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 2 decades [95][1]. 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 [96], [110]. It is also possible to obtain from a Magnetic Resonance image of the head a reasonable segmentation into skull tissues, white matter, grey matter, and cerebro-spinal fluid [113], or to measure some functional properties of the heart from dynamic sequences of Magnetic Resonance [91], Ultrasound or Nuclear Medicine images [97].

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.

[1] 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 [89], [85]. Regarding the target applications, a good review of the state of the art can be found in the book *Computer Integrated Surgery* [84], in N. Ayache's article [92] and in the more recent synthesis [95]. The scientific journals *Medical Image Analysis* [87], *Transactions on Medical Imaging* [88], and *Computer Assisted Surgery* [86] are also good reference material.

One can have a good vision of the state of the art with the proceedings of the most recent conferences MICCAI'2005 (Medical Image Computing and Computer Assisted Intervention) [81], [82] or ISBI'2004 (Int. Symp. on Biomedical Imaging) [83].

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)[2] and multi-modal images[3] 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[4] 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 [101].

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[5]) 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 [114].

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

[2] 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.

[3] 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.

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

[5] Green Fluorescent Protein.

anatomy and functions, different contrast agents, etc.), requires specific image analysis methods (one can refer to the recent tutorial [107] and to the Mouse Brain Atlas Project [90]. 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[6].

Studying the variability of biological shapes is an old problem (cf. the remarkable book "On Shape and Growth" by D'Arcy Thompson [112]). Significant efforts have been made since that time to develop a theory for statistical shape analysis (one can refer to [94] for a good synthesis, and to the special issue of Neuroimage [111] 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 [103]: 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.

[6]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 [105].

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 [106], [100], [93], [108], [98]). While these models and new ones need to be developed, refined or validated, a grand challenge that we want to address in this proposal 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. [109], [104] and the development of new data assimilation methods coping with massive numbers of measurements and unknowns.

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

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

These different levels of modeling are closely related to each other, and several physiological systems may interact together (e.g. the cardiopulmonary interaction [102]). 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 [99], [100]). 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. Baladin

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 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.

4.2. 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.

4.3. 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).

4.4. Tensor ToolKit (TTK)

Participant: Pierre Fillard [Correspondant].

The Tensor ToolKit (TTK) is an ITK (http://www.itk.org) addon dedicated to tensor image processing. While ITK's main goal is to provide implementations of state-of-the-art methods for scalar (or vector) image processing, the TTK provides a set of filters for tensors. Based on the Log-Euclidean framework developped by the team, the TTK implementation contains filters for Diffusion Tensor MRI estimation, extrapolation, filtering and resampling. Some of these filters can obviously be used for other types of tensor images. Optimization routines for PDE solving are also included (first order gradient descent). Finally, the TTK comes with converters that turn a tensor image to a vector image and vice-versa. Thus, all ITK filters for vector processing are readily recylcled for tensor processing.

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.

We are interested in the delineation of anatomical structures of the lower abdomen in the frame of dose calculation for conformational radiotherapy, and for that purpose we develop a semi-automatic segmentation method. We approach the issue of boundary finding as a process of fitting a series of deformable templates to the contours of anatomical structures.

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.

An initial simplex mesh undergoes both global and local deformations to fit the boundaries of a given anatomical structure in a set of tomodensitometric (CT) images, and the result can later be interactively modified and/or corrected by the user. We initially apply this method to the segmentation of the bladder, an example of which can be found in Figure 1. One of the difficulties we have found is the computation of the initial position of the model within the 3D image. To solve this, we rely on the fact that the bones in the pelvic zone are structures that present a shape and position that is quite stable among individuals, and that they can be easily seen and segmented in CT images. We therefore estimate the position of salient points in the pelvic bone and femoral heads, which will constitute viable and robust landmarks to estimate the initial position and orientation of the bladder model. The model will then undergo 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 [50].

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

5.2.2. Partial Volume Effect Quantification and Multiple Sclerosis Lesion Segmentation in Brain MRI

Keywords: *CSF, EM, Expectation Maximisation, MRI, atlas, brain, cerebro-spinal fluid, gray matter, histogram, joint histogram, lesion, manual segmentation, multiple sclerosis, partial volume effect, segmentation, statistical, validation, white matter.*

Participants: Guillaume Dugas-Phocion, Grégoire Malandain, Christine Lebrun, Nicholas Ayache.

This work is performed in close collaboration with Christine Lebrun (Neurology Departement), and Stéphane Chanalet (Radiology Department), at Pasteur Hospital, Nice.

Non-invasive imaging techniques are particulary useful for the treatement and medication of functional brain disease. In multiple sclerosis, MRI is used to extract internal and external biomarkers, and the diagnosis process makes a heavy use of the many available modalities via Barkhov criteria. Obtaining quantitative results from MRI, like lesion number, lesion load is more difficult, but is highly interesting to strengthen the robustness of diagnosis process, following of patient state and clinical trials. For these reasons, a segmentation of multiple sclerosis lesions in multi-sequence MRI is necessary.

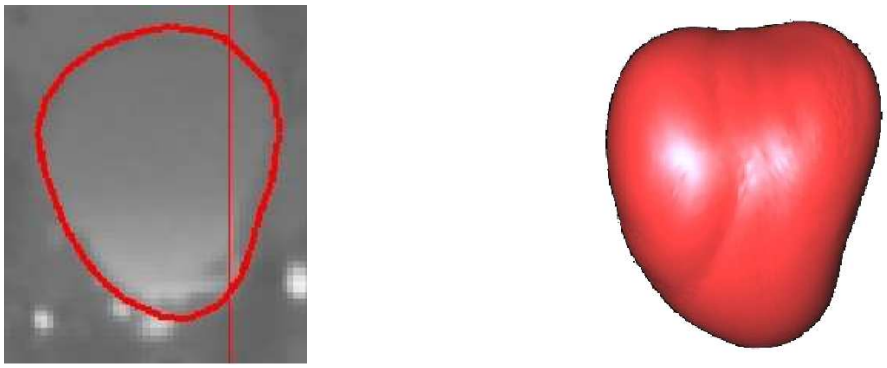
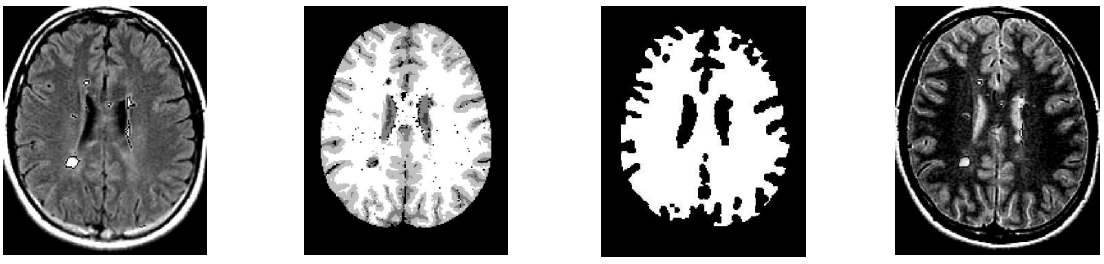


Figure 1. An example output of our method, displayed in 2D and 3D. As we see, in the original image there is a considerable lack of contrast, which would make the manual delineation very difficult. However, our method is able to adjust to the bladder's boundaries quite accurately.

To obtain this segmentation, a robust segmentation pipeline is required. The ideal system must be generic enough to be useful to many kind of users – neurologists, researchers, clinical drug developers. It should be able to produce many kind of biomarkers that are related to the disease – lesion load, brain atrophy etc. – the reproductibility of which must be evaluated. This require a fine knowledge of image acquisition and their clinical usage for this disease.

In our work, we attempted to solve the following problem: how to build a multi-sequence MRI analysis system, with multiple sclerosis as direct application. As a first step, we placed the image database – 43 subjects, 80 acquisitions of 4 sequences: T2 FSE, DP, T2 FLAIR, T1 – in a standardised spatio-intensity space: intra-patient rigid registration, affine registration of a statistical atlas, bias correction. A brain tissue segmentation system is then applied, taking into account vessels and partial volume effect from the dual T2/DP images. From this segmentation, a first lesion detection is done using the T2 FLAIR sequence. The T1 MRI is used to extract a reasonnable region of interest and remove flow artifact from T2 sequences, which finally leads to a MS lesion mask in T2 modalities. These results have been compared to expert segmentation and validated [51].



T2 FLAIR lesions *T2/DP segmentation* *T1 ROI mask* *Lesions (DP)*

Figure 2. Some segmentation results. While the T2 FLAIR has a high detection potential for multiple sclerosis (left), we use the T1 image to produce a confidence ROI (middle left) and the tissue segmentation from T2/DP images (middle right) to produce a final lesion segmentation (right)

5.2.3. Interactive intensity- and feature-based non-rigid registration framework for 3D medical images

Keywords: *feature-based registration, hybrid registration, intensity-based registration, interactive registration, non-rigid registration.*

Participants: Antoine Azar, Nicholas Ayache, Chenyang Xu [Siemens SCR], Frank Sauer [Siemens SCR], Xavier Pennec.

