figure 10. Left: The Deckel-Maho milling machine holding the flexible microprobe. This micrometric precision machine was used to evaluate the accuracy of our mosaicing algorithm. Right: Mosaic of a normal bronchial area, right upper lobe carina. Courtesy of L. Thiberville, Rouen University Hospital, France.

In 2005, we proposed an algorithm using image sequence mosaicing techniques to widen the field of view (FOV) and enhance the possibilities offered by FCM. In [57], [61], we further developed this algorithm to compensate for the motion distortions arising from the laser scanning.

In the field of biomedical imaging, the issue of validation for image processing tasks is essential. In order to get some ground truth data to evaluate the accuracy of our mosaicing algorithm, we used the micrometric precision computer numerical control milling machine shown in Fig. 10. In [57], we showed that our algorithm was able to automatically recover the motion imposed by the milling machine. This paper was awarded the Best MICCAI Paper published in Medical Image Analysis journal in 2006.

Because of its small size, the fiberoptic probe can be introduced into the working channel of a flexible bronchoscope. This makes it possible to use FCM to study the bronchial autofluorescence at the microscopic level in vivo. In [56], our mosaicing was successfully used in this clinical setting as shown in Fig. 10.

5.4. Computational Anatomy

5.4.1. Log-Euclidean Processing of Tensors

Keywords: *DTI*, *Log-Euclidean*, *Tensors*, *regularization*, *statistics*.

Participants: Vincent Arsigny, Pierre Fillard, Xavier Pennec, Nicholas Ayache.

Symmetric positive-definite matrices (or SPD matrices) of real numbers, also called here tensors by abuse of language, appear in many contexts. In medical imaging, their use has become common during the last ten years with the growing interest in Diffusion Tensor Magnetic Resonance Imaging (DT-MRI or simply DTI). SPD matrices also provide a powerful framework to model the anatomical variability of the brain. More generally, they are widely used in image analysis, especially for segmentation, grouping, motion analysis and texture segmentation. They are also used intensively in mechanics, for example with strain or stress tensors. SPD matrices are also becoming a common tool in numerical analysis to generate adapted meshes to reduce the computational cost of solving partial differential equations (PDEs) in 3D.

Defining a complete operational framework to interpolate, restore, enhance images of tensors is necessary to fully generalize to the SPD case the usual statistical tools or PDEs on vector-valued images. Last year, we proposed a novel and general processing framework for tensors, called Log-Euclidean. It is based on Log-Euclidean Riemannian metrics, which have excellent theoretical properties, very close to those of the recently-introduced affine-invariant metrics and yield similar results in practice, but with much simpler and

faster computations. This innovative approach is based on a novel vector space structure for tensors. In this framework, Riemannian computations can be converted into Euclidean ones once tensors have been transformed into their matrix logarithms, which makes classical Euclidean processing algorithm particularly simple to recycle. Two journal articles have been published this year on this topic: [33] on the theoretical aspects of the Log-Euclidean framework for tensors and [34] for its application to diffusion tensor processing.

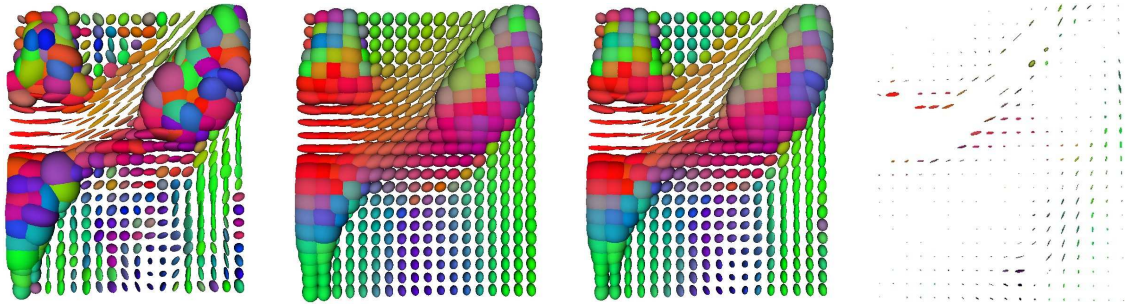


*Figure 11. Regularization of a clinical 3D DTI volume. Left: close-up on the top right ventricle and nearby. Middle Left: Euclidean regularization. Middle Right: Log-Euclidean regularization. Right: highly magnified view (*100) of the absolute value (the absolute value of eigenvalues is taken) of the difference between Log-Euclidean and affine-invariant results. Note that there is no tensor swelling in the Riemannian cases, contrary to the Euclidean case, where the result is spoiled by the classical "swelling effect". Log-Euclidean and affine-invariant results are very similar, the only difference being slightly more anisotropy in Log-Euclidean results. But Log-Euclidean computations were 5 times faster and much simpler!*

We also proposed a new methodology to analyze DT-MRI data sets of a rather low quality, typical of clinical acquisitions. We handle the Rician nature of the noise thanks to a Maximum Likelihood (ML) approach, combined with an anisotropic regularization term. We showed that this can correct for sides effect caused by the Rician noise: tensors tend to be smaller than normal. This work has been accepted for publication at ISBI this year [71]. An extended version, with a detailed quantitative analysis of 7 algorithms to estimate and regularize DT-MRI is currently submitted.

5.4.2. A statistical atlas of the cardiac fiber architecture

Keywords: *DT-MRI*, *atlas*, *cardiac fiber architecture*, *heart*, *tensor statistics*.

Participants: Jean-Marc Peyrat, Maxime Sermesant, Xavier Pennec, Hervé Delingette, Chenyang Xu [Siemens SCR, USA], Elliot McVeigh [Lab of Cardiac Energetics, NHLBI, USA], Nicholas Ayache.

This work was funded in part by Siemens Corporate Research (NJ, USA).

While the main geometrical arrangement of myofibers has been known for decades, its variability between subjects and species still remains largely unknown. Understanding this variability is not only important for a better description of physiological principles but also for the planning of patient-specific cardiac therapies. Furthermore, the knowledge of the relation between the myocardium shape and its myofiber architecture is an important and required stage towards the construction of computational models of the heart since the fiber orientation plays a key role when simulating the electrical and mechanical functions of the heart.

The knowledge about fiber orientation has been recently eased with the use of diffusion tensor imaging (DT-MRI) since there is a correlation between the myocardium fiber structure and diffusion tensors. DT-MRI also has the advantage to provide directly this information in 3D with a high resolution but it is unfortunately not available *in vivo* due to the cardiac motion. There has been several works in the past decade that have studied the variability of fiber orientation from DT-MRI. Those studies estimated the fiber direction as the

first eigenvector of each tensor and for instance compared its transmural variation with that observed from dissection experiments. We extended those studies by building a statistical model of the whole diffusion tensors. This tensor analysis allows us to study the variability of laminar sheets which are associated with the second and third eigenvectors.

To achieve it, we proposed a framework [87] to register and reorient DT-MRIs in a same reference frame based on anatomical MRIs in order to compute first and second order statistics on diffusion tensors in a Log-Euclidean framework at each voxel. We also developed statistical tools [96] to translate the covariance matrix of the whole tensors into variabilities of eigenvalues and eigenvector's frame orientation.

We applied this framework to a dataset of 9 *ex vivo* canine hearts. From the first order statistics results a smooth average DT-MRI suited to fiber tracking (see Fig 12). The second order statistics reveals high inter-subject similarities of the cardiac fiber orientation. This is the first step towards a validation of using an average model of the cardiac fiber architecture for medical image analysis and electromechanical simulations.

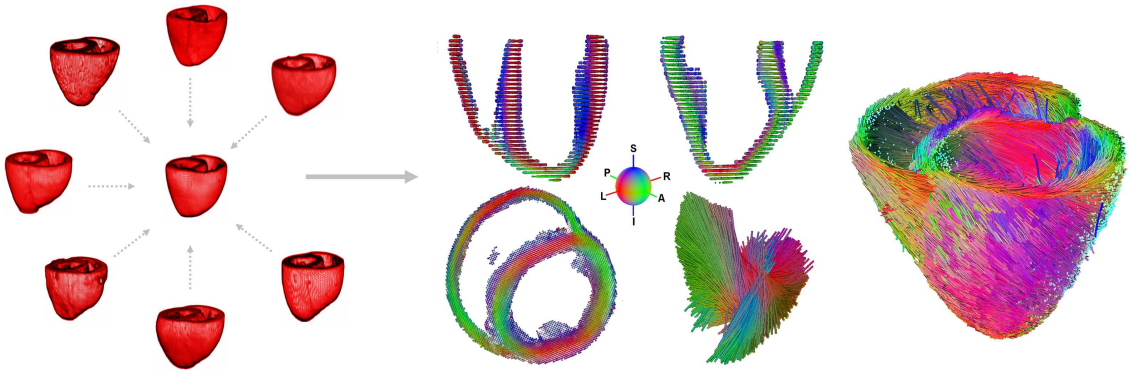


Figure 12. [Left] Registration of ex vivo canine hearts resulting in an average model of the cardiac fiber architecture - [Right] Fiber tracking (computed with MedINRIA) on the average cardiac DT-MRI.

5.4.3. Modeling brain variability

Keywords: *Riemannian geometry*, *brain variability*, *sulci*, *tensor*.

Participants: Pierre Fillard, Vincent Arsigny, Xavier Pennec, Paul Thompson, Nicholas Ayache.

