European Research Council

ERC Advanced Grant 2011 research proposal (PART B1)

Biophysical Modeling & Analysis of Dynamic Medical Images

MedYMA

- Name of PI: Nicholas AYACHE
- Host Institution : INRIA
- Proposal full title: Biophysical Modeling & Analysis of Dynamic Medical Images
- Proposal short name: MedYMA
- Proposal duration in months: 60 months

Proposal summary:
During the past decades, exceptional progress was made with *in vivo* medical imaging technologies to capture the anatomical, structural and physiological properties of tissues and organs in a patient, with an ever increasing spatial and temporal resolution.
The physician is now faced with a formidable **overflow of information**, especially when a **time dimension** is added to the already hard to integrate *3-D spatial*, *multimodal* and *multiscale* dimensions of modern medical images. This increasingly hampers the early detection and understanding of subtle image changes which can have a vital impact on the patient's health.
To change this situation, this proposal introduces a **new generation** of **computational models** for the **simulation** and **analysis** of **dynamic medical images**. Thanks to their **generative** nature, they will allow the construction of databases of **synthetic, realistic** medical **image sequences** simulating various evolving diseases, producing an invaluable new resource for training and benchmarking. Leveraging on their principled **biophysical** and **statistical foundations**, these new models will bring a remarkable **added clinical value** after they are personalized with innovative methods to fit the medical images of any specific patient.
By explicitly revealing the underlying evolving biophysical processes observable in the images, this approach will yield **new groundbreaking image processing tools** to correctly interpret the patient's condition (computer aided **diagnosis**), to accurately predict the future evolution (computer aided **prognosis**), and to precisely simulate and monitor an optimal and personalized therapeutic strategy (computer aided **therapy**). First applications will concern high impact diseases including brain tumors, Alzheimer's disease, heart failure and cardiac arrhythmia and will open new horizons in computational medical imaging.

1. The principal investigator

1a. Scientific leadership profile

I am a Research Director at INRIA Sophia-Antipolis (France) where I lead the **Asclepios** project-team. I was promoted in 2006 at the highest rank (Class Exceptional) for my contributions to research, formation and dissemination.

Content and impact of major scientific contributions: My first scientific contributions were in computer vision (1981-1988), where I introduced new and influential 3-D recognition and navigation tools for autonomous mobile robots (MIT-Press book, 1989). In 1989 I founded the **Epidaure** project-team on Medical Imaging and Robotics first in Rocquencourt, then in Sophia Antipolis in 1992, a team with whom I introduced major contributions for the automated registration and segmentation of multimodal medical images and in surgery simulation and image guided therapy. In 2005, I founded the new project-team Asclepios on Medical Image Analysis and Simulation, with the objective to introduce more geometrical, statistical, biological and physical models of the patients into the images. This proved to be extremely fruitful, leading to highly innovative and influential new publications and results in particular for heart, brain and digestive diseases. Overall, I am the author and co-author of over 400 technical publications, which have received over **14,000 citations** and my **h-number is 64** (Google Scholar, Jan. 2011).

International recognition and diffusion: I received from the French Academy of Sciences and Royal Society highly prestigious prizes (EADS in 2006, Microsoft in 2008), and a large international recognition (ECV'96 prize, Laval Virtual'99 prize, AIMBE'07 fellow, Researcher of the year'07, Miccai'08 significant researcher, Miccai'09 fellow). I was invited to deliver **56 keynote and plenary lectures** at major events all over the world since 1995, plus 37 regular invited lectures since 1989, including the French Academy of Sciences (4 times), the Royal Society, and in front of the French President (1999). I organized and chaired the first CVRMed'95 conference, and chaired or co-chaired 2 international conferences (IS4TM, FIMH'09) and an international program committee (Miccai'07). I am elected **general chair** of the future MICCAI'2012 flagship conference. I Co-founded the international journal Medical Image Analysis in 1995 for which I serve as **Co-Editor in Chief**, which is a reference in the field with IEEE Trans. on Medical Imaging for which I am associate editor.

Effort and ability to inspire younger researchers: I have supervised or co-supervised **52 PhD students**. All of them are enjoying successful careers in academia or industry, a large majority around medical imaging and image processing. Several of my students and younger collaborators created spin-off companies, and I personally co-founded 4 of them. I received with my students and collaborators 8 best paper awards (+3 nominations), and my (co-)supervised PhD Students received **9 best PhD awards** including 2 prestigious Gilles Kahn awards.