This work was conducted in collaboration with Siemens Corporate Research (NJ, USA).

Many algorithms exist in the literature for iconic or geometric non-rigid medical image registration. However, a new class of hybrid algorithms is recently emerging, combining both intensity-based and feature-based components to achieve more accurate registration. This work develops a new 3D hybrid non-rigid registration framework which combines any intensity-based algorithm with smart user-based feature matching [79]. The feature matching exploits user-placed landmark information, and based on saliency and similarity measures, determines optimal correspondences in the neighborhood of each landmark. A dense feature-based deformation field is then generated using a thin-plate spline interpolation. This leads to a new iterative two-step energy minimization which results in a transformation combining both the intensity-based deformation field and the feature-based one. Additionally, the framework allows user interactivity for "live" corrections and guidance of the algorithm in case of errors or inaccuracies. This registration framework is implemented as part of a powerful and flexible software platform named FusionLab, which has been developed at Siemens Corporate Research, Princeton, USA. The software allows powerful visualization modes for clinical use and supports industry-standard formats such as DICOM and XML. Experimental results of our hybrid approach on several different datasets (eg lung, pelvis, brain, etc) show that in each case, the registration benefited from the hybrid approach as opposed to the intensity-based component alone (see figure 3).

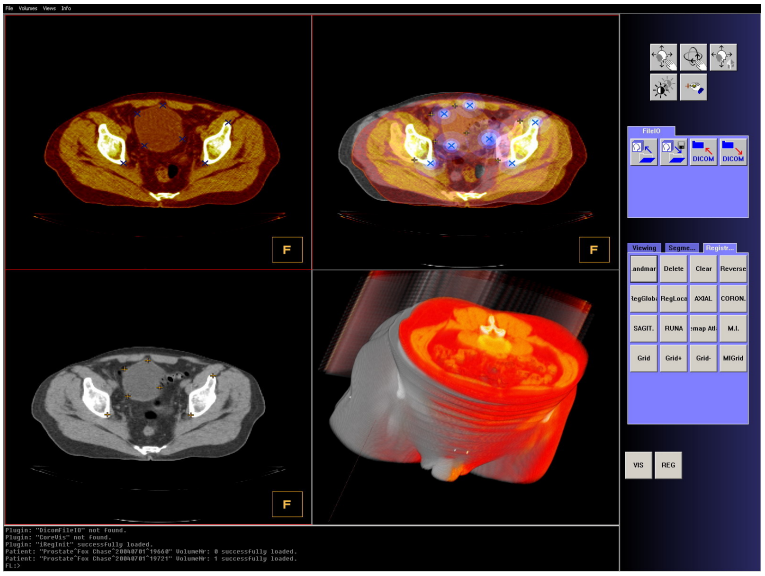


Figure 3. FusionLab software developped at SCR, shown here for the registration of two pelvis datasets. The interactive hybrid registration is guided by user-placed landmarks (in blue).

5.2.4. Incorporating Statistical Measures of Anatomical Variability in Non-Rigid Registration for Conformal Brain Radiotherapy

Keywords: *Nonrigid registration, atlas registration, conformal brain radiotherapy.*

Participants: Olivier Commowick, Radu Stefanescu, Pierre Fillard, Vincent Arsigny, Nicholas Ayache, Xavier Pennec, Grégoire Malandain.

In collaboration with DOSIsoft SA, Cachan and Centre Antoine Lacassagne, Nice

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 and each structure has to be delineated in each slice of a 3D image. 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's 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.

However, due to its multi-subject nature, the non-rigid registration problem is generally difficult. Some registration algorithms [24] using inhomogeneous regularization were recently introduced. It applies a spatial-dependent regularization: strong where the local deformability is low, and weak where it is high. Moreover, the regularization can be direction-dependent thanks to the use of tensors: the amount of deformation allowed can be separately tuned along spatial directions. However, the brain variability between subjects is not well known and this algorithm used a heuristic map of the deformability. We have introduced in [49] a new framework to compute deformability statistics (either scalar or tensor based) over a database of patient MRI. These statistics are then used to guide the regularization of the deformation field. Thanks to this method, we obtain results both quantitatively and qualitatively better results (see figure 4).

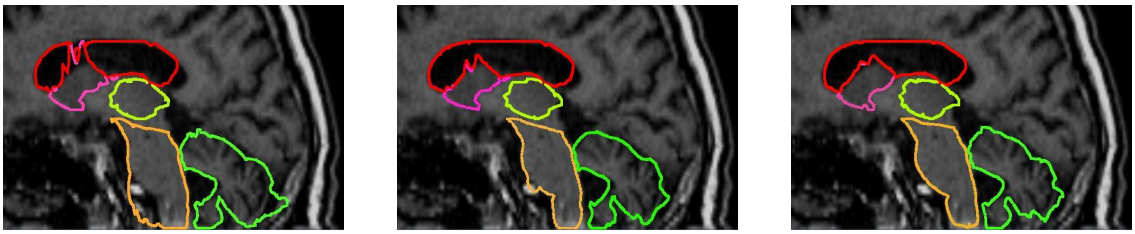


Figure 4. ***Comparative results of the atlas-based segmentation.*** *From left to right: Registration using a heuristic scalar regularization map, a statistical scalar regularization map and a statistical tensor based regularization map.*

5.2.5. Registration with Polyrigid and Polyaffine Transformations

Keywords: *Diffeomorphisms, Histological Slices, Multi-affine Deformations, Non-rigid Registration, Parametric Transformations.*

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

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.

The key advantage of this approach with respect to other parameterizations of deformations is the guarantee of invertibility of the global transformation and the simple form taken by its inverse, which is quite simple to compute. An extended version of this work, applied to the registration of histological slices, has been published this year [25].

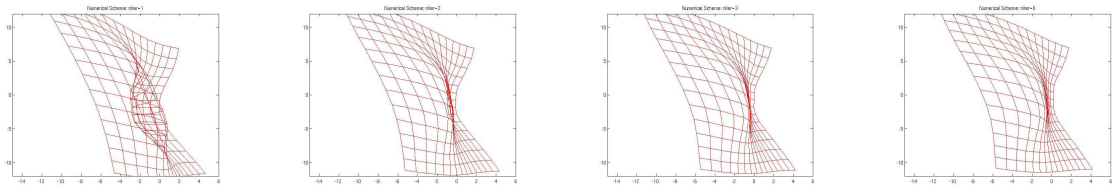


Figure 5. Fusing two affine components while guaranteeing invertibility. In the Polyaffine framework, the global transformation is obtained by the continuous integration of an Ordinary Differential Equation. Practically, this integration is discretized using a finite number of intermediate points, which varies in this figure (from left to right: 0, 1, 2 and 5 ntermediary points). Note how a small number of points suffices to insure the invertibility of the global transformation.

5.3. Biological Image Analysis

5.3.1. 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, 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. The goal of this work is to enhance the possibilities offered by FCM by using image sequence mosaicing techniques in order to widen the field of view (FOV).

The displacement of the fiber bundle probe across the tissue implies a large rigid motion between the frames of the input sequence. Due to the interaction of the contact probe with the soft tissue, a small non-rigid deformation appears on each input frame. Because of those non-linear deformations, classical video mosaicing techniques need to be adapted. In [70], we proposed a Riemannian framework to estimate the global positioning of the input frames. Based on pairwise registrations results between the input frames, we were able to develop a consistent and robust estimator of the global positioning. This algorithm was successfully included as a step of our complete mosaicing algorithm. Other contributions include an efficient and simple method to reconstruct the image mosaic from registered images, and a fine non-rigid frame to mosaic registration in order to compensate for the soft tissue deformations. The effectiveness of the proposed algorithm is shown on a sequence that has been acquired in-vivo on a mouse colon stained by acriflavine at 0,001%. As shown in Fig. (6, right), our algorithm allows for a simultaneous visualization of normal crypts and Aberrant Crypt Foci.