This is joint work with the LONI (Laboratory of Neuroimaging) at UCLA (University of California at Los-Angeles), partly funded by the INRIA associated team program (Brain Atlas): http://www-sop.inria.fr/epidaure/Collaborations/UCLA.

This study builds on the work performed over the last two years to model the brain variability from sulcal lines. The whole process relies on manual delineations of sulcal lines done on MR images[11] affinely registered onto a template (the ICBM 305 space) coming from the LONI team at UCLA through the associated team (see Section 7.3). The mean sulcal lines were previously determined by iteratively optimizing over the position of the mean line and the correspondances with all the instances. We proposed this year to refine the affine transforms based on the sulcal mappings obtained between each subject's instance and the mean lines. This is realized by adding a third step to the previous iterative estimation scheme. The global effect is to concentrate the sulcal curves around the mean lines and to reduce the amplitude of the variability by about 10%, without modifying much the other results.

[11] http://www.loni.ucla.edu/ khayashi/Public/medial_surface/

To compare two populations based on their sulcal tracings, we also proposed to compute global mean curves (including instances of both population), and to put into correspondence theses means and the population means. This allows to provide a common reference for comparing variability tensors of the two populations, without creating a bias towards one population. This work appeared in Neuroimage [42], and in a research report [93].

We are now applying this methodology to the mapping and understanding of gender differences (males vs. females) (see Fig. 13), pathologies (Williams syndrome), and hemispheric differences.

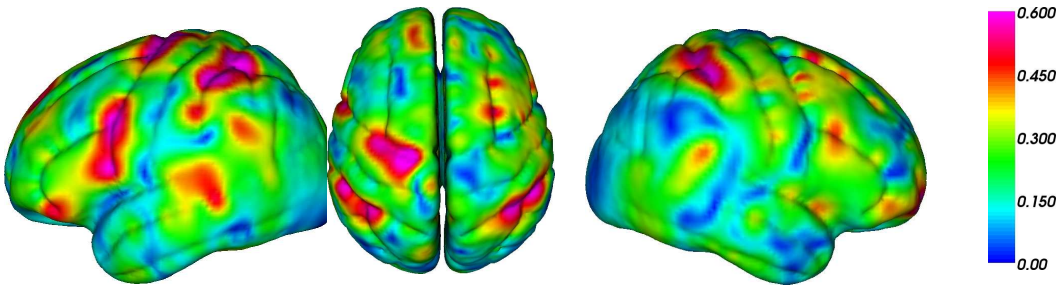


Figure 13. Comparisons of variability maps: A gender study. Hot colors mean high differences in variability between males and females. Left: Left hemisphere. Middle: Top view. Right: Right hemisphere.

5.4.4. Registration Algorithms and Statistics on Deformation : Comparison of methods

Keywords: *Diffeomorphic mapping*, *inter-individual variability*, *non linear registration*, *shape statistics*.

Participants: Stanley Durrleman, Xavier Pennec, Nicholas Ayache, Alain Trouvé [CMLA, ENS Cachan].

There is nowadays a large interest of the scientific community for understanding the brain shape and its variability. The method is usually to extract some anatomical features like sulci or gyri in a population of subjects and to perform a statistical analysis of these features after a group-wise matching. To analyse the influence of the matching method used, we propose in this work to compare the results of the extrapolation of variability on sulcal lines of [42] (see also Section 5.4.3) with the diffeomorphic mapping framework developed in Miller's and Trouvé's teams.

In the diffeomorphic mapping framework, we look for a global coherent deformation of the whole space that best matches the data. This has major advantages: we not only find a correspondence between data points but also the complete trajectories of these points along the deformation process. Moreover, the deformation is not only defined on each data points individually but also on every point in the space. Eventually, the whole deformation could be seen as a geodesic in some space and therefore could be stored and recovered efficiently thanks to a finite number of parameters [124], [145]. Indeed, the whole deformation process is completely defined by the initial vector speed of each data points. Therefore, population-wise statistical analyses of the brain variability can be performed by measuring for instance the covariance matrix of these initial vector speeds.

We expect to see a few differences betwen the two methods because the mapping is defined on the whole space before computing the covariance structure on each point in the diffeomorphic mapping case while the covariance matrix of the displacement is computed on each lines independantly and then diffused in the whole space thanks to the log-Euclidean framework (see [34]) with Fillard's method. We are currently performing experiments on the sulcal lines used in Section 5.4.3. Figure 14 shows the registration of the mean to one subject. Quantitative measurements of the similarity and difference between the two methods are under way.

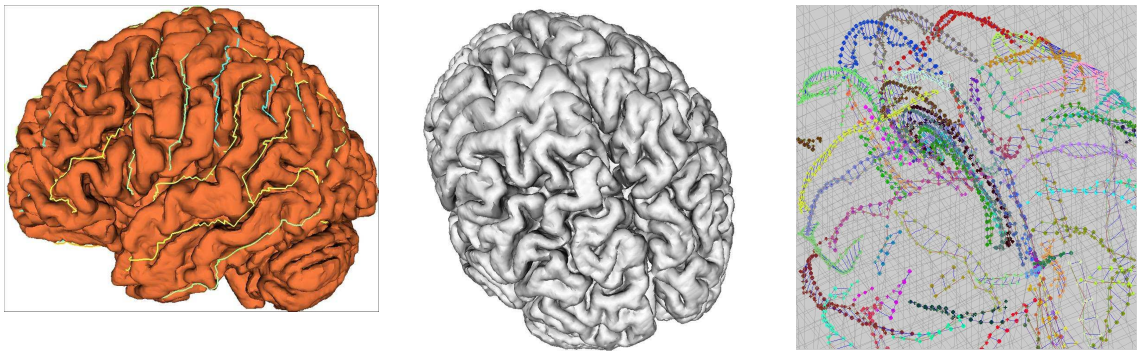


Figure 14. Left: mean sulcal lines are superimposed on the cortex surface. Middle image displays the point of view adopted in the right figure. Right: The blue lines with circles represent the mean set of sulcal lines computed by P. Fillard from a dataset of 34 subjects. This set of lines is registered to one subject's set of sulcal lines (red lines with cross). The matching is realized by a global diffeomorphic deformation of the whole space that is the best compromise between regularity and matching accuracy. The data point's trajectories along this deformation are shown in blue and the registered lines are drawn in green with stars.

5.4.5. Bi-Invariant Means in Lie Groups

Keywords: *Lie groups*, *Log-Euclidean*, *Riemannian geometry*, *bi-invariant means*, *statistics*.

Participants: Vincent Arsigny, Xavier Pennec, Nicholas Ayache.

In recent years, the need for rigorous frameworks to compute statistics in non-linear spaces has grown considerably in the bio-medical imaging community. The registration of bio-medical images naturally deals with data living in non-linear spaces, since invertible geometrical deformations belong to groups of transformations which are not vector spaces. These groups can be finite-dimensional, as in the case of rigid or affine transformations, or infinite-dimensional as in the case of groups of diffeomorphisms.

In this work, we focused on the consistent generalization of the Euclidean mean to Lie Groups, which are a large class of non-linear spaces with relatively nice properties. Classically, in a Lie group endowed with a Riemannian metric, the natural choice of mean is called the Frechet mean. This Riemannian approach is completely satisfactory if a bi-invariant metric exists, for example in the case of compact groups such as rotations. The bi-invariant Frechet mean generalizes in this case the properties of the arithmetic mean: it is invariant with respect to left- and right-multiplication, as well as inversion. Unfortunately, bi-invariant Riemannian metrics do not always exist. In particular, we have showed that such metrics do not exist in any dimension for rigid transformations, which form but the most simple Lie group involved in bio-medical image registration.

To overcome the lack of existence of bi-invariant Riemannian metrics for many Lie groups, we defined a bi-invariant mean generalizing the Frechet mean based on an implicit barycentric equation (see Fig. 15). Alternatively, we also proposed a simpler Log-Euclidean framework approach to statistics of linear invertible transformations, For matrices, the bi-invariant and Log-Euclidean means are both generalizations of the geometric mean of positive numbers, since their determinants are both exactly equal to the geometric mean of the determinant of the data. The Log-Euclidean mean is much simpler to compute, but has fewer invariance properties and is limited to transformations not too far away from the identity, contrary to the bi-invariant mean. A research report detailing this novel framework is available [92].

5.4.6. Log-Euclidean Statistics of Diffeomorphisms

Keywords: *Lie groups*, *Log-Euclidean*, *diffeomorphisms*, *statistics*.

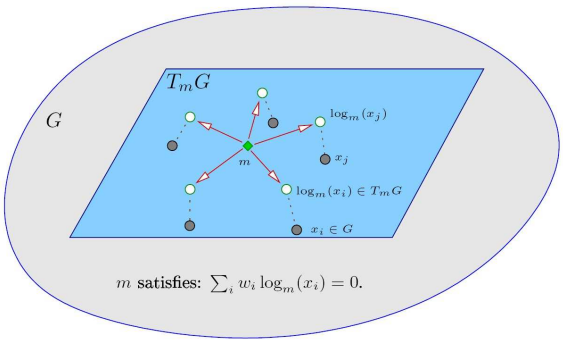


Figure 15. Equation defining Riemannian means, which we generalized to Lie groups without bi-invariant Riemannian metrics to define general bi-invariant means.

