Epidaure: a Research Project in Medical Image Analysis, Simulation and Robotics at INRIA

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(Invited Editorial)

I. Introduction

EPIDAURE[1] is the name of a research project launched in 1989 at INRIA[2] Rocquencourt, close to Paris, France. At that time, after a first experience of research in Computer Vision [1] in the group of O. Faugeras, I was very enthusiastic about the idea of transposing research results of digital image analysis into the medical domain. Visiting hospitals and medical research centers, I was progressively convinced that Medical Image Analysis was an important research domain by itself. In fact I had the impression that a better exploitation of the available medical imaging modalities would require more and more advanced image processing tools in the short and long-term future, not only to assess the diagnosis on more objective and quantitative measurements, but also to better prepare, control and evaluate the therapy.

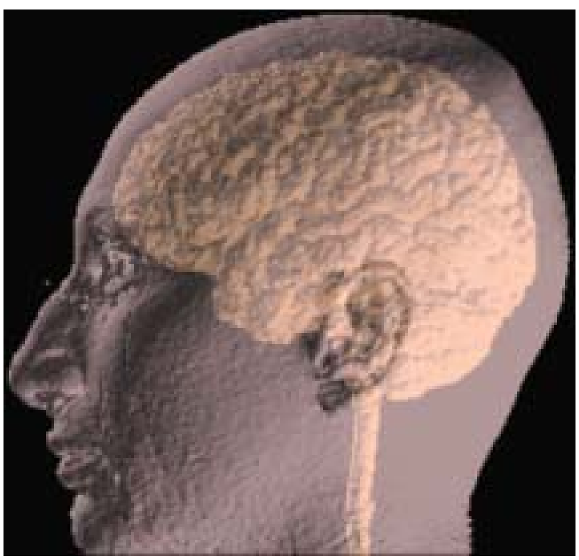

Fig. 1. This image has been the "Logo" of the Epidaure project for a long time. It was also used as a logo of the first CVRMed Conference held in Nice in 1995. (Courtesy of G. Malandain).

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[1]Epidaure is originally the French name of a magnificent site in Greece which used to be the sanctuary of ancient medicine. For computer scientists, it can also be interpreted as a recursive acronym (in French: *Epidaure: Projet Images, Diagnostic AUtomatique, et RobotiquE*).

[2]INRIA is the French Research Institute in Computer Science and Automatic Control.

To compare with the domains of computer vision and aerial imagery where research in digital image processing was extremely active already, I had the feeling that medical image analysis would become a well defined scientific domain by itself. The reasons were multiple, including the fact that new digital representations were available with fully volumetric images composed of voxels instead of pixels, and new measures of intensity physically linked to each medical imaging modality. Moreover, rigidity or polyhedric constraints typically used in computer vision or aerial imagery were no longer valid with anatomical shapes. Also, the objectives of speed and full automation, usual requirements in computer vision and aerial imagery for instance, were partially replaced by robustness and accuracy, often allowing some degree of interaction with the operator. In brief, a new research world was opening, motivating a small group of scientists at INRIA to embark together in a common research project named Epidaure.

The project started in 1989 with a young team of researchers including I. Herlin, J. Lévy-Véhel, O. Monga, followed by J.P. Thirion (1990), a number of external collaborators including L. Cohen, J.M. Rocchisani and P. Sander, and several PhD students including G. Malandain, I. Cohen, C. Nastar A. Guéziec and J.P. Berroir. In October 1992, I decided to move from INRIA-Rocquencourt to the rapidly developping center of INRIA-Sophia Antipolis, close to Nice. It was a major change in the life of the project, as among permanent members, only J.P. Thirion could follow the move. Hopefully, G. Malandain was recruited on a permanent position in 1993, followed by H. Delingette in 1994, X. Pennec in 1998 and M.A Gonzalez-Ballester in 2001. J.P. Thirion left the group in 1997 to join Focus-Imaging, and founded later [3] in 2001, a company specialized in quantifying disease evolution through medical image processing.

The research directions of the project were progressively defined around the following topics: Volumetric Image Segmentation, 3-D Shape modeling, Image Registration, Motion Analysis, Morphometry and Simulation [2] [3]. I will now describe and illustrate some of the scientic contributions of the Epidaure team on these different topics.

II. 3-D Segmentation and Shape modeling

The main objective was to design new tools to extract quantitative information in volumetric images in a hierachical manner [4]. The main contributions were the following ones.

[3]Web site of QuantifiCare company: www.quantificare.com.

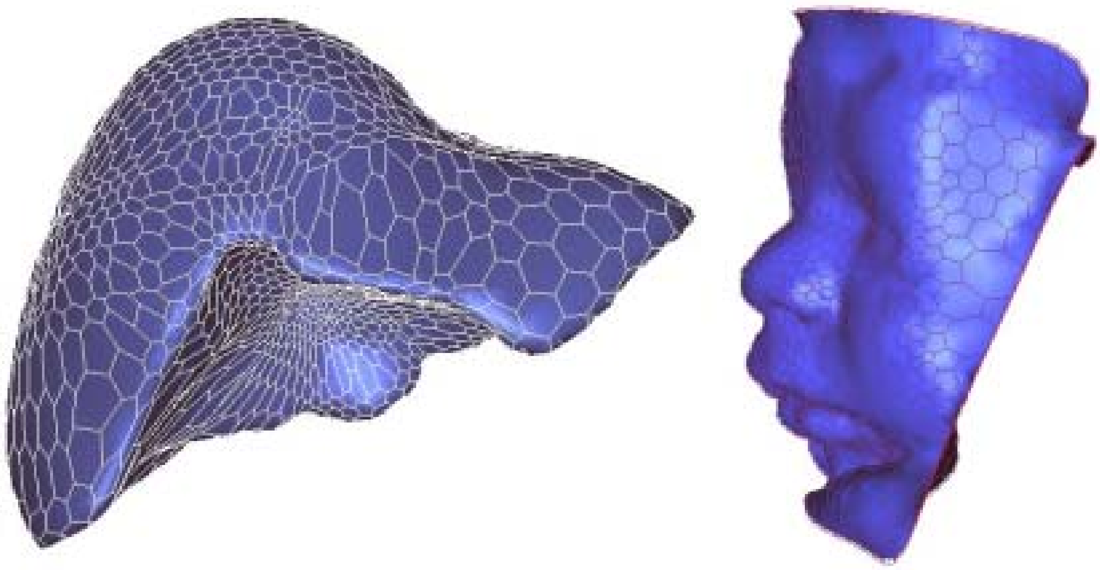

Fig. 2. Segmentation with Deformable Simplex Meshes of the liver surface from a CT image and of a foetus face from a 3-D ultrasound image (courtesy of H. Delingette)

- **3-D edge extraction:** some of our earliest efforts were devoted to the extraction of edges in volumetric images. O. Monga, G. Malandain J.M. Rocchisani and R. Deriche proposed a generalization of the Canny-Deriche edge detectors in 3-D [5] [6]. We then realized that some images could be processed more efficiently if we had access to the original measurements (raw data). This was the case with ultrasound images and CT-Scan images. For ultrasound images, we proposed with I. Herlin a new approach called "sonar space filtering" [7] to extract edges in images acquired in polar coordinates. For CT images, J.P. Thirion [8] proposed an original approach called "geometric tomography" to extract edges directly from the sinogram. Both approaches showed advantages over classical methods.
- **Discrete Topology of Curves and Surfaces:** G. Malandain and G. Bertrand designed new local criteria to characterize the dimension of a manifold described by a set of points in a voxel grid. These criteria are essential to refine for instance the representation of a curve or a surface in a volumetric image [9] and they allow a new characterization of topologically simple points [10]. They were used for the extraction of skeletons [11] [12] which can themselves be used to guide registration procedures [13]
- **Texture-based approaches:** J. Lévy-Véhel and coworkers developped a system called Arthur which combined texture modeling and a sophisticated discriminant analysis scheme to select texture parameters from a training set of images. The system could compute 2-D and 3-D parameters, including advanced fractal and multifractal measurements, which proved to be well adapted to a certain type of medical images [14].
- **Modeling of tubular structures:** Following the pioneering work of G. Gerig at ETH-Zurich, we proposed with K. Krissian and G. Malandain an original technique to segment vessels from a combined iconic and geometric model of vascular structures. The method included a first stage of anisotropic diffusion controlled by the principal directions of curvature of the vessel, followed by a multiscale detection of the center line. The method proved itself quite efficient for the quantification of vascular stenoses, and was evaluated through a collaboration with General Electric Medical Systems [15].
- **Deformable surface models:** Inspired by the work of Terzopoulos and his colleagues, we introduced with L. Cohen and I. Cohen new deformable surface models evolving in noisy volumetric images to segment anatomical shapes [16] [17]. These models were used in a variety of volumetric images [18]. Later, H. Delingette proposed to use deformable discrete meshes, called Simplex Meshes, quite efficient to interactively segment anatomical structures in volumetric images [19] [20]. An important property of simplex meshes stems from the fact that each node has exactly 3 neighbors, therefore allowing a simple approximation of the mean curvature. This property allowed H. Delingette to propose dedicated schemes to preserve the regularity of the deformable surfaces during the segmentation process (cf. Figure 2). Further advances were proposed by J. Montagnat and H. Delingette [21] to combine global and local deformations in a hierarchical manner in order to improve robustness. Specific filtering methods for model-based segmentation of 4D ultrasound images were proposed in [22]. A survey was published by Montagnat and Delingette in [23].
- **Extraction of surface singularities:** with O. Monga and P. Sander we investigated the extraction of differential properties of surfaces (like the computation of first and second fundamental forms) by filtering the image intensity along iso-surfaces [24], [25]. We ex-

ploited the implicit function theorem and the assumption that anatomical surfaces often correspond (at least approximately) to some iso-intensity surface. Then, JP. Thirion and A. Gourdon proposed an efficient algorithm to extract the carefully defined crest lines and extremal points in volumetric images [26] [27]. Crest lines correspond to regions where the maximum principal curvature (in absolute value) is extremal in the direction of principal curvature. Intuitively these lines correspond to salient lines on smooth surfaces, and could be seen as a generalization of polyhedral edges on smooth surfaces (cf. Figure 3). On these lines, extremal points are characterized by the extremality of the second principal curvature too. Both crest lines and extremal points tend to correspond to known anatomical features, in particular in the skull surface. Because these geometric entities are based on curvature properties, they remain invariant by rigid transformations, and were extensively used for rigid registration as described later [28]. The multiscale analysis of crest lines was conducted by M. Fidrich and J.P. Thirion [29] [30].