5.4. Computational Anatomy

5.4.1. Riemannian Elasticity: A statistical regularization framework for non-linear registration

Keywords: *Non-rigid registration, Riemannian geometry, Tensors, inter-individual variability, statistical regularization.*

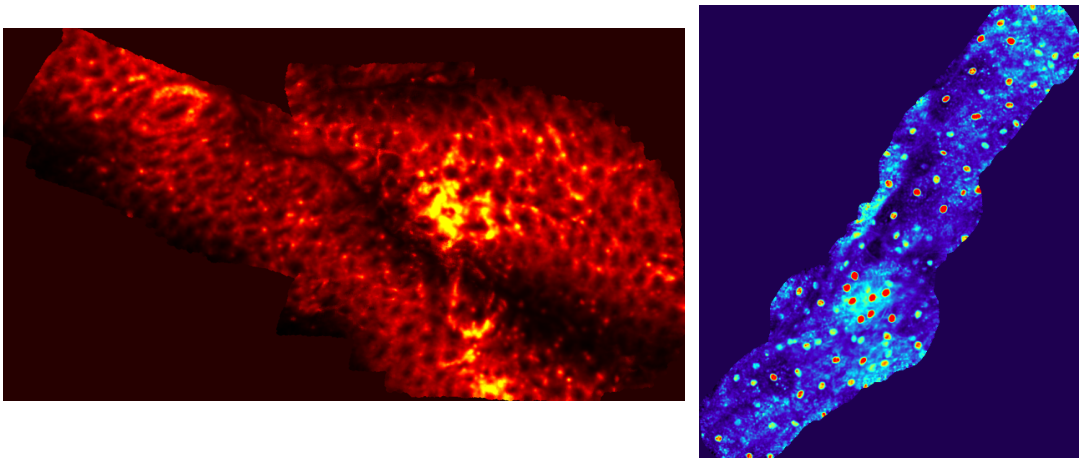


Figure 6. ***Left:*** *Mosaic of 50 live mouse colon images (Fluorescence FCM). The mouse colon, stained by acriflavine, show both normal and aberrant crypts. Images are courtesy of Danijela Vignjevic, Sylvie Robine, Daniel Louvard, Institut Curie, Paris, France.* ***Right:*** *Mosaic of 243 live human mouth images (Reflectance FCM).*

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

As exemplified in Section 5.2.4 above, one often lacks a good model of the transformation variability to choose the optimal regularization in inter-subject registration. We introduce in [64] an integrated and consistent framework to statistically model the variability and to re-introduce it in a regularization criterion for non-linear registration. The basic idea it to interpret the local elastic energy as the distance between the Green-St Venant strain tensor and the identity, which reflects the deviation of the local deformation from a rigid transformation. By changing the Euclidean metric for a more suitable Riemannian one, for instance a Affine-invariant or the Log-Euclidean one (see [37], [42] and Section 5.4.6), we define a consistent statistical framework to quantify the amount of deformation. In particular, the mean and the covariance matrix of the strain tensor can be consistently and efficiently computed from a population of non-linear transformations. These statistics are then used as parameters in a Mahalanobis distance to measure the statistical deviation from the observed variability, giving a new regularization criterion that we called the statistical Riemannian elasticity. This new criterion is able to handle anisotropic deformations and is inverse-consistent.

Riemannian elasticity gives a natural framework to measure statistics on inter-subject deformations. It can also be viewed as the log-likelihood of the deformation probability, which opens the way to Bayesian deformable image registration algorithms. Preliminary results with the isotropic version show that it can be quite easily implemented, and that it provides an effective regularization criterion for non-linear registration algorithms. Future work will include the computation of the deformation statistics (mean and covariance of the logarithmic strain tensor) on a database of brain images to assess their impact on the registration results. We also plan to evaluate carefully how the implementation influences the theoretical inverse-consistency property of the Riemannian elasticity, as this feature may turn out to be very useful for fine measurements of volume changes.

5.4.2. Grid-enabled workflows for rigid registration assessment

Keywords: *GRID, Nonrigid registration, workflow.*

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

This work is done in collaboration with the Rainbow team at I3S, UMR 6070, University of Nice, and is partially supported by the French research program "ACI-Masse de données", http://acimd.labri.fr/ (see Section 7.2.2.

The target application is the evaluation of the accuracy of rigid registration algorithms, based on the the registration results of many image pairs by various algorithms. By finding the "mean" transformations that best explain these observations, we estimate a bronze standard, which is then used to quantify the accuracy of an algorithm. To cope with the large amount of computations required to determine the bronze standard, we deployed this application on the grid infrastructures provided by the EGEE and the Grid'5000 projects by encapsulating the registration algorithms into Web-Services and orchestrating them with a workflow manager [55].

The deployment of the application with classical workflow managers underlined many performance weaknesses, leading us to develop an optimized workflow enactor (hoMe-made OpTimisEd scUfl enactoR - MOTEUR) which aims at exploiting all the parallelisms offered by the grid. In particular, it implements pipelining and synchronization in service-based workflows, which, as we know, has not been done before and leads to a significant speed-up of the execution of the application [76]. A graphical view of the application being executed by MOTEUR is displayed on figure 7.

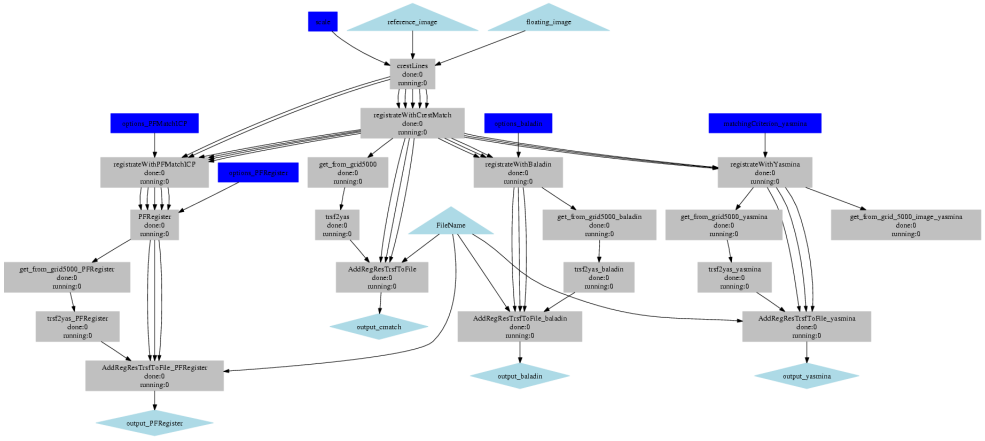


Figure 7. Workflow of the application in MOTEUR.

Our application submits a high number of tasks to the grid during its execution. In order to deal with the overhead introduced by the submission of tasks on production grid infrastructures, we investigated a probabilistic model of the job execution time from which we are able to dynamically determine the optimal number of tasks to submit to the grid given a fixed job to execute [56]. Preliminary experiments demonstrated that using this method, it was possible to reduce not only the total execution time of a job but also the number of tasks submitted to the grid, which offers perspectives from the user's and the infrastructure's point of view.

We are currently working on integrating this probabilistic optimization method into our MOTEUR workflow manager. We then expect to obtain significant results from the medical imaging point of view by being able to execute fastly the bronze standard application on a huge amount of data.

5.4.3. Localization of basal ganglia in Parkinsonian patients

Keywords: *Nonrigid registration, Parkinson disease, atlas registration, deep brain stimulation.*

Participants: Radu Stefanescu, Grégoire Malandain, Nicholas Ayache.

This work has been done in collaboration with Eric Bardinet (CNRS) and Jérôme Yelnick (INSERM), both at the La Pitié Salpêtrière hospital, Paris, and was partially funded by Medtronic, Inc.

Deep Brain Stimulation is a procedure that greatly reduces disabling symptoms in patients with Parkinson's disease. The introduction of the electrode inside the brain is performed through surgery. At the La Pitié

Salpêtrière hospital in Paris, a stereotactic frame, fixed on the patient's head and visible from different modalities (T1 and T2 weighted MR images) is used as a geometrical referential, and guides the electrodes' insertion. The target is first located on pre-operative images, and then the path of the electrodes is planned through the parenchyma in order to avoid high risk structures. In order to achieve the procedure, one has to first localize the central grey nuclei. This is performed by registering the patient image towards an anatomical atlas containing a segmentation of the desired structures, followed by a deformation of atlas structures onto the patient's geometry.

We have investigated different non-rigid registration schemes, in ordre to identify the more robust one. This is done within a retrospective evaluation study [43].

5.4.4. Analyses of Multiple 3D Anatomical Structures with Coupled Statistical Shape Models

Keywords: *EM, EM-ICP, statistical shape model.*

Participants: Heike Hufnagel, Xavier Pennec, Nicholas Ayache.

This work is performed in the framework of the PhD that Heike Hufnagel does at Epidaure project in cooperation with the Institute of Medical Informatics at the university of Hamburg, Germany. Her thesis is supervised by Xavier Pennec and Nicholas Ayache at INRIA and by Heinz Handels of the university of Hamburg.

We are working on the development of methods to perform automatic 3D segmentations based on statistical shape models. The methods might also be used to automatically distinguish healthy and diseased structures. We find that for certain problems it is advantageous to base the statistical analysis of point clouds of shape instances on correspondence probabilities instead of - as mostly done - on exact point-to-point correspondences. This can be realized by using an Expectation Maximization approach when registering the shape instances (as introduced by Granger and Pennec in 2002 for surface registration). Furthermore, we investigate methods to adapt the PCA to multi-modal distributions as we expect that in many cases, there could be several distinct mean shapes depending on unknown variables like genomic pre-dispositions, diseases etc.. In addition, we believe that the shape and location relations of an anatomical structure with regard to their neighbouring structures are interesting information to be used as a priori knowledge in a segmentation process in order to render the result more robust. Therefore, we explore different approaches for coupling neighbouring anatomical structures by geometric parameters.