Participants: Vincent Arsigny, Olivier Commowick, Xavier Pennec, Nicholas Ayache.

Currently, a large variety of non-linear registration algorithms have been proposed to deal with the non-rigid registration of medical images. However, the quantitative comparison of these algorithms remains to be done. To this end, having a consistent framework to compute statistics on general invertible transformations would be very useful. In this work, we introduced a novel parameterization of diffeomorphisms, based on the generalization of the principal logarithm to non-linear geometrical deformations. This corresponds to parameterizing diffeomorphisms with stationnary speed vectors fields. As for matrices, this logarithm can be used only for transformations close enough to the identity. However, our preliminary numerical experiments on 3D non-rigid registration suggest that this limitation affects only very large deformations, and may not be problematic for image registration results. This novel setting is the infinite-dimensional analogous of our Log-Euclidean framework for tensors and linear transformations. In this framework, usual Euclidean statistics can be performed on diffeomorphisms via their logarithms, with excellent mathematical properties like inversion-invariance.

In MICCAI'06 and MFCA'06 [58], [60], we presented two efficient algorithms to compute numerically logarithms of diffeomorphisms and exponentials of vector fields, whose accuracy is studied on synthetic data. Moreover we successfully applied these tools to compute the mean of a set of diffeomorphisms, in the context of a registration experiment between an atlas an a database of 9 T1 MR images of the human brain (see Fig. 16).

5.4.7. Characterization of Spine Deformations and Orthopedic Treatments Effects

Keywords: *3D/2D Registration*, *Anatomical Variability*, *Articulated models*, *Orthopedic Treatments*.

Participants: Jonathan Boisvert, Nicholas Ayache, Farida Cheriet [Polytechnic School of Montreal], Xavier Pennec.

This project is part of a partnership between the Asclepios team, the Montreal's Sainte-Justine hospital and the Polytechnic School of Montreal.

Spine surgeries are very delicate interventions that need to be carefully planned. In the case of scoliosis, a crucial part of the surgical planning process is to classify the patient's spine deformation in accordance to an accepted surgical classification scheme. Those classification schemes then offer guidance to the selection of fusion levels and to the selection of the associated orthopedic instrumentation. However, current classification schemes are two-dimensional while spine deformations are three-dimensional, mainly because analyzing large databases of 3D spine models is difficult and time consuming.

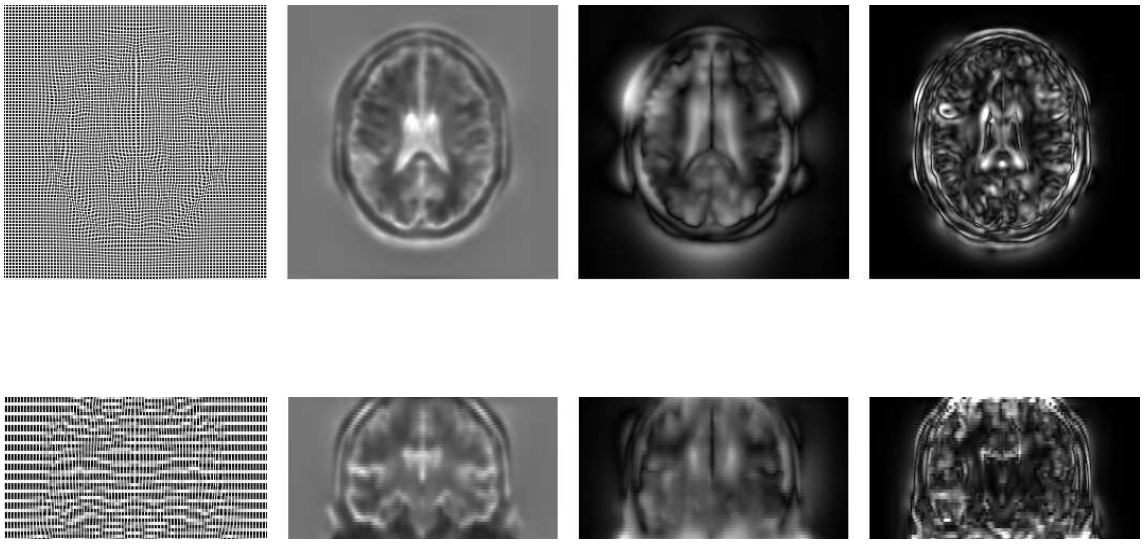
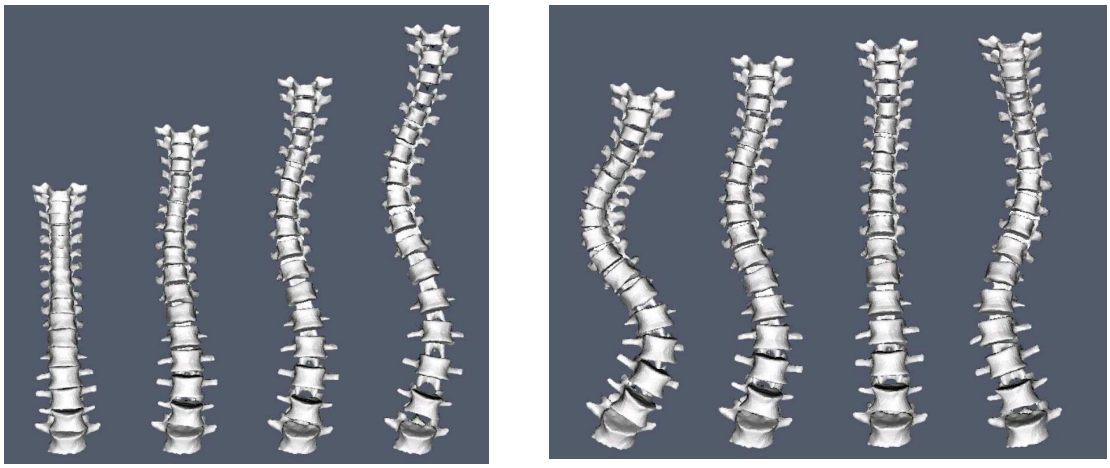


Figure 16. Deformation of atlas with the Log-Euclidean mean diffeomorphism. From left to right, images of: regular grid deformed by Log-Euclidean mean deformations, Jacobian of Log-Euclidean mean deformations, norm of Log-Euclidean mean deformations, and finally norm of difference between mean Euclidean and Log-Euclidean deformations of atlas. The largest mean deformations are observed in the ventricles, on the cortex and the skull; this is due to the anatomical differences between the atlas and the population. On the Jacobian map, we see in particular that high values are obtained in the ventricles: this comes from the fact that the atlas has on average smaller ventricles than in the population. In this example, both means are quite close to each other, although locally, one can observe in the region of large mean deformations relative differences of the order of 30%, for example in the ventricles.

To facilitate this task, we proposed a method [66] that automatically extracts the most important deformation modes from a set of 3D spine models. The spine was expressed as a set of rigid transforms that superimpose local coordinates systems of neighboring vertebrae. To take into account the fact that rigid transforms belong to a Riemannian manifold, the Fréchet mean and a generalized covariance computed in the exponential chart at that point were used to construct a statistical shape model. The principal deformation modes were then extracted by performing a principal component analysis (PCA). The proposed method was applied to a group of 307 scoliotic patients and meaningful deformation modes were successfully extracted (see Figure 17). For example, patients' growth, double curves, simple thoracic curves and lumbar lordosis were extracted in the first four deformation modes.



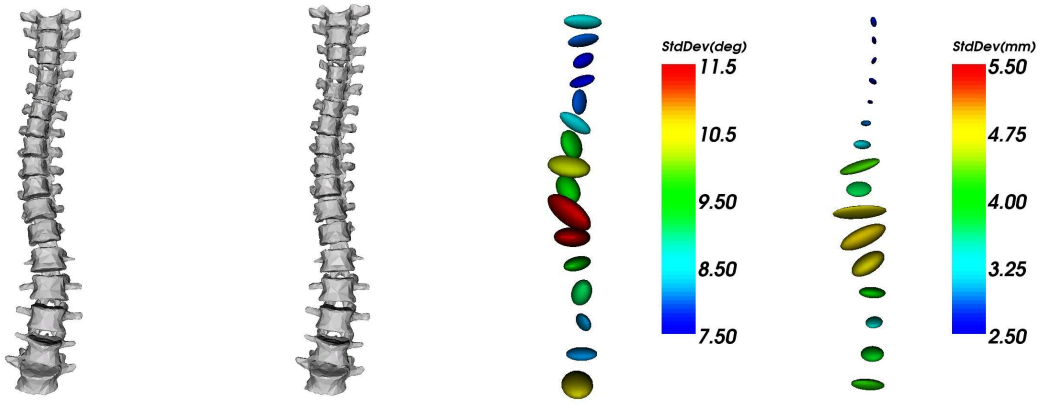
(a) (b)

Figure 17. Scoliotic spine deformation modes. Frontal (postero-anterior) view of the first (on the left) and second (on the right) principal modes. Each mode is depicted by the variation at -3, -1, 1 *and* $+3$ *times its standard deviation.*

Moreover, we were able to show with a logistic regression that there is a statistically significant relationship between conventional 2D surgical classifications such as King's classification and the first four principal deformation modes [63]. Thus, our method can be used to extract clinically significant deformation modes from a set of 3D spine models. This can help surgeons to refine arbitrary classes in 3D (King's or Lenke's classes, for instance), thus helping the design of new clinically relevant 3D classifications.