III. Registration: the Geometric Approach

Registration of medical images appeared soon as a central problem in medical imaging. Influenced by the experience of image registration in computer vision, we explored first the so-called "geometric" approach, in which geometric primitives are extracted in a first stage, and then matched against each other in a second stage.

- **Geometric Hashing:** with A. Guéziec [31] we introduced a new method to match crest lines which has the nice property of exhibiting a sublinear complexity with respect to the number of points and curves. This approach was exploiting a geometric hashing technique, using 5 differential invariants computed at each point along each curve: its curvature, torsion, and 3 angles between the Frenet frame (attached to the curve) and a local frame attached to the underlying surface (defined by the normal and the directions of principal curvatures). This approach was quite successful to achieve a totally automatic registration of high resolution images of the same patient (typically MR-MR or CT-CT registration) with an excellent accuracy. Interestingly enough, this work also applied to the registration of 3-D structures of proteins [32] [33].
- **Quantifying registration accuracy:** To quantify this accuracy, X. Pennec [34] [35] [36] introduced a new formalism to study the uncertainty attached to the rigid transformations estimated from geometric registration methods. A difficulty to overcome was the appropriate modeling of rotations, whose parameters belong to a manifold which is not a vector space (Lie Group). A similar problem was arising when modeling the uncertainty on the geometric primitives used to guide the registration (other than simple points): this was the case with local frames, oriented points, lines, etc. The proposed formalism allowed to rigorously model and propagate the uncertainties between primitives and geometric transformations and we showed that submillimeter accuracy was definitely achievable in the estimation of rigid registration [37] (cf. Figure 4).
- **ICP algorithm for Rigid and Deformable registration:** with J. Feldmar [38], we moved from rigid to deformable registration and from curves to surfaces. We proposed an extension of the ICP (Iterative Closest Point) algorithm to take into account the local curvatures of surfaces, and their variation through the application of affine transformations. The idea was generalized to 3D volumes in [39]. Another extension was applied to the case when one image is a projective one, in order to superimpose video images with medical images, an important step towards augmented reality [40] (cf. Figure 5). This work is currently under extension by S. Nicolau and L. Soler at IRCAD (Strasbourg, Frane) (see also Figure 17 in the Simulation section).
  More recently, S. Granger and X. Pennec revisited the iterative closest point (ICP) algorithm in the framework of the Expected Maximisation (EM) algorithm in order to better control the accuracy of geometric registration in the context of image-guided oral implantology [41] [42].

IV. Registration: the Iconic Approach

After these first successes with geometric approaches, we followed a general orientation towards "iconic" approaches, where no preliminary image segmentation is required because the intensities of superimposed images are directly compared. The price to pay is usually the requirement of a good initial solution and more intensive computations.

- **The Demons algorithm:** revisiting the work of Christensen et al., J.P. Thirion proposed a much more efficient method, called the Demon's algorithm, in order to non-rigidly register monomodal images [43] [44] (cf. Figure 6). The method was placed in a variationnal framework with P. Cachier and X. Pennec in order to explicit the minimisation of a well identified energy and applied to the tracking of anatomical structures in temporal sequences of 3-D ultrasound images [45]. They showed how to compute the non rigid registration field using convolutions [46]. With D. Rey, P. Cachier showed how to insure a symmetric registration field using inversion-invariant energy functions [47]. P. Cachier also proposed a new framework for vectorial regularization involving isotropic energies, filters and splines [48]. With P. Cachier, J.F. Mangin and others, we tried to reconcile the Geometric and Iconic approaches by introducing in the previous approach a term related to the geometric correspondance of sulcal lines. This led to more accurate results for the inter-subject registration of brain images (cf. Figure 7) [49].
- **Unifying and augmenting iconic criterions:** with A. Roche and G. Malandain [50], we proposed a maximum likelihood framework to unify the main criterions proposed in the litterature to compare multimodal images. A. Roche introduced a new criterion from information theory, the correlation ratio [51] which plays an intermediate

Fig. 3. Left: sagittal cross-section from a 3D MR images. Middle and right: crest lines automatically computed on the surface of the brain (courtesy of J.P. Thirion and G. Subsol; Original MR images courtesy of Prof. R Kikinis, Brigham and Women's Hospital, Boston).

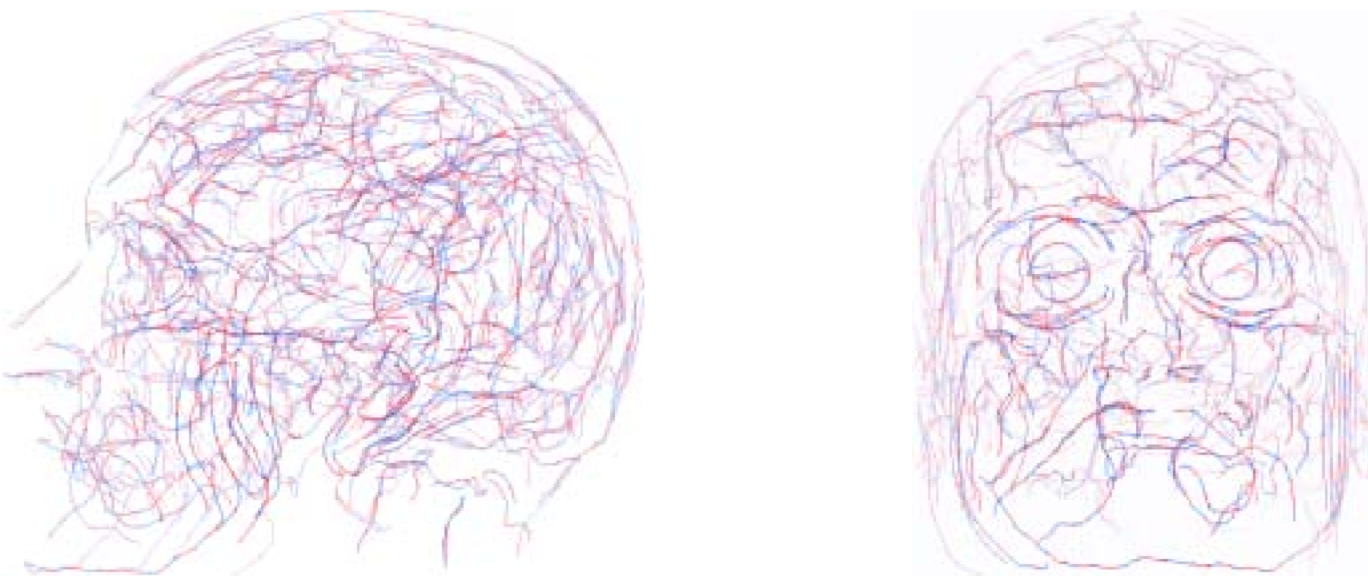

Fig. 4. Crest lines allow accurate and fully automatic registration of high resolution MR T1 images of the same patient. In this figure, only the 240 matched crest lines are displayed. Change of color along a line correspond to the presence of an extremal point on the crest line. One can note that matched crest lines are found on several anatomical surfaces (skin, skull, brain, etc.) Validation experiments showed that an overall accuracy of 0.1 mm was achieved through this registration procedure. (Courtesy of X. Pennec and J.P. Thirion.)

role between linear correlation and mutual information. More precisely, he showed that the choice of an optimal criterion depends on the type of expected relationship between the intensities of the registered images. For instance, an affine relationship between the intensities will lead to the use of a linear correlation criterion, while a more general functional relationship between the intensities will lead to the correlation ratio criterion, and finally a general statistical relationship will lead to the mutual information criterion. An extension of this work to the difficult problem of multimodal registration of multipatient images was published by A. Guimond et al. [52]. Other extensions related to the problem of registration of MR and US images were explored with X. Pennec and P. Cachier with remarkable results in image-guided neurosurgery [53] (cf. Figure 8).