5.4.5. Brain Variability Modeling

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

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

This work is realized in collaboration with the associated team LONI (Laboratory of Neuroimaging) at UCLA (University of California at Los-Angeles).

This study is the continuation of the work initiated last year. Building upon the rigorous Riemannian framework to process tensors prsented in [37], we were able to compute a dense field of covariance tensors modeling the variability of the brain by extrapolating sparse information learned from precise anatomical landmarks, the sulci, to the full brain.

This year, we extended our variability model in two steps. First, we computed asymmetry maps that express the difference of variability between the 2 hemispheres. Two approaches are used: either by extrapolating first the variability tensor to the full brain, and then measuring the "difference" between left and right tensors w.r.t. the mid-sagittal plane, or by finding point correspondances between the corresponding left and rigth sulci, computing the "difference" between left and right variability tensors along each sulcus, and then extrapolating this "difference tensor" to the full brain. We ended up with interesting neuroanatomy results: the highest differences in variability are located in the speech region (Broca's area), which is developing later during brain maturation, thus being more likely to present asymmetries.

Second, we demonstrated how to validate such a variability model. On the one hand, we showed that only keeping a sparse information was enough to recover the full variability information of each single sulcus.

On the other hand, we performed a leave-one-out test in order to check if the model was able to predict the variability of missing sulci. This would mean that missing information could be retrieved thanks to spatial correlation. The results showed that some sulci could be recovered, some could not due to the high contrast in variability in some regions, like around the central sulcus. This work was oraly presented at IPMI 2005 [53].

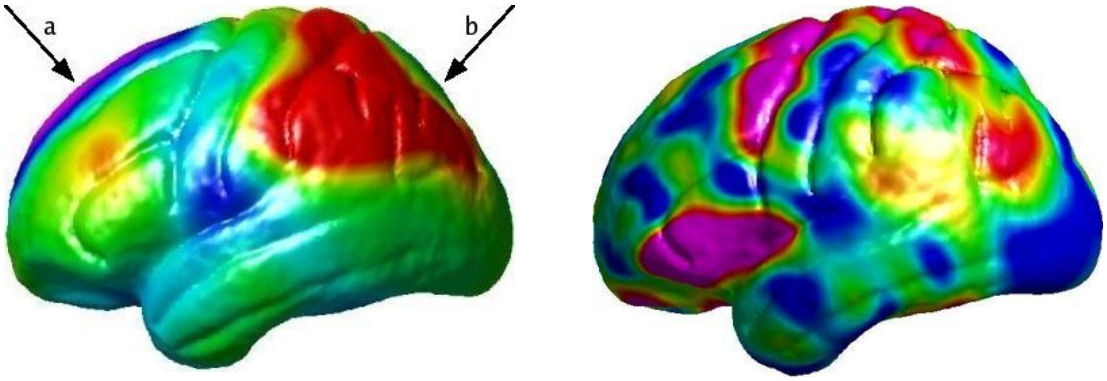


Figure 8. ***Left:*** *A variability map of the cortex. (a): the superior frontal gyrus. (b): the temporo-parietal cortex.* ***Right:*** *An asymmetry map obtained by measuring the difference between left-right tensors w.r.t. the mid-sagittal plane.*

5.4.6. Tensor Processing in the Log-Euclidean Framework

Keywords: *DT-MRI, Lie group, Riemannian geometry, Tensors, brain, interpolation, regularization.*

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

Computations on tensors, i.e. symmetric positive definite real matrices in medical imaging, appear in many contexts. In our field of research, these computations have become common with the use of DT-MRI. But the classical Euclidean framework for tensor computing has many defects, which has recently led to the use of Riemannian metrics as an alternative. Last year, affine-invariant metrics were proposed simultaneously by several teams, including the Epidaure Project [37]. These metrics have excellent theoretical properties but lead to complex algorithms with a high computational cost.

In this work, we introduced a new family of metrics, called Log-Euclidean. These metrics have the same excellent theoretical properties as affine-invariant metrics and yield very similar results in practice. But they lead to much more simple computations, with a much lighter computational cost, close to the cost of the classical Euclidean framework. Indeed, Riemannian computations become Euclidean computations in the logarithmic domain with Log-Euclidean metrics. In [72], we presented the complete theory for these metrics, and showed experimental results for multilinear interpolation, dense extrapolation of tensors and anisotropic diffusion of tensor fields. This work was oraly presented at MICCAI'05 [42]. Moreover, a French patent is pending for the general Log-Euclidean framework for the processing of tensor images [78].

5.4.7. DT-MRI Estimation, Smoothing and Fiber-Tracking

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

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

In this work, we developed and compare several criteria for the estimation of diffusion tensor fields from diffusion weighted images (DWI) that specifically targets clinical data with low signal to noise ratios. More specifically, we combined a maximum likelihood estimator for a Rician noise with an anisotropic

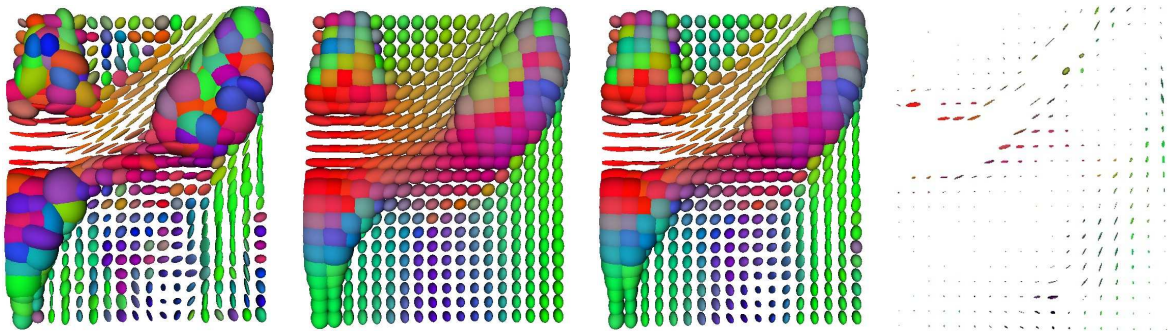


Figure 9. ***Regularization of a clinical 3D DTI volume. Left****: close-up on the top right ventricle and nearby.* ***Middle Left****: Euclidean regularization.* ***Middle Right****: Log-Euclidean regularization.* ***Right****: highly magnified view ($\times 100$) of the absolute value (the absolute 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!*

regularization term. The resulting criterion was efficiently optimized thanks to the previosuly introduced Log-Euclidean framework. We showed that our method prevents tensors to shrink, a side effect caused by the Rician noise using usual least-squares criteria. We also exemplified the benefits of such an approach by tracking fibers in a clinical brain dataset and an experimental acquisition of the spinal cord. Both trackings show a significant improvement of the continuity and smoothness of fibers [74].

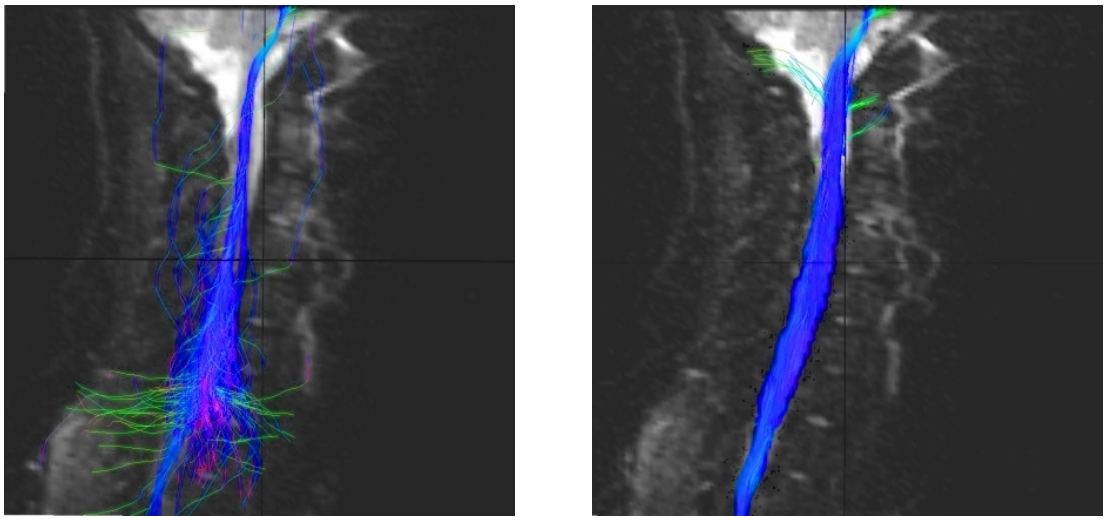


Figure 10. ***Left:*** *Result of tracking fibers of a spinal cord before our framework.* ***Right:*** *Results after our joint estimation and regularization framework.*

5.4.8. Tensor-valued Image Processing

Keywords: *Log-Euclidean, Structure tensor*.