Although corrective surgeries are commonly performed on acute cases of scoliosis, there exist less invasive treatments that are prescribed for more common cases, such as Bracing. However, there is still no consensus about its actual effect. Previous studies were based on global descriptors of the spine shape (Cobb angle, plane of maximal deformity, etc.) and local shape was never directly assessed. We analyzed in [64] the braces effects at a finer scale to find which vertebral levels were significantly affected by this treatment. The 3D spine geometry of a group of 41 patients treated with a Boston brace and a control group of 28 untreated scoliotic patients was digitized with and without brace (first group) or twice without brace (control group). The modifications of the relative poses of successive vertebrae were extracted from 3D reconstructions. As before, the Fréchet mean and a generalized covariance were used to measure the centrality and dispersion of our manifold-valued primitives (illustrated in Figure 18). Multivariate hypothesis tests were used to compare the two groups: Significant differences ($p<0.01$) between the centrality and dispersion measures of the relative poses modifications were respectively found from T1 to T6 and from T8 to L1. This is in accordance with the

back flattening effect and the spatially limited correction found in other studies. However our results offer a more specific evaluation of the localization of those effects.



(a) (b) (c) (d)

Figure 18. Frontal view of the statistical model of the spine shape deformations associated with the Boston brace. From left to right: mean shape prior treatment, mean shape with the brace, rotation and translation covariance of the spine shape deformations.

Our current work now aims at exploiting our statistical model of the spine shape to develop 2D-3D registration method suitable to register an articulated model of the spine to per-operative radiographs, in view of an image guided surgery system for spine surgery. This problem is particularly challenging due to the flexible nature of the spine and the presence of sensitive anatomical structures near the surgical path, like the spinal chord or major blood vessels, which makes an image guided surgery system for spine surgery very useful.

5.4.8. Point-Based Statistical Shape Models Using Correspondence Probabilities

Keywords: *EM-ICP*, *Statistical Shape Models*, *fuzzy correspondences*.

Participants: Heike Hufnagel, Xavier Pennec.

This work takes place in a cooperation with the medical imaging group of the university Hamburg-Eppendorf.

A fundamental problem when computing surface based statistical shape models is the determination of correspondences between the instances. Often, homologies between the point cloud representations are assumed which might be erroneous and might distort the results. In order to find a solution to that, we developed a novel algorithm based on the affine Expectation Maximization - Iterative Closest Point (EM-ICP) registration method. Here, exact correspondences are replaced by iteratively evolving correspondence probabilities which provide the basis for the computation of mean shape and variability model. The performance of this approach is investigated on different kind of organs (kidney, brain, prostate, ganglions...) [125] (see Fig. 19). The method is currently updated to perform automatic classification.

5.5. Computational Physiology

5.5.1. Tumor Growth Modelling

Keywords: *Fisher-Kolmogorov*, *Tensors*, *glioblastoma*, *glioma*, *modelling*, *radiotherapy*, *tumor*.

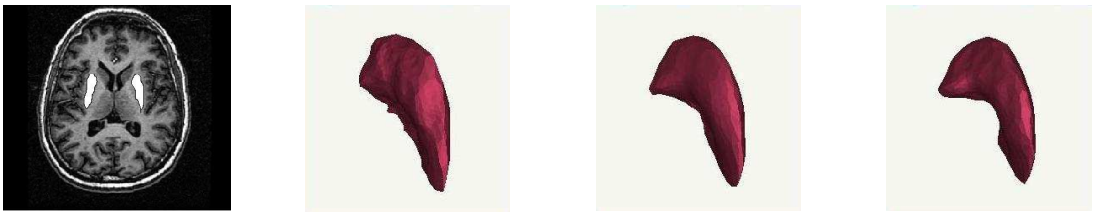


Figure 19. The mean model of the putamen and its deformations according to the first eigenmode.

Participants: Ender Konukoglu, Olivier Clatz, Pierre-Yves Bondiau, Hervé Delingette, Nicholas Ayache.

Tumor growth modelling describes mathematically the dynamics of the tumor growth process. General models try to include as many details of the process as possible but they are difficult to personalize for a given patient due to the problem of observability and the lack of available observations.

Olivier Clatz has applied a macroscopic growth model, which is mathematically simpler and much more flexible, to the patient specific case. This model is based on the reaction-diffusion formalism and uses tissue and structural information of the brain obtained from MR and DT-MR images. Based on this model, we derived a formulation to help radiotherapists determine the irradiation region for a patient taking in account the growth dynamics of the tumor [82]. CT and MR images are not successful in visualizing all the tumor infiltration in the brain, especially regions where tumor cell density is low are not enhanced. Radiotherapists deal with these regions by irradiating them, and because of the lack of visualization they use a constant therapy margin (2cm) around the surrection region. This formulation tries to solve the problem of visualizing regions, where tumor cell density is low, in MR and CT images to help determining irradiation regions. It extrapolates invasion margins of a tumor from its visible part in the MR image (see Fig. 20).

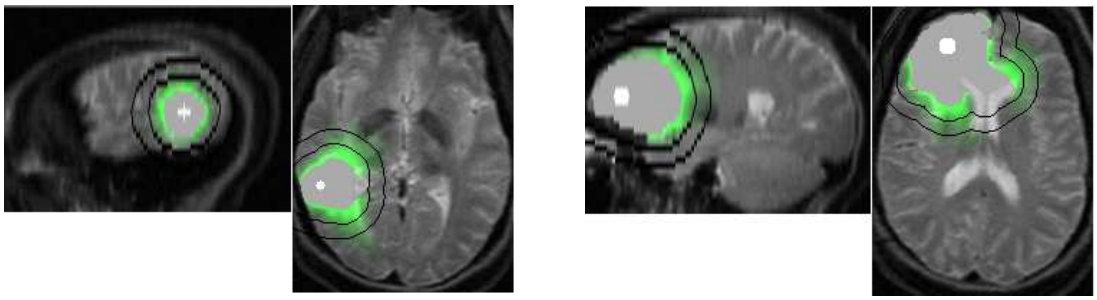


Figure 20. Sagital and axial views of two different artificial tumors. Grey areas are visible parts in the T2-weighted MR image and green shades are extrapolated invasion margins. Black lines denote 1cm and 2cm constant radiotherapy margins which does not seem to correlate well with the growth dynamics of the tumor.

In applying the aforementioned model to any patient, several further steps should be taken, like automatically determining correct patient specific parameters of the model from medical images taken at successive times, including effects of radiotherapy and chemotherapy in the model and including the uncertainty in the model, which is coming from many different sources of which the primary one is the variation of characteristics in different tumor cells.

This research work has been presented at the DIMACS Workshop on Computational Tumor Modeling [98] at Rutgers University, USA, and is now acknowledged at the Center for the Development of a Virtual Tumor[12], supported by the NIH-National Cancer Institute.

5.5.2. Towards patient-specific models of the heart

Keywords: *cardiac resynchronization*, *cardiac image analysis*, *cardiac modeling*, *cardiac pacing*, *data assimilation*, *electrophysiology*, *simulation of cardiac pathologies*.

Participants: Damien Lepiller, Romain Fernandez, Ouafaa Daki, Florence Billet, Maxime Sermesant, Hervé Delingette, Nicholas Ayache.

This work is done in the context of the INRIA national action CardioSense3D[13], and in collaboration with the Division of Imaging Sciences, King's College London, United Kingdom.

The integration of knowledge from biology, physics and computer science makes it possible to combine *in vivo* observations, *in vitro* experiments and *in silico* simulations. From these points of view, knowledge of the heart function has greatly improved at the nanoscopic, microscopic and mesoscopic scales, along with an impressive development of the observations possibilities through medical imaging.

Our work aims at introducing computational models of the heart in clinical applications. Such models can be used to introduce prior knowledge in image analysis methods [54]. We showed that it makes it possible to regularize the segmentation process in a physiological way.

But such models can also be used to estimate hidden parameters of the cardiac function from clinical data, through data assimilation [55]. Such parameters give a much more interesting information for diagnosis, as they really represent the underlying physiology.

Figure 21. Segmentation of the left heart (in red) and the right heart (in blue) from clinical MRI.

In order to build such models, it is necessary to be able to segment the cardiovascular system from medical images (see Fig. 21). More specifically, we work on heart segmentation from MRI, using active models, and on statistical classification of aorta's shape (see Fig. 22). The goal is to achieve the effective segmentation of the atria and proximal arteries in order to complete the current anatomical model where only ventricles are available. This augmented segmentation will participate in improving simulation of the electromechanical activity of the heart.

[12] https://www.cvit.org/
[13] *http://www-sop.inria.fr/CardioSense3D/*

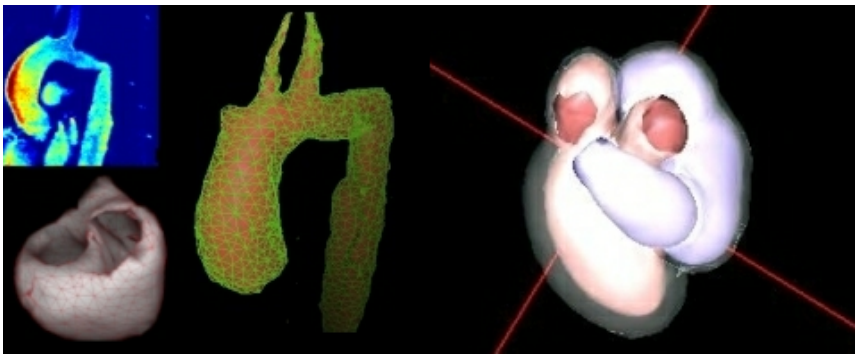


Figure 22. MRI image data, visualisation of segmentations of the muscle and the aorta vein trunk.