- **Building histological atlases:** S. Ourselin and G. Subsol developped a robust block-matching approach in order to build 3-D volumes from 2-D optical cross-sections [54]. With E. Bardinet and others, the approach was adapted and applied to several different problems. For instance, the optical cross-sections can come from microscopic or macroscopic histological images (with or without staining process), in order to correlate the detection of abnormal signals in MRI with post-mortem observations [55]. The optical cross-sections could also come from autoradiographs, and to correlate the detected activity in functional MRI with ground truth provided by autoradiographs

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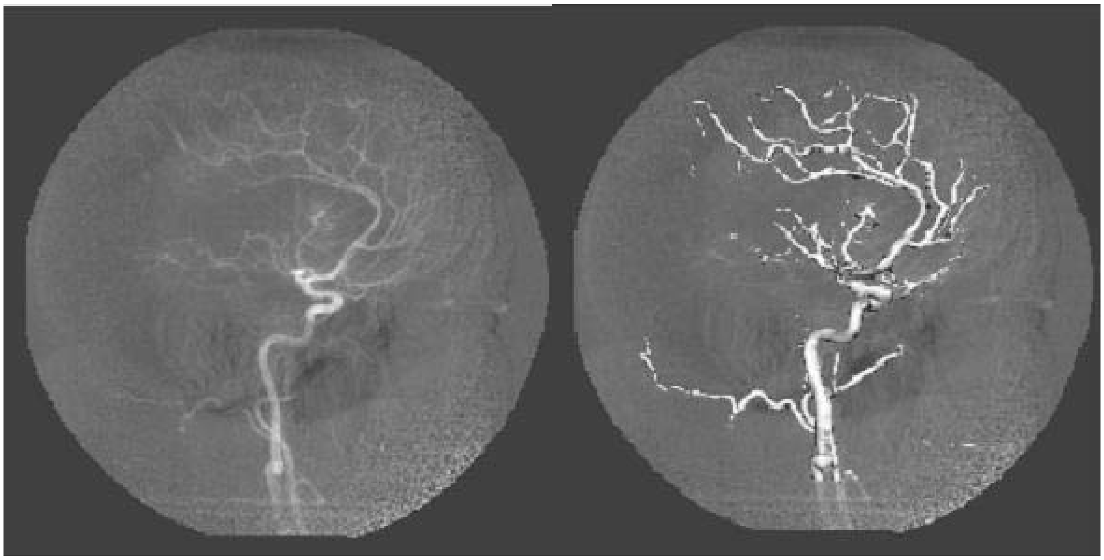

Fig. 5. Augmented Reality combining intra-operative X-ray with pre-operative MR angiographies (Courtesy of J. Feldmar.) 1

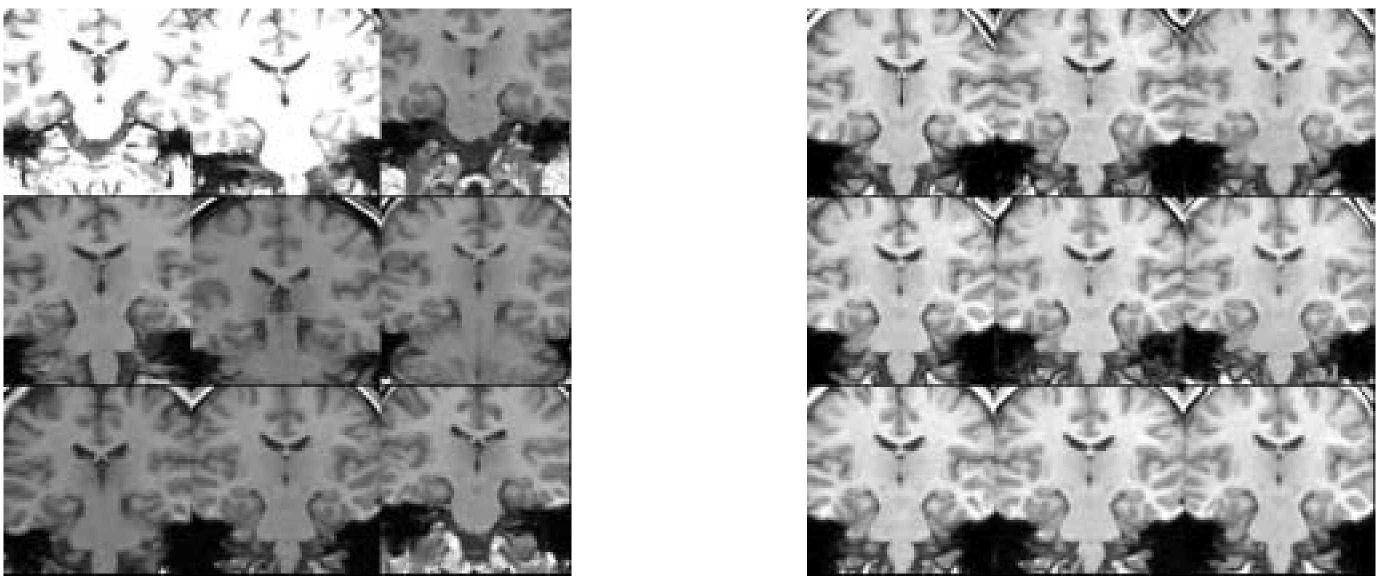

Fig. 6. Iconic registration of brain images of different subjects with the Demons algorithm; Left: One slice (out of a 128) of the original images of 9 different patients. Shapes and intensities are very different. Right: The same 9 patients after non-rigid matching, re-sampling and intensity correction. The computation is performed entirely in 3D. Note that the morphometrical differences are compensated for, but not the local morphological differences. (Courtesy of J.P. Thirion).

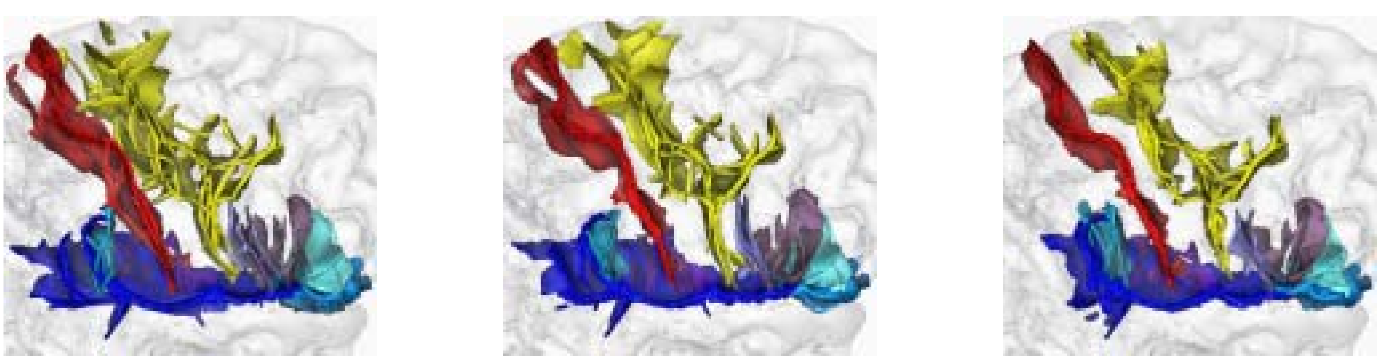

Fig. 7. Reconciling Geometric and Iconic Registration: central (red) and pre-central (yellow) sulci of 5 subjects are shown after affine registration (Left), after deformable iconic registration without sulcal constraints (Middle) and with sulcal constraints (Right) (Courtesy of P. Cachier and J.F. Mangin).