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

To investigate the range of applicability of Riemannian metrics on tensors (either affine-invariant or Log-Euclidean), we applied the proposed framework for anisotropic regularization of diffusion tensor fields to structure tensor images [52]. Structure tensors are often used in computer vision as feature detectors (e.g. edges or corners). They are obtained by convolving the tensor product of an image gradient with a Gaussian kernel. Our attempts to improve the quality of noisy structure tensor images to better detect image features was not completely satisfactory. The reasons are that even if affine-invariant or Log-Euclidean metrics allows to extract low-level features thanks to the affine (or similitude) invariance, they could not lead a tensor eigenvalue to zero, which means in this case a "perfect" edge. This shows that, for this type of problem, the affine-invariant and Log-euglidean metrics are less adapted than the standard Euclidean one, even if they lead to much more stable implementation schemes. This raises the question of how to choose an "optimal" metric given a specific application.

5.5. Computational Physiology

5.5.1. Image guided laparoscopic spine surgery

Keywords: *3D/2D Registration, Anatomical Variability, Articulated models, Augmented Reality, Camera Calibration*.

Participants: Jonathan Boisvert, Xavier Pennec, Nicholas Ayache, Farida Cheriet [Montréal University].

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

This work is the continuation of the one began in 2004 to develop an augmented reality system for laparoscopic spine surgery. Firstly, we developed an algorithm to update the laparoscope's calibration during the surgery in order to take into account variations of the laparoscope's internal parameters caused by modifications of the zoom and focus [73]. This algorithm corrects the distorsions (radial and tangential) using prior measurements of a calibration object. Then, the focal length is updated on-line by using constraints on the image of the absolute quadric (without a calibration object). The knowledge of the camera parameters will enable us to accurately project geometric models of the spine on laparoscopic images and thus help the surgeon in the assessment of important measurements that are invisible on laparoscopic images alone such as the distance from surgical tools to the spinal chord of the patient.

Then, in order to recover the deformation of the spine between the pre-operative X-Ray images and the per-operative laparoscopic images, we investigated a 3D articulated model of the spine. This model consists in the relative configurations of the vertebrae along the spinal chord: the parameters are the rigid transforms that superpose neighboring vertebrae. However, to properly constrain the fit of this articulated model to 2D X-Ray images, it is necessary to capture its statistical behavior. The 3D anatomical variability of the spine shape was therefore studied using bi-planar radiographs of scoliotic patients: the rigid transformation parameters were computed on each vertebra from anatomical landmarks reconstructed in 3D using two radiographs. Since rigid transforms do not belong to a vector space, conventional mean and covariance could not be applied. The Fréchet means and a generalized covariance computed in the exponential chart at that point were used instead [39]. These statistics were computed for each inter-vertebral transforms on a group of 307 untreated scoliotic patients. The variability of inter-vertebral transforms, shown in Fig. 11, was found to be inhomogeneous (lumbar vertebrae were more variable than for the thoracic ones) and anisotropic (with maximal rotational variability in the coronal plane and maximal translational variability in the axial direction). These findings are clinically relevant, and could lead to the optimization of treatment strategies or diagnostic methods (by taking advantage of the strong variability in the coronal plane, for example).

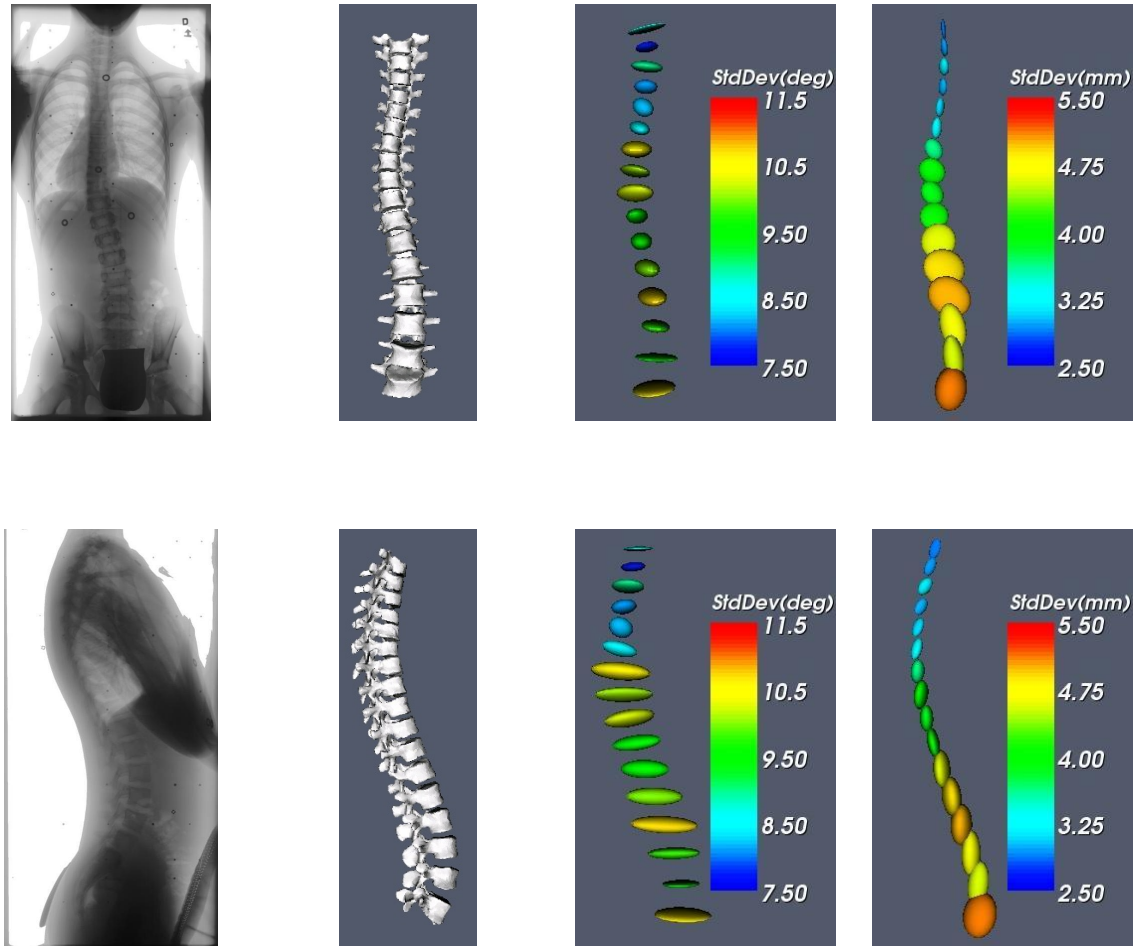


Figure 11. Statistical spine model. From left to right: Example of a Bi-planar radiographs of the human trunk, mean spine model, rotation and translation covariance. Top: Postero-anterior view. Bottom: latteral view.

Future directions include the analysis of global motions of the spine using joint covariance, the development of temporal variability models to assess the evolution of the pathology or the effect of orthopedic treatments (such as corrective surgery or bracing systems) and the integration of this model in registration algorithms.

5.5.2. Respiratory motion correction in Positron Emission Tomography (PET)

Keywords: *Positron Emission Tomography, image reconstruction, nuclear medecine, oncology.*

Participants: Mauricio Reyes, Grégoire Malandain, Jacques Darcourt.

This work is done in collaboration with the Centre Antoine Lacassagne (Nuclear Medicine Department).

It has been proven that respiratory motion renders blurred reconstructed images, affecting lesions detection, diagnosis, treatment planning and following of lung cancer. While current motion correction methodologies are based on external breathing tracking devices or specific data acquisition modes [34]. The proposed approach was designed to work without any external tracking devices, which occur on institutions not having access to such material or in cases where the data was already acquired and no tracking device was present at the moment of its capture. The proposed method presents a retrospective scheme of motion correction based on a motion model plugged to the image reconstruction step [66]. The model takes into account displacements and elastic deformations of emission elements (voxels), which allows to consider the non-rigid deformations produced in the thorax during respiration. Furthermore, the chosen voxel modeling improves computations, outperforming classical methods of voxel/detector-tube.

With the lack of specific patient respiratory information, two estimation models were investigated and developed. A simplified model consists on adapting a known respiratory motion model, obtained from a single subject, to the patient anatomy. The initial known model describes by means of a displacement vector field, the lungs deformations produced between extremal respiratory states. This displacement vector field is further adapted by means of an affine transformation to the patient's anatomy, yielding a displacement vector field that matches the thoracic cavity of the patient.