Recent developments of medical imaging and electrophysiological measures in cardiology also allow the realisation of realistic models of the heart electrophysiology which can be used to help diagnosis. Numerous models of electric propagation through the myocardium have been developed. However, very few calibration methods have been proposed. We proposed a method to adjust the parameters of an integrated 3D model of the left and right ventricles of the heart.

Many of the functional models of the heart are designed to reproduce in a realistic manner the cardiac activity (especially ionic gates and concentrations), often leading to high computational costs and the manual tuning of a very large set of parameters. In our approach, we rather selected a model involving a limited number of parameters, based on Aliev & Panfilov [109]. Thus allowing the identification of the model parameters from clinical measurements on a specific patient by solving the inverse problem.

It is well known that muscle fiber orientations vary across the myocardial wall. Fibres have an important impact on the behaviour of the depolarization wave as the action potential propagation is around 3 times faster in fiber direction than in radial directions. Therefore, a first step was to define an analytical linear fiber model to set the diffusion tensor on each vertex. To adjust a parameter, we browsed the parameter space solving the direct problem with a different parameter value each time, to match reference measures (action potential duration, APD, or depolarization speed) provided by activation times (ie: when the depolarization wave pass by the mesh vertices on the heart surface). The relation between the parameter and the measure is then approximated with a rational model and least square resolution. This method can be used for the entire mesh or one zone at a time (segmentation provided by American Heart Association) or on each vertex.

We obtained very promising results on simulated APD (see figure 23). But before getting the same quality on matching depolarization speed, several difficulties have to be tackled. The stability of the model with regard to its parameters, in particular, has to be studied precisely.

The collaboration with the Division of Imaging Sciences, King's College London[14], in Guy's Hospital provides unique data from their XMR facility which combines X-rays and MRI in the same room. Thus we can obtain anatomy, motion and electrophysiology from the same patient in the same spatial coordinates (see Fig 24).

One aim of this joint work is the development of computer tools allowing the cardiologists to plan the implantation of cardiac pacemakers on patients with arrhythmias. Then, we have to evaluate the heart motion from tagged MRI, this can be done with different image processing tools or using the phase information. Next, we have to estimate the parameters of the heart model in order to minimize the differences between the observed and the simulated motion. Finally, we will develop an optimization method to determine the position and the activation times of the cardiac pacemakers which give the best cardiac output.

[14] http://www.kcl.ac.uk/schools/medicine/research/imaging/

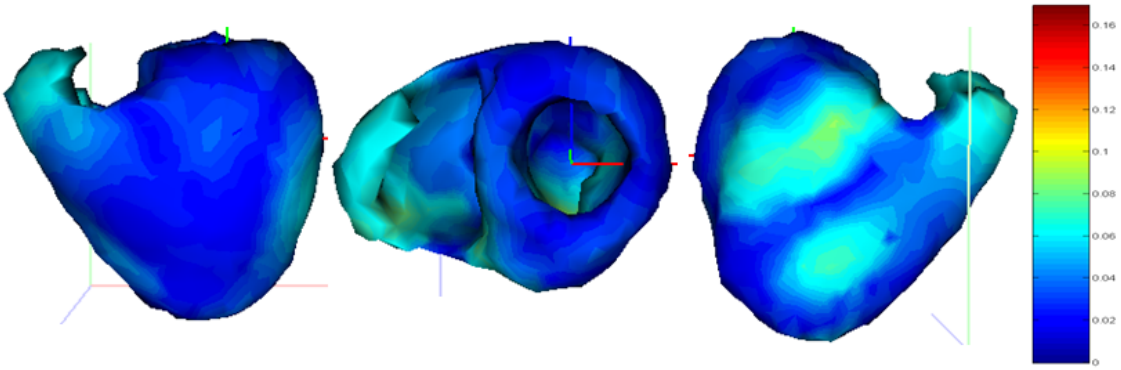


Figure 23. Error map between simulated and reference Action Potential Duration (in seconds)

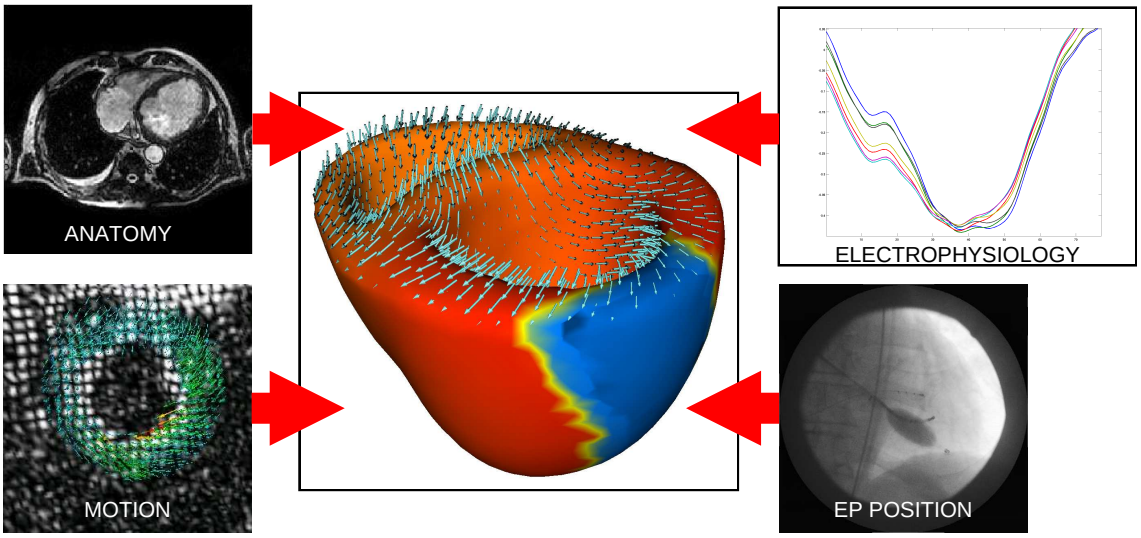


Figure 24. Integration of XMR data providing anatomy, motion and electrophysiology measurements of a patient in the same spatial coordinates allows creation of patient-specific models.

5.6. Clinical and Biological Validation

5.6.1. Evaluation of registration algorithms on a grid infrastructure

Keywords: *accuracy evaluation*, *grid computing*, *rigid registration*.

Participants: Tristan Glatard, Xavier Pennec.

This project is part of a partnership between the Asclepios team, the I3S laboratory and is funded by the AGIR project of the French ACI "Masses de Données".

The accuracy of registration algorithms is critical for many clinical procedures but quantifying it is difficult due to the lack of gold standard (ground-truth) in most clinical applications. To tackle this problem, we studied a bronze standard method which relies on a database of *in vivo* real images representative of the clinical application rather than on simulated or phantom images.

This method considers the ground truth as a hidden variable which is estimated thanks to the redundancy yielded by the computation of the registration of all the possible image pairs of the database with multiple algorithms. This bronze standard estimation maximizes the log-likelihood of the observed transformations.

Accuracy results were obtained on a brain MRI database used for the clinical follow-up of the radiotherapy of brain tumors with four rigid registration methods. Those results showed that the bronze standard method was able to identify non rigidities among the transformations, including image artifacts, high deformations in the tumor area and tilts in the image acquisition. The four studied algorithms exhibited similar sub-voxelic accuracy on this database [78], [76].

Because of its computing and data intensive nature, the bronze standard application benefits from a grid implementation which facilitates algorithm and data sharing and provides computing power to speed-up the execution. A deployment of this application on the EGEE and Grid'5000 grids was done using our MOTEUR [122], [123][94] workflow manager. MOTEUR allows the execution of an application described as a graph of services in a fully parallel mode [75]. Specific algorithms were developed to allow data management in this context [85].

The execution of the bronze standard application on the EGEE production grid showed that such large-scale and multi-users platforms introduce a high and variable overhead that highly penalizes the application. This overhead was quantified and compared to the one measured on local clusters [74] which was found to be orders of magnitude lower. However, the throughput of the clusters is also lower than the one of production grids, which makes them saturate as the size of the input dataset increases, thus highlighting the need for a large-scale grid. Thus, we investigated methods to reduce the impact of the overhead on production grids. In particular, job grouping [73] and job granularity [77] aim at lowering the number of jobs submitted by the application to reduce the probability for a job to face a high overhead. They are based on a trade-off between the reduction of the number of submitted jobs and the exploitation of the parallelism. Another way to reduce the impact of the grid overhead is to set a timeout value to the jobs and to resubmit them when it expires. We noticed that setting a timeout only speeds up the execution when the tail of the distribution of the grid overhead is sufficiently heavy and when failures impact the execution [95]. Those strategies were shown to provide a significant speed-up on the execution time and larger scale experiments on the bronze standard application are thus made possible.