Proven ability to productively change research fields and/or establish new interdisciplinary approaches: I made a successful thematic move from *Computer Vision* to *Medical Imaging and Robotics* when I founded the *Epidaure* team in 1989 and 1992 and a new thematic move with the foundation of the *Asclepios* team in 2005 towards *Computational Anatomy* and *Computational Physiology*, with outstanding international evaluations. I serve on advisory boards of research institutions at the interface between computer science & medicine in several countries (e.g., KCL (London), IRCAD (Strasbourg), Shung Hing Institute (Hong-Kong), ITS-Inserm (Paris), etc.).

1b. Curriculum Vitae

• Born in Paris, 1^{st} November 1958, French Nationality, married, 3 children
http://www-sop.inria.fr/asclepios/personnel/Nicholas.Ayache/

Education
• 1980: *Ingénieur Civil des Mines* (Engineer Degree), Saint-Etienne, with honors
• 1981: Master of Science, Artificial Intelligence, University of California, Los Angeles.
• 1983: *Docteur Ingénieur* (PhD), Object Recognition & Robotics, Univ.Paris XI, with honors.
• 1988: *Docteur d'Etat* (Habilitation), Artificial Vision & Robotics, Univ. Paris XI, with honors.

Professional Academic Experience
• 2006–present: **Research Director** of Class Exceptional (DR0) at **INRIA** (Asclepios Team).
• 1985–2010: **Associate Professor** at **Ecole Centrale Paris**.
• 2005–2007: **VP for Science** of INRIA Sophia-Antipolis Center (500 employees, 30 research groups).
• Aug-Dec 2007: Invited Scientist at **MIT** (CSAIL), **Harvard** (Biorobotics) and Brigham and Women's Hospital (Boston).
• 1989–2005: Research Director and Team Leader at INRIA (Epidaure Team).
• 1981–1989: Senior Researcher at INRIA (Robotvis Team)

Publications, Patents, Softwares
• **9 books:** including monograph (341 pages) published by MIT Press (English) and Masson (French).
• **400 international publications** including *118 Journals* • *228 peer-reviewed and archived conference articles* • *31 book chapters* or invited articles • *12 patents.*
• **14,000 citations**; **h-index: 64** (Harzing's Publish or Perish Jan. 2011); 108 Pubmed publications.
• Several popular software modules or libraries have been developed by our research team, including for instance MedINRIA, CardioViz, SepINRIA, Demons Registration, etc., many of them are publicly available. A recent list at http://www-sop.inria.fr/asclepios/software.php

Editorship (selection)
• 1995–present: **Co-Editor in Chief** (& Co-Founder) of *Medical Image Analysis* journal *(Elsevier)* .
• 1992–present: **Associate Editor** of *Trans. on Medical Imaging (IEEE).*
• 2000–present: **Editorial Board** of *Computer Assisted Surgery* (Wiley)
• 2010–present : **Associate Editor** of SIAM Journal on Imaging Sciences, Springer.
• Editorial Board of *Math. Modeling and Num. Analysis,EDP Sc. and SMAI* (2006-2008).
• Editorial board of *International Journal on Computer Vision*, *Kluwer* (1992–2004)
• Editorial board of *Transactions on Robotics & Automation*, *IEEE* (1988–1993)
• Editorial board of *Computer Vision, and Image Understanding*, *Academic Press* (1994-97)
• Advisory Editor of *Medical Imaging Technology* (1995-) and *Videre*, *MIT Press* (1996-2000)

Supervision of PhD Students
• **Supervisor** or Co-Supervisor of **52** PhD Students who graduated between 1992 and March 2010, of **9** PhD Students currently preparing their PhD, of **5** past Habilitations.