Simulations and phantom experiences were carried out. For the first, the SimSET library (Simulation System for Emission Tomography) was used along with the NCAT phantom, upon which a real respiratory motion was incorporated. For phantom experiences, the methodology was tested against translational movements applied within the data acquisition. For both, simulations and phantom experiences, the results obtained show the ability of the proposed method to correct and compensate the effects of motion during data acquisition [65]. For patient data, the methodology was tested against a dataset composed by five patients with lung cancer (see figure 12). Although no ground truth was available, preliminary results on patient data are encouraging since improvements in contrast recovery and signal to noise ratios were found on each case [67].

5.5.3. Dynamic Model of the communicating Hydrocephalus

Participants: Olivier Clatz, Hervé Delingette.

This work has been done in close collaboration with S. Litrico, service de neurochirurgie, Hôpital Pasteur, Nice France.

We proposed a dynamic model of the communicating hydrocephalus following subarachnoid hemorrhage. The understanding of high-pressure hydrocephalus is closely related to the intracranial pressure regulation, and thus of great interest for the therapy of head injuries. In our model, the cerebro-spinal fluid production-resorption system is coupled with a 3D representation of the brain parenchyma. We introduce a new bi-phasic model of the brain tissue, revoking the assumption of incompressibility and allowing for fluid exchange between the brain extracellular space and the venous system. The time evolution of the ventricular pressure has been recorded on a symptomatic patient after closing the ventricular derivation. A finite element model has been built based on a CT scan of this patient, and quantitative comparisons between experimental measures and simulated data are proposed.

5.5.4. Analysis of the heart motion for the study of heart failure

Keywords: *3D echography, Doppler, cardiac imaging, echocardiography, motion analysis, segmentation, tracking.*

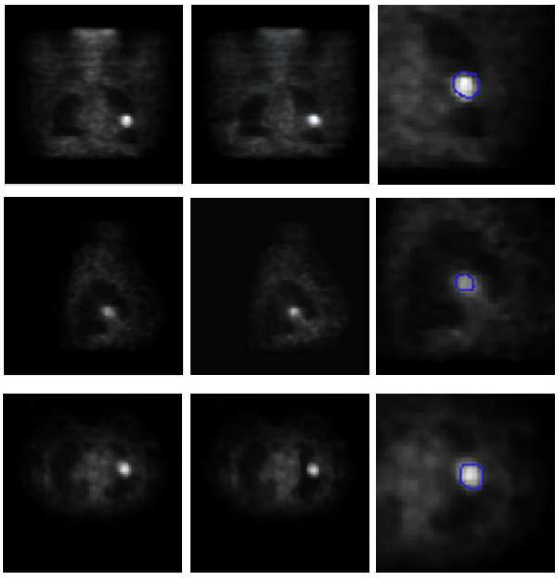


Figure 12. Coronal, sagittal and axial slices for one patient, without motion correction (left column), with motion correction using the statistical motion model (central column), and a zoom of both, the region of interest of the non-corrected image and the motion-corrected contour (right column).

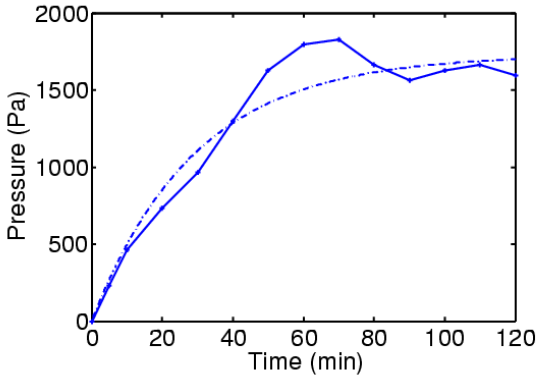


Figure 13. Evolution of the ventricular pressure as a function of time after closing the derivation system. Continuous line: Measure on the patient. Dashed line: Simulated pressure increase with the model.

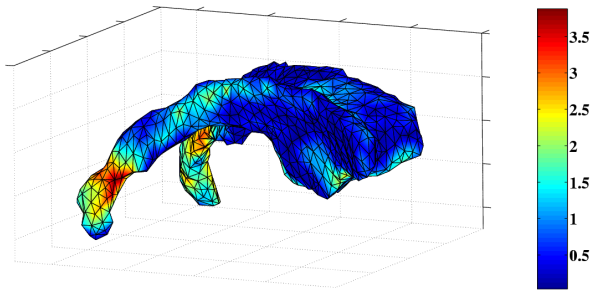


Figure 14. Distribution of the simulation displacement error on the ventricle surface mesh (mm).

Participants: Cécile Marboeuf, Hervé Delingette.

This work is performed in close collaboration with the company Philips Medical Systems Research Paris (Olivier Gérard) in the framework of a 3 year research contract. A clinical partnership exists with the CHU hospital in Caen (Dr Eric Saloux).

The objective of this work, that started in September 2004, is to produce a set of software tools that can help clinicians to better understand, diagnose and cure the phenomenon of cardiac asynchrony, one of the type of heart failure.

A first step consists in the heart motion estimation in twodimensional echocardiographic images. This is achieved by a hierarchical subpixel block matching algorithm, to which we add a spatial regularization. This algorithm has the advantage to be fast, which is an important clinical constraint. The motion field can then be used to create a synthetic tissue doppler image and to compute strain rate and strain, already known by physicians. The main improvement comes from the fact that we know the displacement in every direction and not only towards the ultrasound probe as in Doppler imaging and we can then expect a better determination of the heart movement.

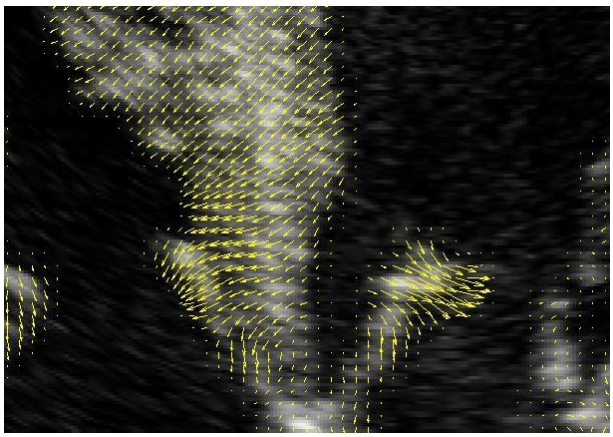


Figure 15. Estimated motion field in myocardium (detail)

This method will then be extended to 3D echocardiography.

5.5.5. *Parameters estimation of an electrical model of the heart from in vivo electrical measures.*

Keywords: *data assimilation, electrical conductivity, electrophysiology, heart modeling, inverse problem, parameter estimation, reaction-diffusion system.*

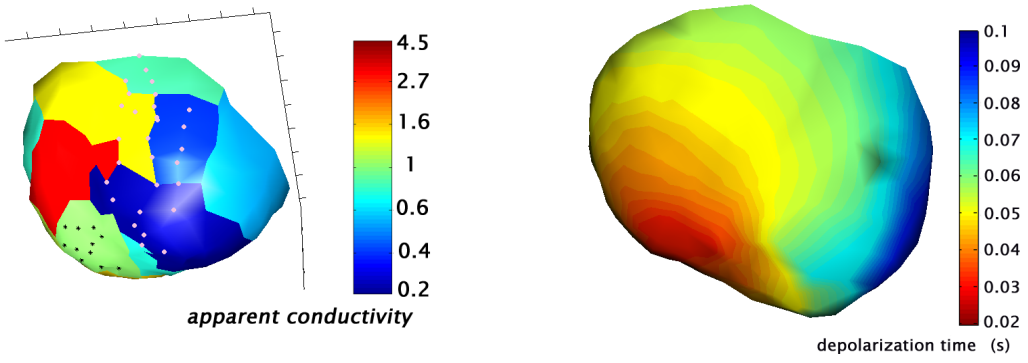
Participants: Valérie Moreau-Villéger, Hervé Delingette, Nicholas Ayache, Sylvain Jaume, Maxime Sermesant, Tristan Picart.

This work has been performed in the framework of the national action CardioSense3D.

This work is part of the INRIA National Action CardioSense3D (http://www.inria.fr/CardioSense3D) in collaboration with two clinical sites : electrical measures on canine hearts have been provided by the Laboratory of Cardiac Energetics, National Heart Lung and Blood Institute, National Institute of Health (E. McVeigh) while those on human hearts are provided by the Cardiac MR Research Group at Kings College London, Guys Hospital (R. Razavi) and University College Londoc (D. Hill, D. Hawkes).