5.6.2. Log-Euclidean DTI analysis in clinical studies

Keywords: *DT-MRI*, *DTI*, *Log-Euclidean*, *fiber tracking*, *regularization*, *tensor*, *tractography*.

Participants: Pierre Fillard, Denis Ducreux [Kremlin-Bicêtre hospital, Paris].

The applicative power of the previously proposed Log-Euclidean framework for DTI processing was assessed through different studies lead in collaboration with MD. Denis Ducreux, radiologist at the hospital Kremlin-Bicêtre, Paris. In [41], we inspected the usability of DTI and fiber tracking in spinal cord astrocytomas, which are rare neoplasms that can result in alteration of the spinal cord structural integrity (Fig. 25 left). Our objective was to visualize the deformation of the posterior spinal cord lemniscal and corticospinal tracts in 5 patients with low-grade astrocytomas compared with 10 healthy volunteers by using 3D fiber-tracking reconstructions. In [40], we showed that DTI, as a pretherapeutic routine investigation in brain tumours, can be helpful as an additional tool to morphological MRI in evaluating the prognosis of patients. Finally, in [45], we illustrate the value of diffusion tensor imaging and tractography in the diagnosis and follow-up of central pontine myelinolysis (Fig. 25 right).

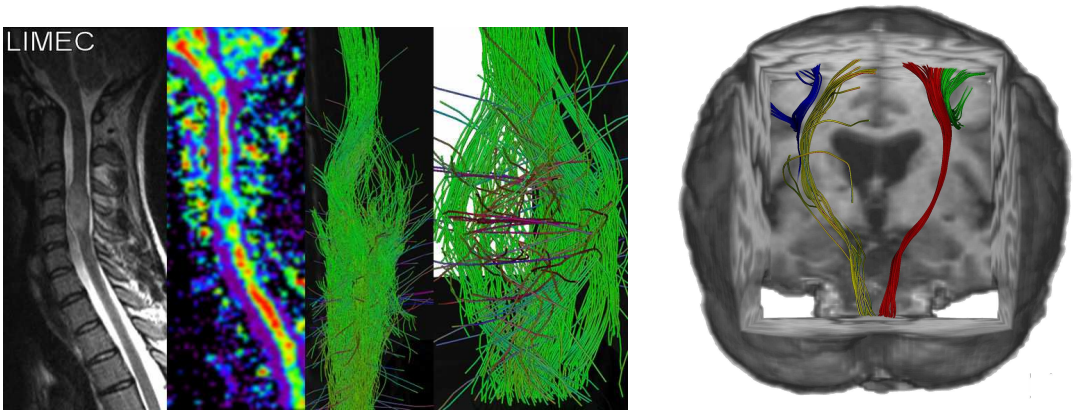


Figure 25. Two examples of Log-Euclidean DTI processing. Left: A spinal cord astrocytoma and its effect on fiber tracking. Right: Fiber tracking in the diagnosis of central pontine myelinolysis. The left corticospinal tract is affected. Original data courtesy of MD. Denis Ducreux (LIMEC), Kremlin-Bicetre Hospital, Paris.

6. Contracts and Grants with Industry

6.1. Maestro

Participants: Olivier Commowick, Jimena Costa, Hervé Delingette, Grégoire Malandain [Correspondant].

MAESTRO[15] is an integrated project funded by the EC. It features a program on research and development on major clinical and technological aspects for the innovative radiotherapy treatments which are crucial for patient safety. The integrated project incorporates basic translational research on hi-tech equipment for clinics in close collaboration with industrials, research centres and European health services.

Within this project, Asclepios is involved, in collaboration with Dosisoft, in the automatic delineation of structures for radiotherapy planning (cf [69], [70], [80], [81]).

6.2. Philips

Participants: Hervé Delingette [Correspondant], Cécile Marboeuf, Maxime Sermesant.

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

Philips Medical System Research in Paris has contracted the Asclepios team to investigate the analysis of 2D and 3D echocardiographic images in order to better understand, diagnose and cure the phenomenon of cardiac asynchrony, one common type of heart failure.

A first study has focused on the tracking of 2D echocardiographic images based on block-matching, the output being compared to the motion information provided by the Doppler Tissue Imaging. We plan to extend this work for segmenting, tracking and analysing the motion of the mitral valve and myocardial surfaces in 3D echocardiographic images.

6.3. Odysseus

Participants: Hervé Delingette [Correspondant], François Poyer, Nicholas Ayache.

This EUREKA project involves three industrial partners (Karl Storz, SimSurgery and France Telecom), a cancer research institute (IRCAD) and three groups from INRIA (Alcove, Asclepios and Evasion). Its objective is to build computer-aided diagnosis, surgery planning and surgery simulation software to increase the efficacy of therapies against cancer of the lower abdomen. In this project, Asclepios is involved in the development of soft tissue models in a surgery simulation platform.

To this end, Asclepios is collaborating with the INRIA teams Alcove and Evasion and the CIMIT center in Boston (USA) to develop a platform named SOFA (Simulation Open Framework Architecture)[16] . SOFA code is now being developed with the INRIA Gforge and is a generic, versatile and open platform that includes many software components useful for real-time medical simulation. In 2006, we have focused on the management of topological changes which occur when simulating suturing or dissection. SOFA has been demonstrated during a plenary meeting in June in Boston and during one workshop in August at Stanford University.

6.4. Health-e-Child

Participants: Xavier Pennec [Correspondant], Nicholas Ayache, Maxime Sermesant, Hervé Delingette, Stanley Durrleman, Ender Konukoglu.

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 paediatric 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 paediatric 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 paediatricians make the right decisions.

Based on our previous works on anatomical statistics and on the modelling of the heart and brain tumours that integrate in particular image and electrophysiological data, the role of the Asclepios team is to model the pathologies that Health-e-child is focussing on. The method is to increase the scope of the integration to more biomedical data (clinical, epidemiological, genetic, etc.) and with practices in place on the different sites. The main difficulty lies in that fact that children's organs are still growing and the pathology interacts with this growth and affects the future evolution of the organs concerned. It is therefore essential to be able to distinguish changes due to pathology from those due to growth. Furthermore, it is also vital that the generic models can be adapted to the specificities of each child. This is why the statistical approach is another important aspect of our modelling, and our participation in the project enables us to access large distributed image data bases to that end. On the other hand, the statistical dimension should make it possible to demonstrate hidden links between different data, for example, between a type of anatomical symptom and a genomic characteristic.

6.5. Siemens

Participants: Jean-Marc Peyrat, Hervé Delingette, Xavier Pennec, Nicholas Ayache.

[16] http://www.sofa-framework.org

A contract has been established in 2005 between Asclepios and Siemens Corporate Research, Princeton, for establishing a methodology to predict and evaluate the accuracy and robustness of registration methods in image guided surgery, with application to concrete clinical problems. After the departure of Antoine Azar, the subject has been shifted toward the modeling of the cardiac anatomy. This study involves in particular Jean-Marc Peyrat through his PhD in the Asclepios team (see also Section 5.4.2).

6.6. CIFRE PhD Fellowships

6.6.1. Dosisoft

The work of Olivier Commowick on the design and evaluation of digital antomical atlases and dedicated to non-rigid registration tools for radiotherapy planning is supported by a PhD fellowship from the Dosisoft company.

6.6.2. Mauna Kea Technologies

The work of Tom Vercauteren on the mosaicing and analysis of temporal sequences of *in vivo* confocal microscopic images is supported by a PhD fellowship from the Mauna Kea Technologies company.

6.6.3. Philips Medical Systems

The work of Cécile Marboeuf on the analysis of ultrasound images is supported by a PhD fellowship from the Philips company.

7. Other Grants and Activities

7.1. Regional initiatives

7.1.1. Regional PhD fellowships

Guillaume Dugas-Phocion and Ender Konukoglu are 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, Valérie Moreau-Villéger.

The national action CARDIOSENSE3D has been launched in May 2005 on the topic of cardiac simulation. This 4-year action gathers the expertise of four INRIA research teams (Asclepios, Macs, Reo and Sosso2) 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. ACI Masse de Donnée AGIR

Participants: Xavier Pennec [correspondant], Tristan Glatard, Johan Montagnat [I3S].

Grid Analysis of Radiological Images Data http://www.aci-agir.org/ (in French: Analyse Globalisée des données d'Imagerie Radiologique - AGIR) is a multi-disciplinary research project with focus on leveraging medical imaging algorithms through grid systems, funded by the French Research Ministry through the ACI (Action Concertée Incitative) Masses de Données.

AGIR gathers researchers in computer science, physics and medecine from CNRS, INRIA, Universities, INSERM, and hospitals. Its goals are to to define and validate new grid services that address some of the requirements of complex medical image processing and data manipulation application ; and new medical image processing algorithms that take advantage of the underlying grid infrastructure for computing and data intensive needs. The project started in september 2004, and supports the PhD of T. Glatard, jointly supervised by X. Pennec at ASCLEPIOS and J. Montagnat at RAINBOW (I3S, Nice University). We refer the reader to Section 5.6.1 for the scientific results of the project.

7.2.3. ATP CIRAD Meristem Grant

Participants: Romain Fernandez [CIRAD], Christophe Godin [Virtual Plants], Jean-Luc Verdeil [CIRAD], Grégoire Malandain [Correspondant], Olivier Devillers [Geometrica].