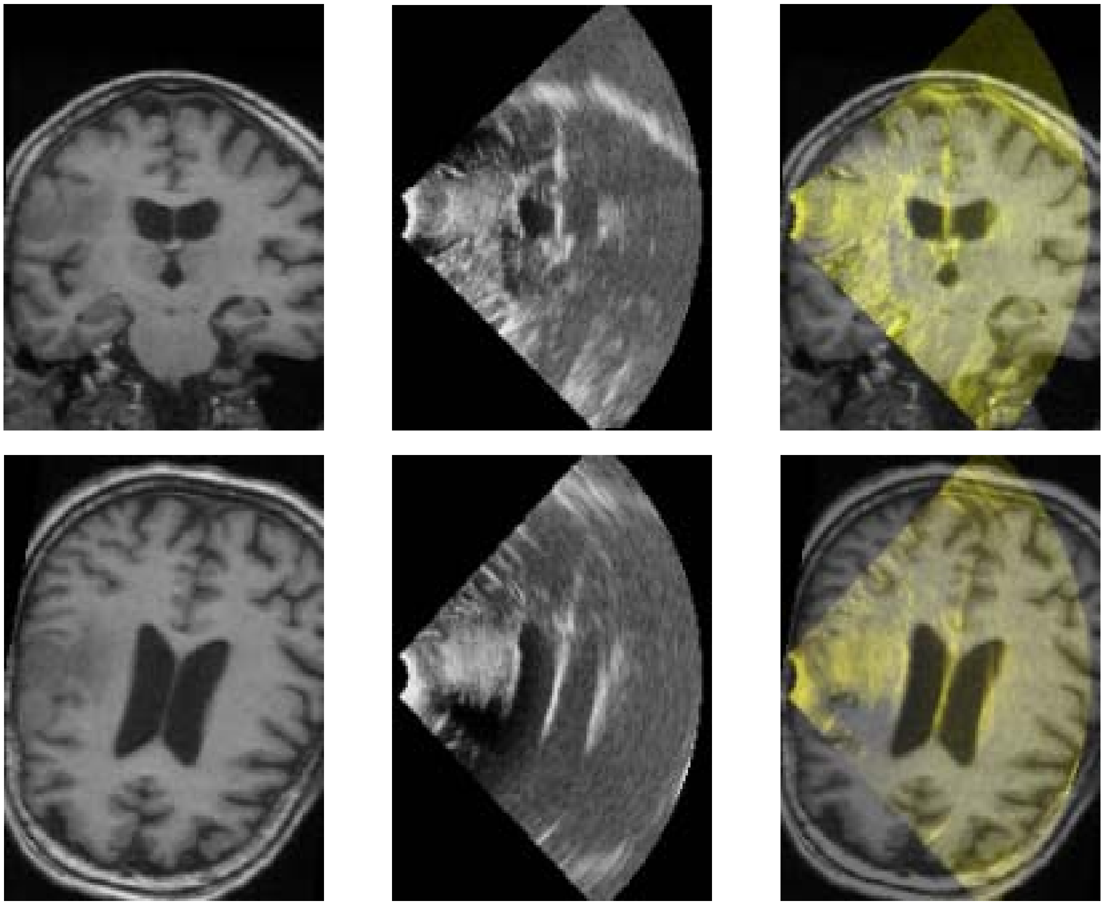

Fig. 8. Iconic registration of an intra-operative 3-D ultrasound image with a pre-operative MR image for image-guided neuro-surgery; The superimposition of the two images after registration (on the right) shows a very good alignement, and validation studies demonstrate an accuracy of the order of 1 mm. (Courtesy of X. Pennec, A. Roche and L. Auer).

(European project MAPAWAMO). Another project was the construction of high resolution atlases of the basal ganglia from optical cross-sections, followed by their fusion with pre-operative MR images, in order to better control the introduction of electrodes in the subthalamic nuclei for the treatment of Parkinson disease [56] (cf. Figure 9). Extensions to accelerate the method on parallel architectures were investigated by Stephanescu, Ourselin and Pennec [57].

V. Modeling and Analyzing Cardiac Motion

The analysis of cardiac images has been an important research topic within the Epidaure project.

- **Active contours and differential landmarks:** with I. Herlin and I. Cohen we proposed an original model of active contours to follow the boundary of ventricles and cardiac valves in temporal sequences of ultrasound images [58]. Later, with S. Benayoun, we introduced differential criterions to compute deformation fields from temporal sequences of volumetric images. The idea was to detect and use points of high curvature to guide the matching process, and useful results were published in [59].
- **Modal analysis:** with C. Nastar, we introduced for the first time an elementary physical model of the left ventricle in order to decompose its periodic motion into a set of principal modes of deformation, the temporal evolution of each mode being itself compressed through a Fourier analysis [60]. C. Nastar later founded the company LookThatUp (LTU).
- **Deformable superquadrics:** with E. Bardinet and L. Cohen, we tried to constrain the shape of the left ventricle (LV) with a parametric model deforming itself under the action of parameterized deformations. We showed that it was useful to model the shape with superquadrics, and the deformations with volumetric splines whose control points could move smoothly. The fitting of the parameters was done through the minimisation of a functional energy computed in the temporal sequence of images. The approach was successful in nuclear medicine, and was published in [61] and [62] (cf. Figure 10).
- **Planispheric coordinates and 4-D modeling:** with J. Declerck we decided to introduce a new geometric transformation from 4-D space to 3-D space taking into account the specific geometry of the LV. We called it “planispheric”, as a reference to the maps used by geographs. We showed that this approach allowed the recovery of a cardiac motion continuous in time and space, and the extraction of new parameters whose signification was

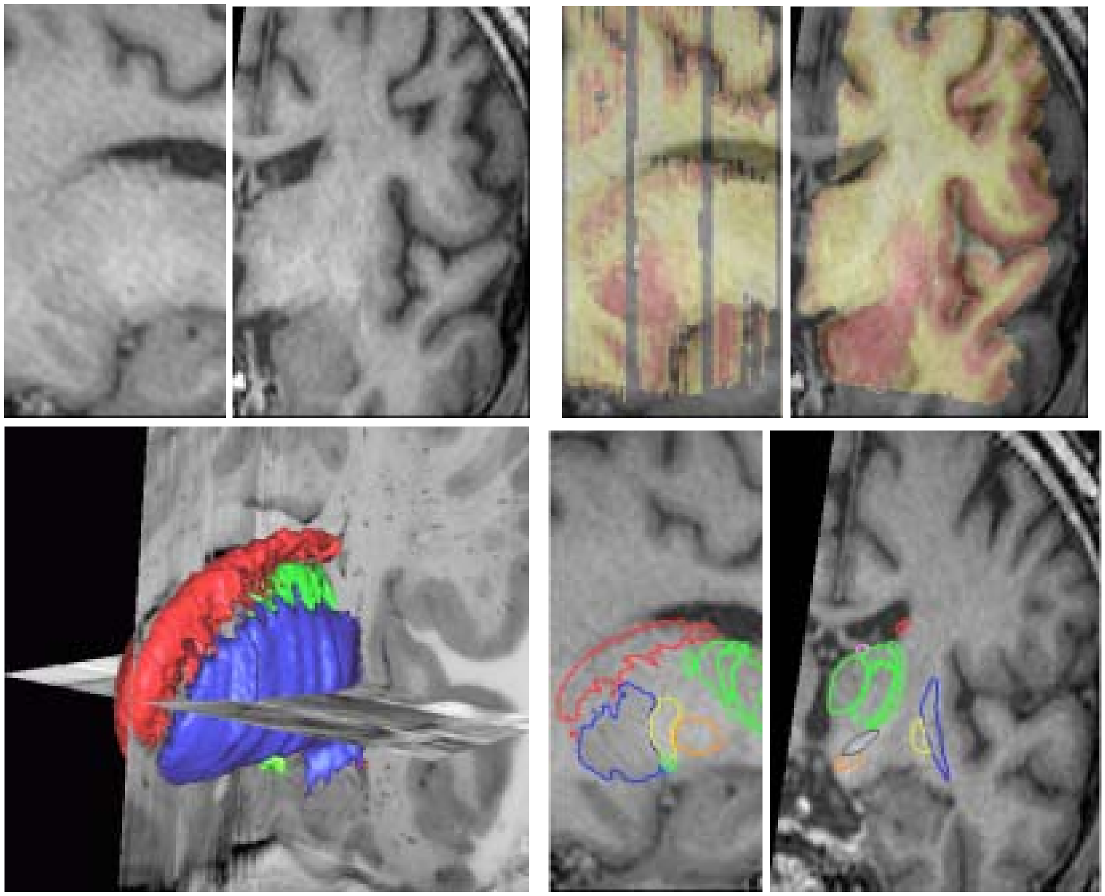

Fig. 9. Automatic 3-D reconstruction of histological atlas from 2-D stained cross-sections and fusion with post-mortem MR images. Top left: post-mortem MR sagittal and coronal cross-sections; Top right: automatic superposition of reconstructed 3-D histology; Extraction of deep grey nuclei surfaces from 3-D histology (bottom left)and superposition on post-mortem MR (bottom right). This atlas can then be registered with MR images of patients with Parkinson disease in order to better locate the subthalamic nuclei in an image-guided stereotactic neurosurgery procedure (Courtesy of E. Bardinet, S. Ourselin, J. Yelnik and D. Dormont).

easier to understand for cardiologists. The method was applied with success in nuclear medicine [63], and then to tagged MRI, in collaboration with E. McVeigh at the Johns Hopkins [64] (cf. Figure 11). Other studies of J. Declerck were concerned with the automatic comparison of stress and rest perfusion images in nuclear medicine [65].

- **Introducing ”physiological” active models:** More recently, we decided to go one step further, and to introduce a new generation of deformable models incorporating some physiological properties. The idea was to model the electrico-mechanical activity of the heart to excite a deformable model from the knowledge of the electrocardiogram (ECG). Then, the geometry of the model must be precisely adjusted to contours measured in a time series of cardiac images using standard attraction techniques of active contours. The advantage of such an approach is the potentially improved robustness with respect to sparse or missing image data, which should allow a better use of 4D ultrasound images (cf. Figure 12). This is a quite ambitious project, involving several groups at INRIA and outside INRIA (D. Hill at Guy's Hospital and E. McVeigh at NIH). More details can be found on the web site of the ICEMA action[4] and early developments are reported in [66] [67] [68].

VI. Morphometry

The Epidaure project was involved in the quantitative study of shapes through several actions. The first one was related to the automatic averaging and indexing of anatomical structures, while the second and third (measuring brain dissymmetry and measuring temportal evolutions in brain images) were part of a European Project called Biomorph, coordinated by Alan Colchester (Kent University). The main objective of this project was the development of improved techniques for measurement of size and shape of biological structures (morphometry).

- **Averaging and indexing anatomical structures:** the study of averaging anatomical structures was the primary concern of the PhD thesis of G. Subsol. He proposed a method based on the matching and avering of homologous crest lines between subjects which proved to be quite successfull on skull images [69] [70]. The method was also applied to compare the evolution of the skull

[4] ICEMA2 web site: www-rocq.inria.fr/sosso/icema2/icema2.html.