We study the problem of estimating the electrical conductivity of cardiac tissue from a set of temporal in vivo recordings of extracellular potentials. The underlying electrical model is the reaction-diffusion model on the action potential proposed by Aliev and Panfilov. The strategy consists in building an error criterion based upon a comparison of depolarization times between the model and the measures. After a global adjustment, we propose a minimization of the quadratic error between the model and the measures according to one of the parameter. We allow this parameter to have local variations. The chosen parameter is the diffusion coefficient of the model that wa call apparent conductivity. Indeed, its variations reflect both the variations of conductivity and the variations of the reaction parameters. By taking into account the causality of the propagation of the electrical wave, the minimization problem becomes a succession of one dimensional minimization problems solved using Brent's method. We apply this approach to real measures in normal cases and also in the case of an infarcted heart. In this last case, we observe a strong correlation between the regions where a low apparent conductivity is estimated and the infarcted regions (Figure 16). This work was published in [61] and was accepted in [35].

We are currently working on the extension of this method to estimate electrophysiological parameters on the whole myocardium of a human heart. A first attempt was made using a simpler model [69].



(a) (b)

Figure 16. Estimation of apparent conductivity for the case of the anterior infarct. (a) Apparent conductivity estimated. The bright circles indicate the location of the infarct while the points marked with a dark star indicate the pacing sites. The depolarization time distribution computed with these apparent conductivity values is displayed in (b).

5.6. Clinical and Biological Validation

5.6.1. Registration of brain images with an anatomical atlas for radiotherapy planning

Keywords: *Nonrigid registration, atlas registration, conformal brain radiotherapy, irradiation, tumors.*

Participants: Olivier Commowick, Grégoire Malandain, Pierre-Yves Bondiau, Nicholas Ayache.

In collaboration with DOSIsoft SA, Cachan and Centre Antoine Lacassagne, Nice

The treatment of cerebral tumors may involve surgery, radiotherapy, or chemotherapy. Thanks to recent technological advances (on-line definition of the shape of the irradiation beam, irradiation intensity modulation during the treatment), conformal radiotherapy allows a high precision irradiation (homogeneous dose distribution within complex shapes), permitting an improvement of local control and the reduction of the complications. In order to determine the best characteristics of the treatment planning, and to provide the patient follow-up, it is necessary to accurately locate the tumor and all the structures of interest in the brain. An automatic segmentation algorithm of all the critical structures in a patient image is then an invaluable tool for radiotherapy.

Registering a brain atlas on the patient's MRI for labeling brain structures is an interesting alternative to manual segmentation.We have the compared and evaluated both approaches in [27].

6. Contracts and Grants with Industry

6.1. Medtronic

Participants: Grégoire Malandain [Correspondant], Radu-Constantin Stefanescu, Xavier Pennec, Nicholas Ayache.

Epidaure participates to a collaboration between CNRS, INRIA, INSERM and Salpétrière Hospital partially funded by Medtronic. Epidaure is involved into the design and evaluation of dedicated non-rigid registration tools for the localization of deep grey nuclei in 3D MR images (cf section 5.4.3).

6.2. Maestro

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

MAESTRO 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, Epidaure is involved, in collaboration with Dosisoft, in the automatic delineation of structures for radiotherapy planning (cf section 5.6.1 and [49], [50]).

6.3. Philips

Participants: Hervé Delingette [Correspondant], Cécile Marboeuf.

Philips Medical System Research Paris has contracted the Epidaure 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.

6.4. 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, Epidaure 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, Epidaure is involved in two tasks : the improvement of CT-scan image segmentation based on deformable simplex meshes, and the development of soft tissue models in a surgery simulation platform.

On the latter topic, Epidaure is collaborating with two other INRIA research teams, Alcove and Evasion, to develop the SOFA (Simulation Open Framework Architecture) platform. In 2005, we have focused on the development of concepts that are essential for a generic, versatile and open platform. Those concepts are then being translated into C++ software libraries, taking advantage of object-oriented programming. A beta version of this platform is planned to be delivered in the first 6 months of 2006.

6.5. Siemens

Participants: Antoine Azar, Xavier Pennec, Nicholas Ayache.

In image guided surgery, the accuracy and the reliability of the registration result are critical issues for the surgeon to trust the guiding system. This is all the more true when the image guiding system is aimed at replacing other traditional, but more invasive, landmarks.

A contract has been established between Epidaure and Siemens Corporate research 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. This study involves in particular Antoine Azar, through his master and subsequent PhD in the Epidaure team (see also Section 5.2.3).

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 non-rigid registration tools for radiotherapy planning (cf section 5.6.1) is supported by a PhD fellowship from the company Dosisoft.

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 (see Section 5.3.1) is supported by a PhD fellowship from the company Mauna Kea Technologies.

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. Action d’Envergure Nationale 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 4 INRIA research teams (Epidaure, Macs, Reo and Sosso2) on this multi-disciplinary research topic.

CardioSense3D has three main objectives :

1. To build a cardiac simulator that couples 4 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 Globalisées des données d'Imagerie Radiologique - AGIR) is a multi-disciplinary research project with focus on leveraging medical imaging algorithms trough 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, University, 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 compute and data intensive needs [54], [32].

The project started in september 2004, and supports the PhD of T. Glatard, jointly supervised by X. Pennec at EPIDAURE and J. Montagnat at RAINBOW (I3S, Nice University). In 2005, AGIR meeting were helds in Orsay in january and november, and in Mai in Nancy. T. Glatard, J. Montagnat and X. Pennec also participated to the "journées PaRISTIC (Panorama des Recheches Incitatives en STIC)" in Bordeaux in november with one oral presentation and one demonstration on registration for oncology and complex workflows (see Section 5.4.2 for scientific results).

7.2.3. QUALICORE

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

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. Epidaure is in charge of the MR image processing package.

7.2.4. INRIA investigation Grant REGLO

Participant: Grégoire Malandain [correspondant].

The *Cooperative Research Initiative* named *REGulation of Ovulation (REGLO)*, coordinated by F. Clement 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.

7.2.5. 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 Silico* and coordinated by A. Habbal from the OPALE team, aimed to study the develop mathematical models of the healing process and to validate them with image processing procedures [80].

7.2.6. 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 *Philips Research France* and he is 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).

7.2.7. Collaboration with national hospitals

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

7.2.7.1. IRCAD, hôpitaux de Strasbourg

Pr. Marescaux and L. Soler : hepatic surgery simulation segmentation of abdominal structures from CT scan images [45], [44], [46] and augmented reality for guidance in hepatic surgery [36], [62].

7.2.7.2. 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 [43]. Pr. D. Dormont and Dr. J.-P. Brandel are our collaborators for the GIS *Infections à prions* [33], [58], [57]

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

Pr. Jacques Darcourt co-supervises the thesis of Mauricio Reyes on breathing motion correction for PET reconstruction (cf section 5.5.2) [66], [65], [67].

Dr. Bondiau participates in our research on atlas registration for radiotherapy planning [27] and on tumour growth simulation [47], [29].

7.2.7.4. CHU de Nice, Hôpital Pasteur

We continue our collaboration with Pr. M. Chatel, Dr. C. Lebrun-Frenay and C. Bensa of the neurology department, and with Dr. Chanalet of the radiology, within the framework of a study on the temporal evolution of MS lesion load [51].

7.3. Foreign associated team

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

Since its creation in September 2001, the associated team program between the Epidaure 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 summer 2003, we investigate a new axis on the study of the anatomical variability of the brain, in the framework of the PhD theses of V. Arsigny and P. Fillard. Our strategy is to construct a statistical model of manually delineated landmarks at the surface of the cortex: sulcal lines. Using the algorithm developed in 2003 by V. Arsigny, we compute the mean curve for each sulcal line and the point to point correspondance with each instance in all subjects. Then, we compute the covariance matrix at each point along the mean sulcal line, and extrapolate this variability tensor to the whole brain thanks to the statistical computing framework developped for this type of Riemannian manifolds [37]. An important part of the work of this year was to improve the implementation of the optimization procedures in order to obtain stable and reproducible variability results. These results are qualitatively in accordance with the known variability of different brain structures. We have also set up quantitative tests to validate our methodology (see Sec. and [53]).

P. Thompson, X. Pennec, V. Arsigny and P. Fillard participated to the conference IPMI 2005 in Glenwood Spring (Colorado, USA), where the methodology and the results were presented [53]. X. Pennec also present the results obtained through this associated team at the University of North-Carolina Chapel-Hill (USA) in July, at the University of Utah at Salt Lake City (USA) in August, and at a tutorial at MICCAI 2005. N. Ayache made an invited talk at UCLA in November.

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.

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).
- G. Malandain is a member of the editorial board of the journal *International Journal on Computer Vision* (Kluwer).
- H. Delingette is a member of the editorial board of the journal *Medical Image Analysis* (Elsevier).

8.1.2. Participation in the organization of conferences

N. Ayache is a member of the Executive board of the MICCAI Conference. He is executive secretary of the newly created scientific MICCAI society. We was also the member of several reviewing boards in 2005.