Contractor for Virtual Plants: CIRAD. From December 2005 until December 2008

3D imagery and geometrical modeling of meristems. The aim of this Action Thématique Programmée of CIRAD is twofold. We first intend to design 3D visualization techniques of the meristem architecture at cellular and molecular levels. Second, we aim at developing a generic geometric model of the meristem able to support various treatments and modelling processes at cell scale (characterization of meristem geometry, cell growth, mechanical forces, circulation of hormone fluxes, ...). Data will be collected from bi-photon microscopy at CIRAD (in the context of the RIO imaging platform) on rice, a model plant for agronomy, and on other perennial species to characterize the state of the meristem at different phenological states or for different environmental constraints. The project includes several teams from CIRAD, INRA and IRD, and 3 INRIA projects: Asclepios, Geometrica and Virtual Plants.

7.2.4. QUALICORE

Participants: Grégoire Malandain [correspondant], Jean-Christophe Souplet, Christine Lebrun [Neurology, Pasteur Hospital, Nice].

QUALICORE is a phase IV pharmaceutical study which is funded by SERONO and that aimed at evaluated the quality of life of MS patients under treatment. Five national hospitals participate to it, namely Clermont-Ferrand, Dijon, Marseille, Montpellier and Nice. Asclepios is in charge of the MR image processing package.

7.2.5. INRIA Cooperative Research Initiative REGLO

Participants: Johan Debayle, Grégoire Malandain [correspondant].

The *Cooperative Research Initiative* named *REGulation of Ovulation (REGLO)*, coordinated by F. Clément from the SOSSO2 team, aims to study the follicular development in mammals, and proposes mathematical models that allow to follow the granulosa cell population, and then to predict the outcome of the follicular development (ovulation or degeneration) with respect to the hormonal environment.

7.2.6. COLOR Medmesh

Participant: Hervé Delingette [correspondant].

This work is conducted in collaboration with the Geometrica, Odyssée, Caiman teams and the Inserm Unit U751 in Marseille

The INRIA local initiative named *Medmesh* is coordinated by Mariette Yvinec (Geometrica). It aims to develop meshing techniques for the generation of meshes extracted from medical images and suited for applications such as visualisation, simulation and therapy planning.

7.2.7. COLOR Ab in vivo Ad in silico

Participants: Grégoire Malandain [correspondant], Nicholas Ayache.

This work is conducted in collaboration with Hélène Barelli (IPMC, Sophia-Antipolis)

The INRIA local initiative named *Ab in vivo Ad in vilico* and coordinated by A. Habbal from the OPALE team, aims to study the mathematical models of the healing process and to validate them with image processing procedures [99].

7.2.8. Consulting for Industry

- Nicholas Ayache is member of the Scientific Council of Dosisoft (Paris), a subsidiary from the Gustave Roussy Institute and the Curie Institute (Paris). He is scientific consultant for the company Mauna Kea Technologies (Paris).
- Hervé Delingette is a scientific consultant for the company Median and a member of the scientific council of the company QuantifiCare.
- 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) and a scientific consultant for the company Median.
- Xavier Pennec is a scientific consultant for the company Median and a member of the scientific council of the company QuantifiCare.

7.2.9. Collaboration with national hospitals

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

7.2.9.1. 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 [134], [135].

7.2.9.2. Hôpital de la Pitié-Salpétrière, Paris

Dr. J. Yelnik (INSERM U.289), Pr. D. Dormont, and E. Bardinet (CNRS) are our partners in a collaboration with Medtronic [114].

7.2.9.3. 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 [82].

7.2.9.4. 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.

7.2.10. Collaboration with international hospitals

7.2.10.1. Guy's Hospital, London, United Kingdom

Maxime Sermesant is a part-time research associate in the Interdisciplinary Medical Imaging Group, Division of Imaging Sciences, Guy's 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

Participants: Xavier Pennec [Correspondant], Vincent Arsigny, Pierre Fillard, Nicholas Ayache, Caroline Brun [LONI, UCLA], Natasha Lepore [LONI, UCLA], Paul Thompson [LONI, UCLA].

Since its creation in September 2001, the associated team program between the Asclepios laboratory at INRIA and the laboratory of NeuroImaging at the UCLA School of Medicine has enabled an active collaboration between both structures, with the objective of comparing and analyzing the performances and behaviors of image processing algorithms devoted to the building of brain atlases.

Since 2004, we study the anatomical variability of the brain, in the framework of the PhD thesis of P. Fillard. Our strategy is to construct a statistical model of manually delineated landmarks at the surface of the cortex: sulcal lines. The mean sulcal lines are determined by iteratively optimizing over the position of the mean line and the matchings with all the instances. Then, covariance matrices are computed on each lines independently and then diffused in the whole space thanks to the log-Euclidean framework. This year, the results previously obtained with the statistical model of 72 sulcal lines were extended to take into account the influence of the spatial affine normalization and the number of tensors picked as model parameters. The results were published in [42] (see also Section 5.4.3). Another publication is currently prepared with P. Thompson on the neuroscientific interpretations of the results on the brain asymmetry obtained with new statistical methods to probe the co-variability of symmetrical points.

Following the visit of A. Leow in January 2006 and N. Lepore in June 2006, a new collaboration axis was initialized on tensor based morphometry. The goal is to perform statistics on the Cauchy-Green Tensor of deformations between subjects [128] using the log-Euclidean [33] or the affine invariant metric [50] and to reuse these statistics as a regularization criterion for non-linear image registration [86]. A working meeting between X. Pennec, N. Lepore and C. Brun (PhD student at UCLA) was held on this subject at the MICCAI and MFCA conferences in Copenhagen in October, and several articles are currently under way.

P. Thompson, X. Pennec, N. Ayache participated to the Symposium ISBI'06 in Washington DC, USA, April 06. X. Pennec, N. Ayache, P. Fillard, C. Brun and N. Lepore participated to the MICCAI'06 conference in Copenhagen, Denmark, October 2006. X. Pennec organized the first workshop on the Mathematical Foundations of Computational Anatomy on October 1st at Copenhagen. V. Arsigny, P. Fillard, N. Lepore et C. Brun did participate to this event with presentations related to the associated team themes by V. Arsigny, N. Lepore and X. Pennec. X. Pennec presented results from the associated team program at invited talks at the Shape Space workshop at the Institute for Mathematics and Applicatioons (IMA, Minneapolis, USA) in April 2006, at Jonhs Hopkins University, and at the 15th ERNSI workshop on system identification, Linkoping, Sweden, septembre 2006.

8. Dissemination

8.1. Promotion of the Scientific Community

8.1.1. Journal editorial boards

Medical Image Analysis N. Ayache is co-founder and co-editor in Chief with J. Duncan (Professor at Yale) of this scientific Journal created in 1996 and published by Elsevier. Its impact factor in 2003 was 4.4, it was 3.2 in 2004, and 3.14 in 2005.

IEEE Transactions on Medical Imaging N. Ayache is associated editor.

N. Ayache is a member of the editorial board of the following journals *Medical Image Technology* (Japanese journal) and *Journal of Computer Assisted Surgery* (Wiley).

H. Delingette is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier).

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

8.1.2. Participation in the organization of conferences

N. Ayache is program chair of MICCAI'07 and a member of the executive board of the MICCAI society. he was a member of the scientific board of ISBI'06.

H. Delingette was the co-organizer and the general chair of the International Workshop entitled "From Statistical Atlases to Personalized Models: Understanding Complex Diseases in Populations and Individuals" held on Oct 6th 2006 in Copenhagen. He served as area chair for the conference Miccai'06 and was a member of the program committees of the conferences MICCAI'06, ECCV'06, ISBMS'06, GRAPP'06, CIARP'06, CVAMIA'06. He was also member of the review committee of the international conferences CVPR'06 and ISBI'06.

G. Malandain was member of the scientific board of CARI'06, CVAMIA'06, DGCI'06, ISBI'06, and MICCAI'06.

X. Pennec was the general chair of the first International Workshop on Mathematical Foundations of Computational Anatomy (MFCA'06), held on October 1st in conjunction with MICCAI'06 in Copenhagen. He was a member of the programm committees of the workshops MMBIA'06, WBIR'06, SA2PM'06, Deform'06. He was also member of the review committees of the international conferences CVPR'06, MICCAI'06, ISBI'06.

8.1.3. Scientific animation

N. Ayache is chairing the "comité des projets de l'INRIA Sophia-Antipolis", and is a member of the scientific direction of INRIA-Sophia-Antipolis. He is a member of the Evaluation Committee of INRIA.

G. Malandain is chairing the CDL (*Commission de Développement Logiciel et d'Expérimentation*).

X. Pennec is a member of the committee of the SPECIF PhD award since 2006. He was also an evaluator for the ANR-CIS program and for the Research Networks Program in Medical and Biological Imaging of the High Council for Scientific and Technological Cooperation between France and Israel in 2006.

H. Delingette is member of the local computer infrastructure user committee (CUMIR) and the local committee in charge of the scientific selection of visiting scientists applications (Comité Nice).