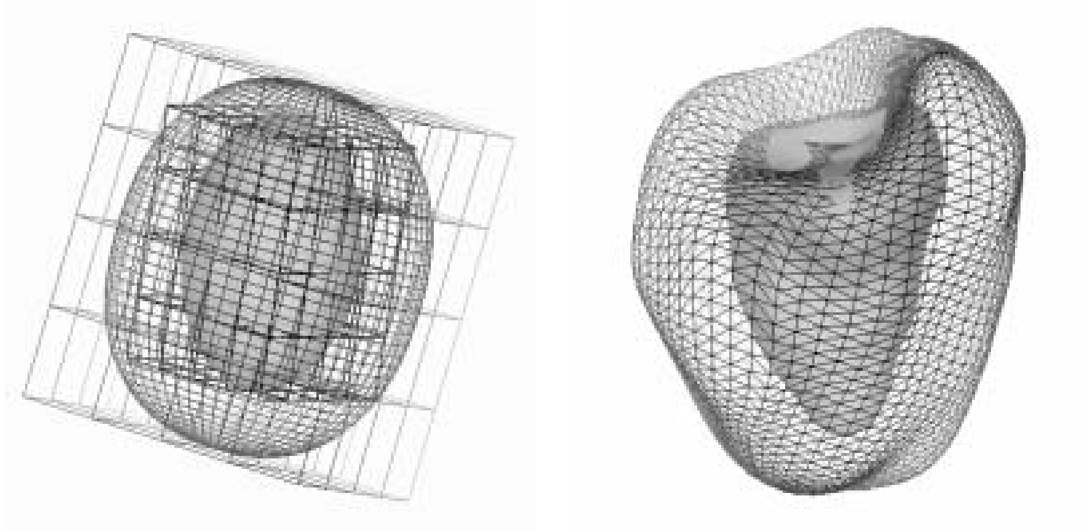

Fig. 10. Deformable superquadrics used to model and track the motion of the cardiac left ventricle in nuclear medicine (Courtesy of E. Bardinet and L. Cohen).

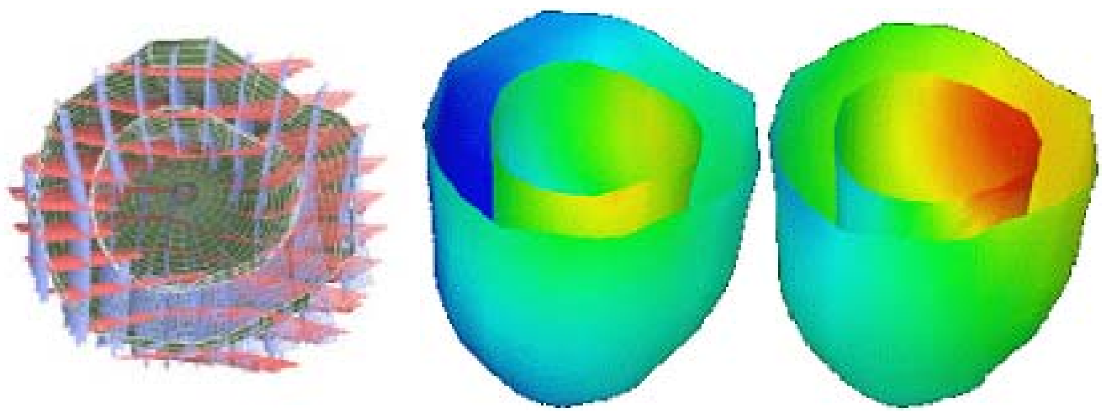

Fig. 11. A planispheric parametrization of the left ventricle is used to model and track the motion of individual points in the cardiac left ventricle from tagged MRI. Left: tracking of the tagging planes; Middle and Right: measured radial contraction and torsion are shown in false colors (Courtesy of J. Declerck and E. McVeigh).

through aging, or even through ages, by comparing for the skulls of a comtemporary and prehistoric men [71](cf. Figure 13).

However the method was difficult to apply to human brain structures, because of the large variability of crest lines between individuals. Another direction was investigated by A. Guimond and J.P. Thirion who proposed a general scheme based on the study of dense deformation fields obtained by appropriate iconic registration methods. The idea was to choose an arbitrary volumetric image as a reference image, and to compute all transformations between the other images and this reference image. By averaging transformations they showed that it was possible to compute a new reference image, and the method could then be iterated until convergence. The results were quite promising [72]. A. Guimond also explored the use of non-rigid registration techniques for the exploration of large databases of MR images [73].

- **Measuring brain dissymmetry:** we concentrated first on the design of statistical measures of brain dissymmetry in volumetric images to compare schizophrenic patients with normals. Actually, a theory developped by Pr. Tim Crow (Oxford) was predicting a significant reduction of dissymmetry among schizophrenic patients, which had to be confirmed by quantitative experiments. First, S. Prima and S. Ourselin designed a method to compute the mid-sagittal plane in 3D brain images in a robust, objective and reproducible manner [74].

Then, S. Prima, J.P. Thirion, G. Subsol and N. Roberts (Liverpool) proposed an original measure of dissymmetry: this measure requires first to symmetrize one of the two hemispheres with respect to the previously defined mid-sagittal plane, and then to compute at each point of a given hemisphere an elastic registration between a small region around this point and the homologous region in the other and symmetrized hemisphere. In case of perfect symmetry, a rigid registration is found, whereas in case of imperfect symmetry, a local deformation is

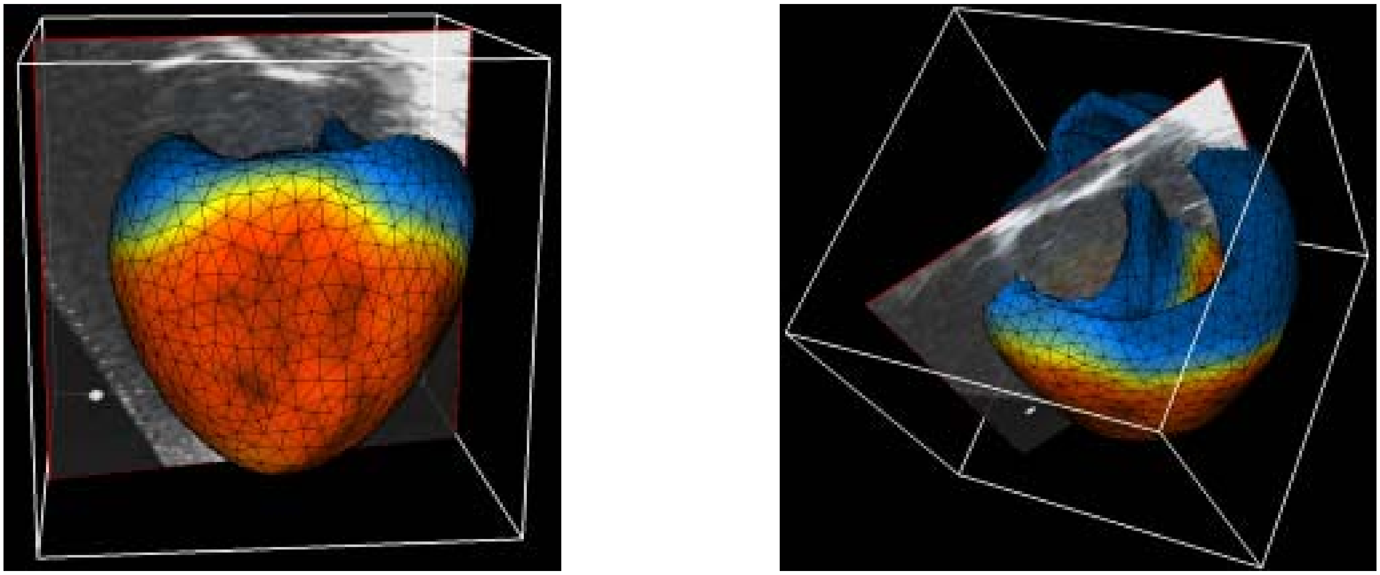

Fig. 12. A new class of electromechanical models of the heart for the segmentation and analysis of cardiac images. Colors correspond to the values of the simulated action potential, which triggers the mechanical contraction. These models will also be used to simulate the effects of radiofrequency ablation surgery (Courtesy of M. Sermesant and Y. Coudière).

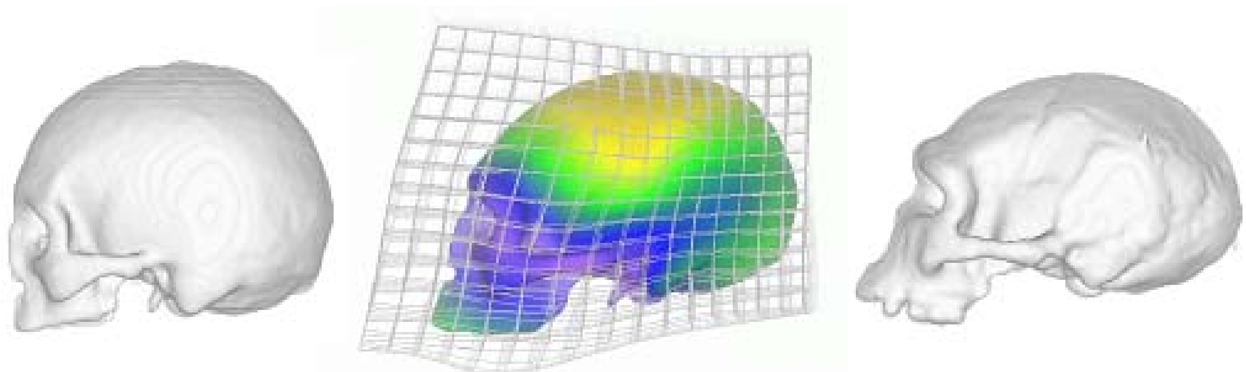

Fig. 13. Crest lines were used to compare the skulls of a modern man (left) with the skull of a prehistoric man (the man of Tautavel, right). Hundreds of crest lines were automatically registered under the supervision of experts, and a global deformation field was computed in 3-D (illustrated by the center image). These results were presented during one year at the "Musée de l'Homme" in Paris for the Millenium. (Courtesy of G. Subsol, B. Mafart and M.-A. de Lumley).

found. A quantitative measure of dissymmetry can be obtained by measuring how far the transformation is from a rigid transformation. Prima and Thirion proposed to use the logarithm of the Jacobian of the deformation (which is zero for a rigid transformation, positive for local expansions, and negative for local contractions).