G. Malandain was member of the scientific board of DGCI 2005, GRETSI'05, IPMI 2005, and MICCAI 2005.

H. Delingette was member of the scientific board for MICCAI 2005, VRIC 2005, IbPRIA 2005, ORASIS 2005, VRIPHYS 2005

X. Pennec was member of the scientific board for MICCAI 2005.

8.1.3. Scientific animation

N. Ayache was co-chairing the "comité des projets de l'INRIA Sophia-Antipolis" until august 2005 and is now chairing it since 1st Sept. 2005, and a member of the scientific direction of INRIA-Sophia-Antipolis. He is a member of the Evaluation Committee of INRIA.

H. Delingette was a member of the Evaluation Committee of INRIA until Sept. 2005.

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.

Master I3, Université Paris Sud H. Delingette is co-responsible with R. Deriche of a 21 h module about medical imaging and computer vision of which he has taught 12 h.

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)

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.

IT University, Copenhagen, Danmark X. Pennec gave with S. Joshi (UNC-Chapel Hill, USA) and Mads Nielsen (IT University, Copenhagen) a one week Ph.D. course on non-linear shape modelling (December 5-9).

8.3. PhD Theses and Internships

8.3.1. PhD defended in 2005

1. Julien Dauguet, *L'imagerie post mortem tridimensionnelle cérébrale : constitution et apport pour l'analyse conjointe de données histologiques anatomo-fonctionnelles et la mise en correspondance avec l'imagerie in vivo*, École Centrale Paris. June 23, 1005. Committee: C. Saguez (President), N. Ayache (Supervisor), I. Bloch (Referee), F. Maes (Referee), V. Frouin, P. Magistretti, P. Hantraye. This PhD was localized at CEA/SHFJ, Orsay.
2. Céline Fouard, *Extraction de paramètres quantitatifs dans des images médicales 3D de réseaux vasculaires*, Nice-Sophia Antipolis University. January 21, 2005. Committee: N. Ayache (President), M. Revenu (Referee), E. Thiel (Referee), J.-P. Marc-Vergnes, D. Asselot, G. Malandain (Supervisor). This PhD was funded by a CIFRE fellowship from the compagny TGS.
3. Valérie Moreau-Villéger, *Analyse du fonctionnement cardiaque à partir de données échocardiographiques et électrophysiologiques*, ENS Cachan, December 15, 2005. Committe: R. Deriche (President), N. Ayache (Supervisor), H. Delingette (Co-supervisor), P. Clarysse (Referee), A. Frangi (Referee), L. Cohen.
4. Mauricio Antonio Reyes Aguirre, *Respiratory Motion Compensation in Emission Tomography*, December 6, 2005. Committee: I. Bloch (Referee), I. Buvat (Referee), L. Blanc-Féraud, G. Malandain (Supervisor), J. Darcourt (Co-supervisor).
5. Radu-Constantin Stefanescu, *Thérapie guidée par l'imagerie médicale : Parallélisation et validation d'algorithmes de recalage*, Nice-Sophia-Antipolis University, March 23, 2005. Committee: N. Ayache (Supervisor), C. Barillot (President), P-Y Bondiau, D. Hill (Referee), X. Pennec (Co-supervisor), D. Vandermeulen (Referee).

8.3.2. Current PhDs

1. Vincent Arsigny, *Statistical analysis of shapes - Application to anatomical atlases*, École Polytechnique.
2. Antoine Azar: *Interactive registration of medical images using statistical information*. École des Mines de Paris. In collaboration with Siemens Corporate Research.
3. 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.
4. Olivier Clatz, *Modeling of the biomechanical behavior of the brain: application to the prediction and simulation of neurosurgery*, École des Mines de Paris.
5. Olivier Commowick, *Digital anatomical atlases for radiotherapy planning*. University of Nice-Sophia-Antipolis. Cifre contract with Dosisoft, Paris.
6. Jimena Costa, *Segmentation of anatomical structures of the abdomen with deformable models*. École des mines de Paris.
7. Guillaume Dugas-Phocion, *Modeling and segmentation of mutiple sclerosis lesions in multi-sequences MR images*, École des Mines de Paris.
8. Pierre Fillard, *Statistical modeling of the anatomical variability of the cortex*, Nice-Sophia Antipolis University.
9. Tristan Glatard, *Computing with Massive Medical Image Databases on the GRID for the evaluation of clinical image analysis protocols*. Nice-Sophia Antipolis University. PhD in collaboration with J. Montagnat at the Rainbow team, I3S, Nice-Sophia Antipolis University.
10. 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.
11. Ender Konukoglu, *Modeling and control of tumor growth with medical imaging*. Nice-Sophia Antipolis University.
12. Cécile Marbœuf, *Analyse fine du mouvement du cœur dans le cadre de l'insuffisance cardiaque*, École des Mines de Paris. Cifre collaboration with Philips.
13. Jean-Marc Peyra, *Electro-mechanical models of the heart activity personnalized from medical images*, Nice-Sophia Antipolis University.
14. Tristan Picart, *Analyse de la fonction cardiaque à l'aide d'un modèle électromécanique du cœur*, Nice-Sophia-Antipolis University.
15. Jean-Christophe Souplet, *Analysis of Multiple Sclerosis MRI images*. Nice-Sophia-Antipolis University.
16. 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 Céline Fouard and M. Pouget (as President), R. Stefanescu and J. Dauguet (as supervisor), and A. Paccini. He also participated to the HDR thesis committee of J.F. Mangin and P. Clarysse (as referee), and N. Paragios.

Grégoire Malandain participated to the PhD thesis committee of Céline Fouard and Mauricio Reyes as supervisor.

Hervé Delingette was the examiner of the thesis of O. Chassagneux (E, Centrale de Paris), A. Gouaillard (INSA Lyon), Miriam Amavizca (INPG Grenoble), Y. Rouchdy (INSA Lyon), A. Maciel (EPFL, Lausanne), A. Benassarou (Univ. de Reims) and participated to the PhD thesis of V. Moreau-Villéger.

Xavier Pennec participated to the PhD thesis committee of Radu Stefanescu as co-supervisor.

8.3.4. Training activities

1. Antoine Azar, *An Interactive Intensity- and Feature-Based Non-Rigid Registration Framework for 3D Medical Images*. Master IGMMV, University of Nice-Sophia Antipolis, 2005.
2. Olivier Duhamel, *Validation de modèles mathématiques en biologie à l'aide du traitement d'image*. Université Paul Sabatier, Toulouse, 2005.

8.4. Participation to workshops, conferences, seminars, invitations

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

- **Nicholas Ayache** gave invited lectures at Isracas (Tel-Aviv, mai), Robotics Science (MIT, juin), Siemens (Princeton, juin), Medical Image Understanding (Bristol, Juillet), Shun Hing Intitute (Hong-Kong, Oct), CVBIA (Pekin, Oct), UCLA (Los Angeles, Oct).
- **Grégoire Malandain** gave an invited lecture on medical image segmentation in the "Des images au 3D" workshop organized at ENSTA (Paris) by the Club 29 "Traitement du signal" of the GDR ISIS. He gave lectures at two EPUs ("Enseignement Post-Universitaire") for medical phycisists on image registration (Créteil and La Clusaz, France), a number of lectures at the spring school "Traitements mini-invasifs en médecine et chirurgie : défis mathématiques et numériques" (Montréal, Canada), and a lecture in the CEA-EDF-INRIA "Numerical Simulations of Blood Flows" school on vessel reconstruction from medical images.
  He gave an invited talk on the 3-D reconstruction from serial cross-section at the TAIMA'05 (Hammamet, Tunisie) workshop.
- **H. Delingette** gave invited talks on Medical Image Segmentation, Soft Tissue Modeling and Cardiac Modeling at the Image Analysis workshop organized by INRA in Dourdan, at the "INRIA Industry" meeting on 3D reconstruction in Rocquencourt, at the European School of Medical Robotics in Montpellier, at the ERNSI'2005 workshop on system identification in Louvain-la-neuve, at the first meeting of the European Cardiac Simulation Group in Manchester(UK) and presented the CardioSense3D action at a meeting of INRIA board of directors.
- **Xavier Pennec** gave invited talks on at theStatistical Computing on Riemannian Manifolds at the residential session on Singularities and applications at the CIRM (Luminy, France) in February, at the University of North-Carolina Chapel-Hill and at the University of Utah (USA) in July, and at the tutorial on statistics for anatomical geometry at MICCAI'05 in Palm Spring (CA, USA) in october.

8.5. Nominations and prizes

- **Nicholas Ayache** joined in 2004 the Advisory Committee of the newly created Shun Hing Institute of Avanced Engineering in Hong-Kong (4 year term) and participated to a review panel in Hong-Kong in Oct. 2005; he also joined in 2004 the High Council for the promotion of science and technology between France and Israel, and participated to the selection of proposals in 2005.

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