M. Sermesant was an evaluator for the Biotechnology and Biological Sciences Research Council (BBSRC), United Kingdom.

8.2. University teaching

École Centrale de Paris. N. Ayache is responsible of 2 modules on medical imaging (formation and analysis of medical images)(45 hours of lectures + 45 hours of small classes) with the participation of N. Ayache, H. Delingette, G. Malandain, R. Vaillant (GEMS) for the lectures) and E. Bardinet, B. Grosjean, and S. Jbabdi for the small classes. These 2 modules are common to the DEA MVA of ENS Cachan "Mathematiques, Vision et Apprentissage", and to the Master IDB of École Centrale de Paris.

Ecole des Ponts et Chaussées H. Delingette has presented an overview of medical image analysis during a 3h course.

Ecole Supérieure de Chimie, Physique et Electronique (ESPCE). P. Fillard gave 8 hours of lecture on medical imaging, more specially MRI and DT-MRI, as well as an introduction to programming in VTK.

Master IGMMV, université de Nice Sophia-Antipolis. G. Malandain is responsible of one module of 15 hours (medical image analysis).

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)

8.3. PhD Theses and Internships

8.3.1. PhD defended in 2006

1. Vincent Arsigny, *Processing Dtata in Lie Groups: an Algebraic Approach. Application to Non-Linear Registration and Diffusion Tensor MRI* École Polytechnique, November 29, 2006. Committe: N. Ayache (Supervisor), I. Bloch (Referee), O. Faugeras, J. Gallier (Refereee), S. Mallat (President), X. Pennec (Co-supervisor), M. Sigelle (Invited).

2. Olivier Clatz, *Modeling of the biomechanical behavior of the brain: application to the prediction and simulation of neurosurgery*, École des Mines de Paris, February 10, 2006. Committee: N. Ayache (Supervisor), H. Benali (Reviewer), P.-Y. Bondiau, J.-L. Chenot (President), H. Delingette (Co-Supervisor), S. Litrico (Invited), E, Mandonnet (Invited), Y. Payan (Reviewer)
3. Guillaume Dugas-Phocion, *Modeling and segmentation of mutiple sclerosis lesions in multi-sequences MR images*, École des Mines de Paris. March 31, 2006. Committee: N. Ayache (Supervisor), Ch. Barillot (Reviewer), M.-A. González-Ballester, Ch. Lebrun, G. Malandain (Co-Supervisor), J.-Fr. Mangin (Reviewer), J.-Ph. Thirion.

8.3.2. Current PhDs

1. Florence Billet, *Analyse de la fonction cardiaque à l'aide d'un modèle électromécanique du cœur*, Nice-Sophia-Antipolis University. Cardiosense3D.
2. Jonathan Boisvert, *Articulated models for augmented reality: application to minimally invasive spine surgery*. Cotutelle (joint supervision) University of Nice-Sophia-Antipolis / Polytechnique School of Montreal, Canada.
3. Olivier Commowick, *Digital anatomical atlases for radiotherapy planning*. University of Nice-Sophia-Antipolis. Cifre contract with Dosisoft, Paris.
4. Jimena Costa, *Segmentation of anatomical structures of the abdomen with deformable models*. 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. Pierre Fillard, *Statistical modeling of the anatomical variability of the cortex*, Nice-Sophia Antipolis University.
7. Tristan Glatard, *Computing with Massive Medical Image Databases on the GRID for the evaluation of clinical image analysis protocols*. Nice-Sophia Antipolis University. In collaboration with J. Montagnat from the Rainbow team, I3S, 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. Ender Konukoglu, *Modeling and control of tumor growth with medical imaging*. Nice-Sophia Antipolis University.
10. Jean-Marc Peyrat, *Electro-mechanical models of the heart activity personnalized from medical images*, Nice-Sophia Antipolis University.
11. Jean-Christophe Souplet, *Analysis of Multiple Sclerosis MRI images*. Nice-Sophia-Antipolis University.
12. Tom Vercauteren, *Mosaicing and analysis of temporal sequences of* in vivo *confocal microscopic images*. École des Mines de Paris.

8.3.3. Participation to thesis committees

Nicholas Ayache participated to the PhD thesis committee of Valérie Moreau-Villéger (advisor), Saad Jbabdi (referee), Olivier Clatz (advisor), Guillaume Dugas-Phocion (advisor), Gwenaelle Douaud (examinator), Muriel Perrin (referee), Vincent Arsigny (advisor), Christophe Lenglet. He also participated to the HDR thesis committee of Grégoire Malandain, Hervé Delingette, Cyril Poupon (referee), and Xavier Pennec.

Hervé Delingette was the examiner of the thesis of M. Marchal (Univ. J. Fourier Grenoble), O. Palombi (INPG Grenoble), L. Brix (U. of Aalborg, Denmark), P-F. Villard (Univ. Lyon I), D. Marchal (Univ. de Lille). He was the examiner on the Venia Legendi manuscript of M. Harders (ETH Zurich). He participated to the PhD thesis of O. Clatz.

Grégoire Malandain participated as a referee to the PhD thesis committee of V. Boldea (Univ. Lyon II), L. Aït-Ali (Univ. Rennes I) and B. Delhay (INSA Lyon). He also participated to the PhD thesis committee of G. Dugas-Phocion as co-supervisor.

Xavier Pennec participated to the PhD thesis committee of V. Arsigny as co-supervisor.

8.3.4. Training activities

1. Romain Fernandez, *Segmentation of the cardiovasccular system and characterisation of the aortic cross*. Master IGMMV, University of Nice-Sophia Antipolis, 2006.
2. Damien Lepiller, *Adjustment of a volumetric model of cardiac electrical activity*. Master IGMMV, University of Nice-Sophia Antipolis, 2006.
3. Ouafaa Daki, *Estimation of myocardium motion from tagged MRI*. Master 1, University Joseph Fourier, Grenoble, 2006.
4. Romain Vauchelles, *Mise en place d'un programme d'analyse d'images en wound healing et mise en évidence du rôle de l'activiation de Arf 1 par le GEF ARNO dans la migration cellulaire*, Master Imagerie pour la Biologie, Université de Rouen, 2006.

8.4. Habilitations

1. Hervé Delingette. *Modélisation de structures déformables*, Habilitation à diriger des recherches, Université de Nice - Sophia Antipolis, March 2006.
2. Grégoire Malandain. *Les mesures de similarité pour le recalage des images médicales*, Habilitation à diriger des recherches, Université de Nice - Sophia Antipolis, March 2006.
3. Xavier Pennec. *Statistical Computing on Manifolds for Computational Anatomy*, Habilitation à diriger des recherches, Université de Nice - Sophia Antipolis, December 2006.

8.5. 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 invited lectures at the University of North Carolina (Distinguished lecture of the Computing Science Triangle), Nice (Journées de l'Académie des Sciences en région), Bergamo (Haemodel Conference on Computational Physiological Fluids), Copenhagen (Microscopic Biological Image Processing Workshop).
- **Hervé Delingette** gave invited talks on Medical Image Segmentation, Soft Tissue Modeling and Cardiac Modeling at the university of Aalborg (Danemark), at the Euron'06 Robotics winter-school in Benidorm (Spain), at the laboratory of Cardio-energetics of the NIH in Bethesda (USA), at the INRIA-Industry meeting in Rocquencourt, at a presentation organized by the scientific magazine "Pour la Science" in Paris, at the ISSIR'06 robotics workshop in Montpellier, at the Ercim meeting on Physiological modeling in Nice.
- **Grégoire Malandain** gave an invited lecture on medical image segmentation in the summer school *Imagerie Anatomique* (Paris, may 2006). He gave an invited talk at the Biocare Molecular Imaging Workshop (Leipzig, october 2006), a satellite workshop of the ESTRO (European Society for Therapeutic Radiology and Oncology) meeting and at the INRIA-Industry meeting in Rocquencourt.

- **Xavier Pennec** gave invited plenary talks on Statistical Computing on Riemannian Manifolds for Computational Anatomy at the Shape Space workshop (IMA, Minneapolis, USA, April 3-7 2006), at the Mathematics and Image Analysis Conference (Paris, September 18-21 2006), and at the 15th ERNSI workshop on System Identification (Linköping, Sweden, September 20-21). He was also invited to give a seminar at Johns Hopkins University in April 2006.
- **Maxime Sermesant** gave an invited talk titled "Integrating Medical Imaging and Mathematical Models for Planning and Therapy of Cardiac Arrythmias" at the Imaging Network Ontario Symposium, Toronto, Canada.

8.6. Nominations and prizes

- **Nicholas Ayache** received the EADS-Académie des Sciences grand prize in Information Sciences and Applications in December 2006. He joined in 2004 the Advisory Committee of the newly created Shun Hing Institute of Avanced Engineering in Hong-Kong (4 year term) and he also joined in 2004 the High Council for the promotion of science and technology between France and Israel.
- **Tom Vercauteren** has been awarded the Best Paper at MICCAI'06 (October 4, 2006, Copenhague) for the article on "Robust Mosaicing with Correction of Motion Distortions and Tissue Deformation for *in vivo* Fibered Microscopy" published in Medical Image Analysis. The paper is co-written with Xavier Pennec, Grégoire Malandain, and Nicholas Ayache.
- **Jonathan Boisvert** received the Best Paper award during the AMDO 2006 conference (July 11-14, 2006, Spain) for his paper "Principal Spine Shape Deformation Modes Using Riemannian Geometry and Articulated Models". The article is co-written with Xavier Pennec, Hubert Labelle, Farida Cheriet and Nicholas Ayache.

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