This measure provides an intuitive interpretation of the result, as symmetric regions correspond to vanishing values of the measure, whereas dissymetric regions show significantly larger absolute values of the measure, with a sign depending on the hemisphere in which the studied region appears larger. Other measures were also proposed in [75], and a new methodology was proposed to compare two populations after intensity and spatial normalization [76]. The final result was that, at this stage, no significant statistical difference could be found between schizophrenic patients and normal subjects. Although negative, this result was quite important in showing the importance of well controlled quantitative measurements before drawing final conclusions on 3D anatomical shapes (cf. Figure 14).

- **Measuring temporal evolutions in brain images:** still in the Biomorph project, the Epidaure team was also involved in the subtle detection of temporal changes in time series of MR images of patients with multiple sclerosis. This topic was studied first by J.P. Thirion and G. Calmon [77] who proposed a deformation analysis to detect and quantify active lesions, with criterions similar to the ones above-described (actually these criterions were introduced by Thirion and Calmon before the studies on brain dissymmetry). The method was then expanded and tested by D. Rey [78] (cf. figure 15) who also explored other directions, introducing statistical tests in the normalized temporal (or longitudinal) series [79] [80].

  S. Prima also proposed original statistical tests to ana-

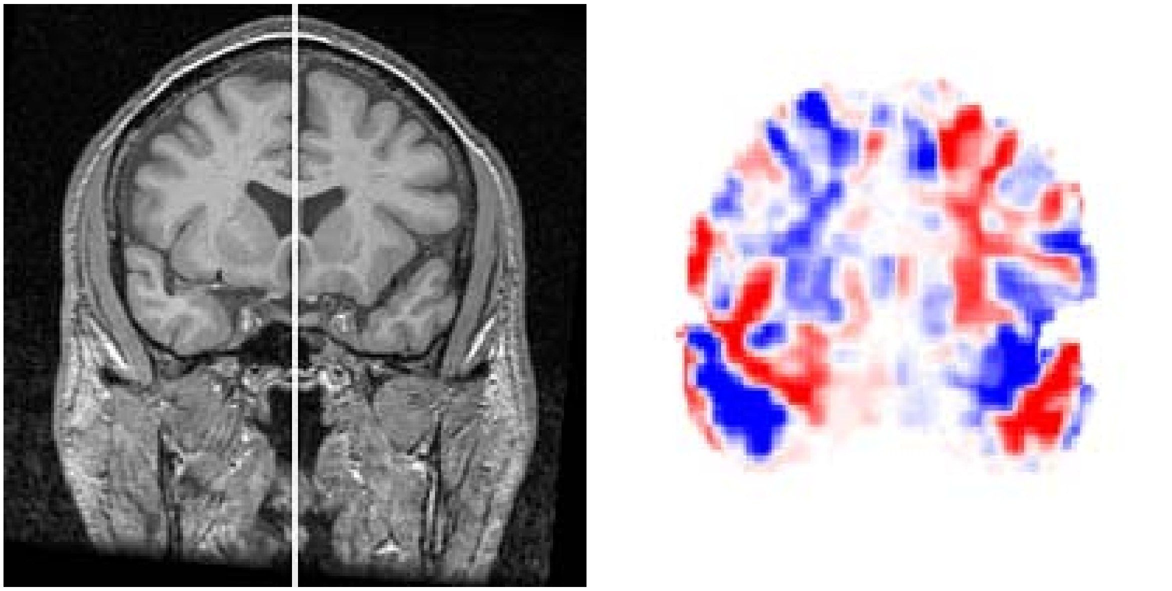

Fig. 14. Measuring brain dissymmetry with quantitative 3-D tools: after an automatic detection of the mid-sagittal plane (Left), a non-rigid registration is applied locally between a small region around each point in one hemisphere, and a symmetrized version of its homologous region in the other hemisphere. The deformation field (not shown here) is analyzed in order to reveal and quantify local dissymmetries, which are represented (Right) in false colors (white color corresponds to symmetrical regions, red (resp. blue) corresponds to regions which appear larger (resp. smaller) in the other hemisphere. (Courtesy of S. Prima).

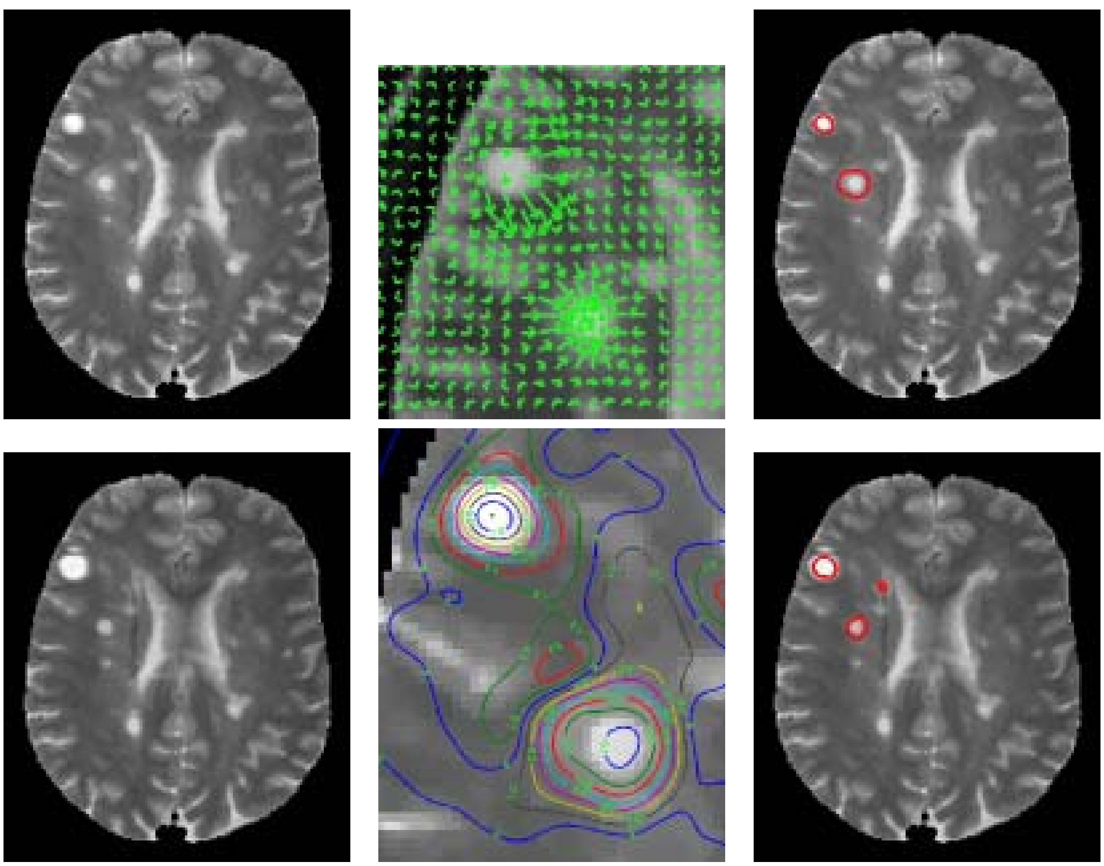

Fig. 15. Automatic Detection of evolving lesions in T2 MR images. Left: 2 images of the same patient acquired 2 weeks apart; Middle up: zoom of the computed apparent deformation field; Middle down: isovalues of the computed logarithm of the jacobian of the deformation field; Right: thresholded jacobian reveals evolving lesions (all computations done in 3-D after automatic spatial and intensity normalisation); (Courtesy of D. Rey. Original images courtesy of R. Kikinis).

lyze longitudinal series in collaboration with L. Collins (Montreal Neurological Institute) [81]. G. Subsol, J.P. Thirion and N. Roberts (Mariarc, Liverpool) studied the deformation of cerebral ventricules [82] or the measure of the cerebral atrophy [83] through time series of MR images.

VII. Surgery Simulation

We started to work on the problem of surgery simulation in 1993, initially with S. Cotin, J. Pignon and H. Delingette. At the beginning we concentrated on the cutting and displacement of bones and face tissues in cranio-facial surgery, but we soon decided that it was more adequate to study the simulation of laparoscopic surgery. Indeed, the context of minimally invasive surgery was appearing as more adequate for simulation, as the surgeon was already working with specific instruments through a limited number of degrees of freedom, observing the operating field on a video screen. Moreover, a specific training was required, in particular to achieve a good hand-eye synchronisation, and was currently available only with passive mechanical systems (endotrainers) or with animals.

A major difference between surgery simulators and flight simulators stems from the fact that it is not sufficient to model the geometry of the structures of interest. Actually, a surgery simulator must provide much more than a simple visual navigation around these structures. It is also necessary to model physical properties in order to allow interactions such as touching organs, gliding instruments, and eventually cutting and/or suturing tissues and vessels. For this, not only a good visual feedback is necessary, but also a realistic force feeback, imposing strong constraints on the computing time. Finally, the modeling of physiological properties like for instance the respiration or the blood circulation is also required to reach the level of realism expected by surgeons.

We decided to start the research in this field in the context of hepatic (liver) surgery. We wanted to choose a volumetric organ which would be more deformable than the brain into the skull. At that time (1994), modeling minimally invasive procedures for liver surgery was considered as close to science-fiction by a number of eminent surgeons. This was not the case for Pr. J. Marescaux at IRCAD[5], who had a specific vision of the future of minimally invasive surgery, and was ready to participate with us in this adventure [84].

- **Geometric modeling:** With L. Soler, G. Malandain, J. Montagnat and H. Delingette we started the geometric modeling of the liver from clinical CT images. We built first a generic model from the data of the "visible human", and then we transformed this model into a deformable model which could adapt itself to the geometry of an arbitrary given patient. Additional processing was done to extract the principal vessels, in particular the portal vein and its main vascular territories. This information is crucial for the surgeon to plan the surgery [85]. The system is currently used at IRCAD on a clinical basis [86] [87], [88]. Current development includes the projection of the reconstructed 3-D model including vascular territories on a projective 2-D view of the operative field. Some preliminary experiments are illustrated in Figure 17.
- **Physical modeling: pre-computed linear elastic models:** with S. Cotin and H. Delingette, we attacked the difficult problem of physical modeling. We chose to adopt the framework of continuum mechanics and finite elements. Under the hypothesis of small deformations, we limited the study to linear elastic materials in a first stage. We introduced a new method of pre-computations which allowed a drastic reduction of the computing time by... 4 orders of magnitude! We demonstrated for the first time the real-time interaction with a liver model discretized with about 10,000 tetrahedra: visual deformations were updated at the rate of 25Hz, while reaction forces were computed at the rate of 300Hz [89],[90] (cf. Figure 16). Part of this work was also done in close interaction with M. Bro-Nielsen who spent part of his PhD period in our group and introduced condensation methods to speed-up the computation of deformations (see for instance [91]).
- **Tensor mass models allowing deformations and cuttings:** To allow cuttings we also had to introduce a new model, called tensor-mass [92] because of its similarities

[5]IRCAD: Institut de Recherche contre les Cancers de l'Appareil Digestif.

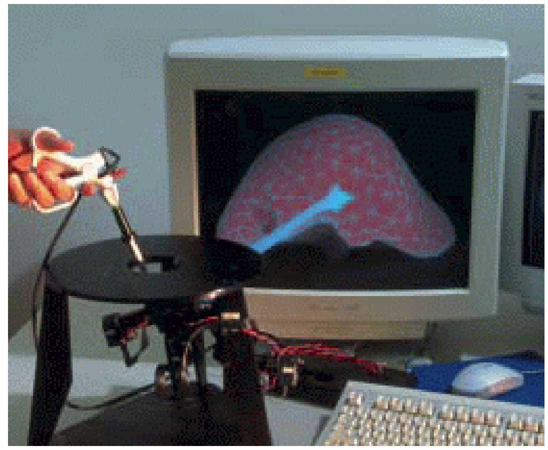

Fig. 16. First demonstration of real-time interaction with a deformable model of the liver including visual and haptic feedback (Courtesy of S. Cotin and H. Delingette).

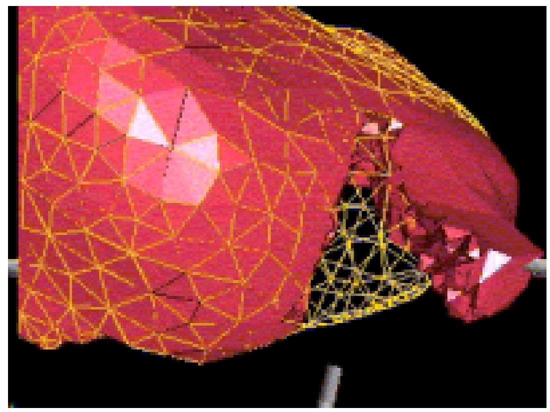

Fig. 19. Simulation of non-linear elastic deformations and cuttings using tensor-mass models (Courtesy G. Picinbono and H. Delingette).

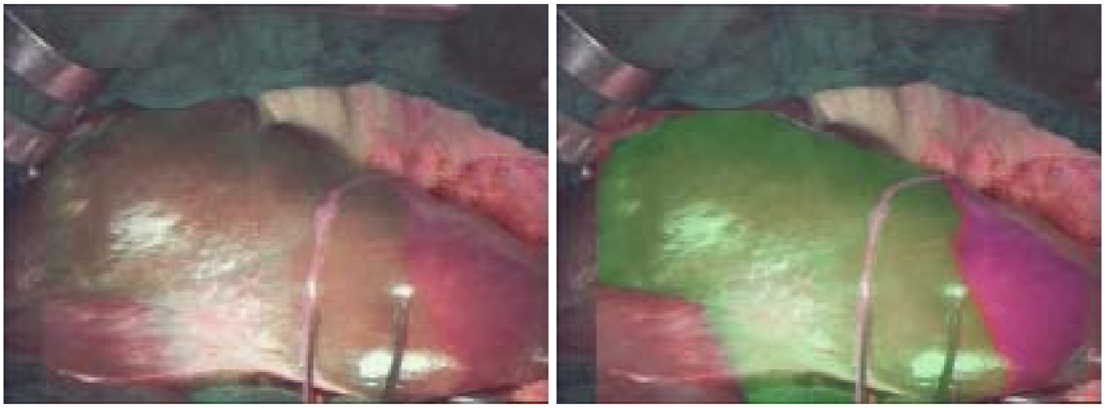

Fig. 17. A geometric model of the liver is reconstructed from standard pre-operative CT images and includes an automatic parcellisation into main vascular territories; This model can then be combined with an intra-operative image video image of the liver (Left) to create an augmented reality visualization (Right) used to guide the surgery procedure (Courtesy of L. Soler and J. Marescaux).

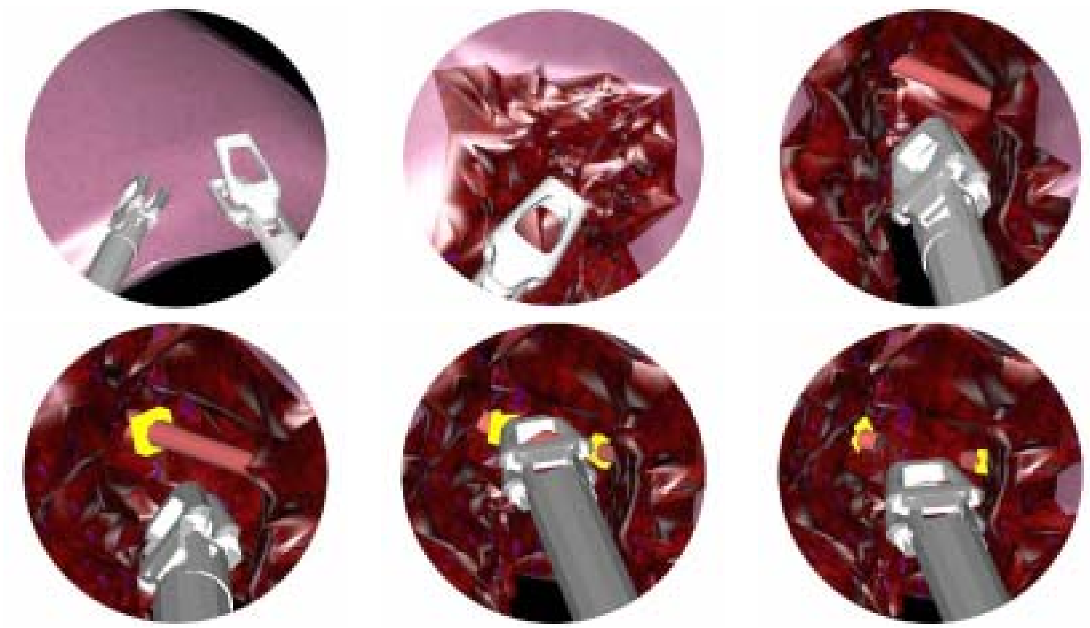

Fig. 18. Introducing vessels into a deformable model of the liver (Courtesy of C. Forest and H. Delingette).

with spring-mass systems used in the computer graphics community. Both systems share the possibility of removing parts of the mesh, but the advantage of the tensor-mass system we introduced is that it implements a true volumetric elastic behavior, which is much more realistic than the behavior exhibited by spring mass systems. As pre-computations are no longer possible when cuttings occur (as the topology changes), it is important to limit the tensor-mass mesh to a limited number of pre-specified regions. We showed that it was possible to combine into a coherent manner pre-computed meshes with tensor-mass meshes in hybrid models were deformations can be computed everywhere very fast, and cuttings only in dedicated regions.

- **Non linear models and interaction modeling:** non linear models were required for larger displacements. With G. Picinbono and H. Delingette, we extended the previous tensor-mass models to account for large displacements. The model has an adaptative behavior, as its complexity increases with the size of the deformation [93] [94]. Its presentation was awarded a prize at the conference ICRA'2001 [95]. (cf. Figure 19). Additional details on the modeling of the interactions and force-feedback can be found in [96] [97].
- **Preserving manifold properties:** cutting anatomical structures poses a number of specific problems, one of them being to preserve nice topological properties of the underlying discrete mesh. This was studied carefully by C. Forest and H. Delingette [98] [99] who also introduced vessels within the liver parenchyma to increase the realism of the simulation (cf. Figure 18).

A pluridisciplinary research action called AISIM was conducted with several research groups at INRIA and outside of INRIA specialized in biomechanics, graphics, scientific computing and image processing, in order to optimize the quality of the simulation. Results can be found on the web site of this action.[6] A summary paper will appear in the Communications of the ACM [100]. We organized with H. Delingette an international symposium on surgery simulation and soft-tissue modeling [101].

VIII. Perspectives

Medical Image Analysis, Simulation and Robotics is now established as a scientific discipline with a promising future supported by the sustained development of new technologies and by their increasing dissemination within the medical community [102] [103] [104] [105]. We organized the first international conference on Computer Vision, Virtual Reality and Robotics in Medicine in Nice in 1995 (CVRMed'95) [106], a conference which then fused with MRCAS (Medical Robotics and Computer Assisted Surgery) and VBC (Visualization and Biomedical Computing) to establish MICCAI (Medical Image Computing and Computer Assisted Surgery) as the annual flagship conference of the field since 1998.

Our current research efforts cover a broad range of activities from the development of new methodological and theoretical tools to their actual integration and clinical validation within medical environments. Below are some of our current orientations for the coming years.

- **Physical and Physiological Modeling:** important efforts should be devoted to a more accurate modeling of the physical and physiological processes underlying the formation of the images [107]. This is particularly true for instance in cardiac imagery where an adequate modeling of the electro-mechanical activity of the heart will lead to a better joint exploitation of medical images and electrophysiological signals [108], and also to a better simulation of new forms of intervention like radiofrequency ablation for instance. In the same spirit, a better biophysical modeling of evolving lesions will also lead to a better detection and measure of their evolution. It is quite likely that the quantitative analysis of medical images will also play a crucial role in the study of the actual effects of new medicines. The introduction of accurate biomecanical and physiological models in surgical simulators will provide a dramatic improvement in the realism of a new generation of training systems.
- **Building anatomical, histological and functional atlases:** the construction of statistical atlases, both anatomical, histological and functional will play an important role in the field. Some open problems are related to the statistical analysis of shapes and textures, a very active research area in which we are involved, in particular through a collaboration with the Loni group at UCLA (Pr. A. Toga and P. Thompson) and the Pitié-Salpêtrière Hospital in Paris. The development of new statistical tools are also central in the analysis of fMRI signals. This is part of our current work in collaboration with the SHFJ department of CEA [109] [110] (cf. Figure 20) and with the Odyssée and Vista research projects at INRIA[7]. New statistical methods will be required to automatically discriminate "pathological" images from "healthy" ones [111] [112] [113]. It is likely that the exploitation of large databases distributed over the planet will require Grid Computing techniques.
- **Scalable Microscopic and Macroscopic Models :** the introduction of volumetric microscopic imagery both *in vivo* and *in situ* will provide new opportunities for fusing micro and macroscopic information in a more systematic manner (cf. Figure 21). A potential outcome will be the possibility to acquire for instance image-guided confocal microscopic images providing the same information as classical biopsies, with the advantage of real-time information and minimally invasive procedures[8]. The development of scalable models going from nanoscopic to macroscopic scales will certainly play an important role in the joint analysis of microscopic and macroscopic images, with the huge potential of molecular imaging for genomics studies. Also, specific data-mining procedures based on the image content still have to be invented.
- **Image-Guided Therapy and Medical Robotics:** Image-Guided Radiotherapy is an important area of research for which we plan to build and evaluate new systems with Nice Hospital and Institut Gustave Roussy in Paris. We also plan to pursue our work on image-guided liver surgery with IRCAD in Strasbourg, and on image-guided neurosurgery with the Pitié-Salpêtrière Hospital in Paris and probably soon with Brigham and Women's Hospital in Boston. Real-time registration and deformation analysis will certainly require specific software and hardware solutions involving for instance parallelism and Grid Computing. The development of medical robotics also poses a number of challenging problems, both for image-guided therapy (see for instance the work of the CHIR group and Eve Coste-Manière at INRIA.)[9] and for surgery simulation. The coupling of image analysis, both pre-operative and intra-operative with medical robotics opens new avenues for applications, including for instance a virtual suppression of cardiac and/or respiratory motions during the intervention.

These directions are by no means exhaustive of all the possible directions of research in the field. The permanent evolution of the current technologies and the regular introduction of new ones creates a constant emergence of new problems, maintaining an exceptional level of exciting research activity, which I feel is not going to decrease during the next decade(s)!

IX. Acknowledgments

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[6]Web site of AISIM: www-sop.inria.fr/epidaure/FormerCollaborations/aisim.

[7]www-sop.inria.fr/odyssee; www.irisa.fr/vista .

[8]Web site of Mauna Kea Technologies : www.maunakeatech.com

[9]www-sop.inria.fr/chir.

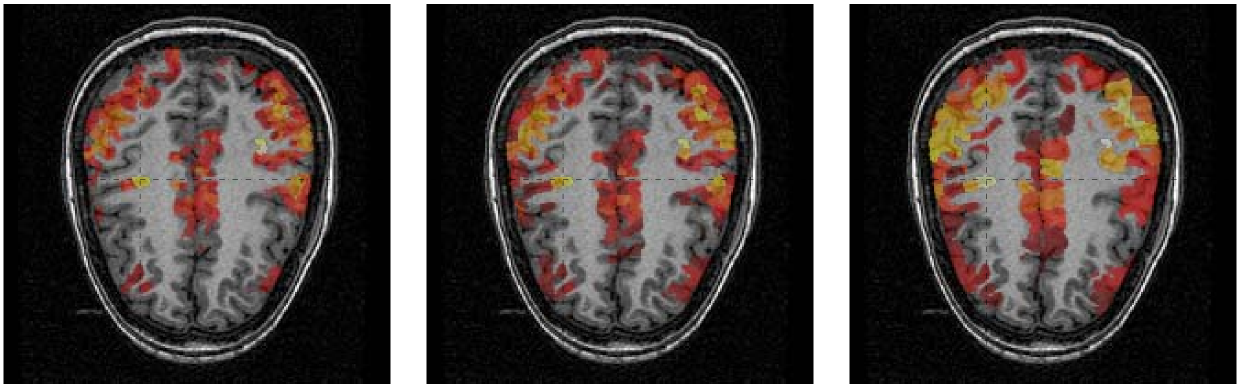

Fig. 20. Activation t-maps computed from functional MRI and after an automatic parcellisation of the cortex at various levels of resolution and for ($p < 0.05$). From left to right: t map computed with 4900, 1700 and 340 parcels. The obtained results show a better sensitivity than a standard voxel-based approach (Courtesy of G. Flandin and J.B. Poline).

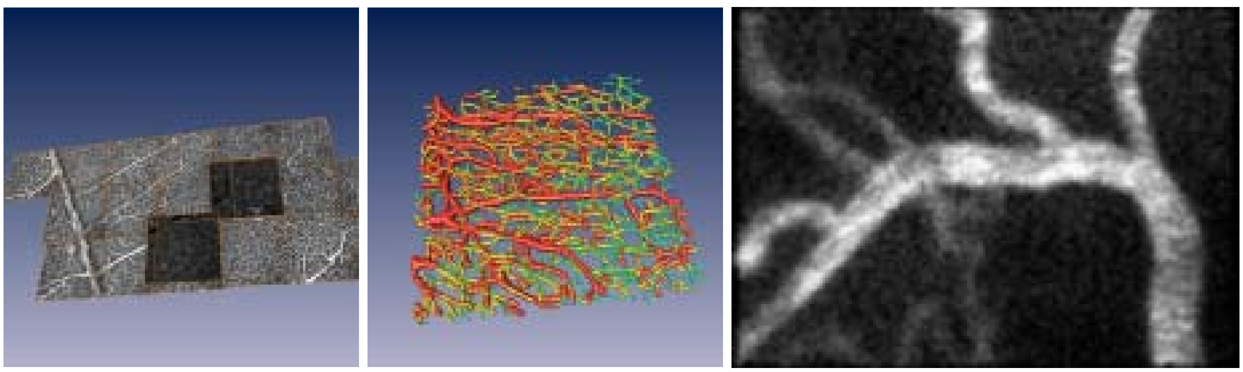

Fig. 21. Left and Center: 3-D reconstruction of micro-vessels from a mosaic of confocal microscopic images (Courtesy of C. Fouard, G. Malandain and J.P. Marc-Vergnes). Right: In vivo and in situ acquisition of micro-circulation images (Courtesy of Mauna Kea Technologies and Pr. E. Vicaut).

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