Teaching (selection)
• Ecole Centrale Paris (1985–2010);(joint course with ENS Cachan) • Univ. Nice Sophia-Antipolis (1996–2000); • Paris XI (Orsay) (1988–2000)

Start-up Companies
Co-founder of 4 industrial companies: • **Noesis** (general image processing, 1985) • **Realviz** (special effects and image processing, 1998) • **Mauna Kea Technologies** (biomedical molecular imaging, 2000) • **QuantifiCare** (medical image processing, 2001)

Nominations to Scientific Councils (selection 2004–2011)
• 2010–: *Advisory Board* of **Medical Engineering Centre**, St. Thomas Hospital & KCL, London
• 2010–: *Visiting Committee* of **LIAMA** in Beijing
• 2009–2012: *Advisory Committee* of **Japan** Initiative in Computational Anatomy
• 2008–: *Scientific Council* of the French *Inst. of Technologies for Healthcare* of **INSERM**
• 2006–: *Advisory Committee* for *Biology and Health* of **ANR** (French Agency for Research)
• 2006–2008: *Steering Committee* of the French Research Program on Medical Imaging of **INSERM**
• 2004–: *High Scientific Council* for **France-Israel** Cooperation
• 2004–2010: *Advisory Committee*, **Shun Hing Institute** (Hong-Kong).

Best Paper Awards (selection 2001-2010)
• *MICCAI'2010 Workshop* (with M. Lorenzi et al.)
• *MICCAI'2008* (with S. Durrleman, et al.).
• *IEEE EMBS 20008* Summer School, Berder (with Thomas Mansi et al.).
• *MICCAI'2008* (with Thomas Yeo et al.)
• *Elsevier Prize 2006* (with T. Vercauteren, et al.)
• *Art. Motion and Def. Objects 2006* (with J. Boisvert, et al.)
• *MICCAI'2003* (with V. Arsigny and X. Pennec).
• *Robotics & Automation 2001* (with H. Delingette et G. Picinbono).

Distinguished Dissertations of PhD Students (selection)
• 2010: S. Durrleman, 2nd **Gilles Kahn** Prize, awarded by Specif and French Academy of Sciences.
• 2009: J. Boisvert, best PhD co-supervised between *France and Quebec*.
• 2009: P. Fillard, special mention for best PhD in Biomedical Engineering from *SFGBM-IEEE* France.
• 2008: O. Clatz, special mention for best PhD in Biomedical Engineering from *SFGBM-IEEE* France.
• 2007: V. Arsigny, 2nd **Gilles Kahn** Prize, awarded by Specif and French Academy of Sciences.
• 2007: O. Clatz, best PhD award from newspaper *Le Monde*.
• 2004: C. Forest, best PhD award from newspaper *Le Monde*.
• 2003: M. Sermesant, 2nd **SPECIF** award and 3rd *Télécom Valley* award.

Funding ID
We obtained with my team a budget of external funds of approximately 3.4 million Euros to support our research activities during the period 2008-2012. Major part of this funding came from the following European projects: Care4me, Health-e-Child, 3D Anatomical Human, Euheart, Virtual Physiological Human, Passport, Maestro. In 2012, only Care4me, Euheart and VPH will be active, for a maximum remaining amount of 570Keuros. These projects will stop during year 2012.

Approximately 200Keuros came from French funding agency (ANR) through the projects Neurolog and Karametria (which end in 2012) and 250Keuros came from the Microsoft Prize Funding (which ended in 2010).

For the period 2011-2014, I obtained a new funding from Microsoft Research (MSR) Cambridge (UK), and from the MSR-INRIA research center of Saclay, for a total amount of 360Keuros.

1c. 10-year track record

For the 2001-to-present period alone, *Publish or Perish* records an h-number of **39** and **6,778** citations for my publications (since 1984, my h-number is **64** for over **14,000** citations).

Top 10 publications as senior author: Since 2001, my most cited articles are:
1. X Pennec, P Fillard, and N Ayache. A Riemannian Framework for Tensor Computing. International Journal of Computer Vision, 66(1):41-66, January 2006. **268 citations**
2. V Arsigny, P Fillard, X Pennec, and N Ayache. Log-Euclidean Metrics for Fast and Simple Calculus on Diffusion Tensors. Magnetic Resonance in Medicine, 56(2):411-421, August 2006 **288 Citations** (including *92 citations* of previous MICCAI'05 conference paper) **+ 61 citations** of companion paper in SIAM J on Matrix Analysis and Applications 29(1):328-347, 2007.
3. A. Guimond, A. Roche, N. Ayache, and J. Meunier. Multimodal Brain Warping Using the Demons Algor. & Adapt. Intens. Corr., IEEE Trans. on Med. Imaging, 20(1):58-69, 2001 **161 citations**
4. A Roche, X Pennec, G Malandain, and N Ayache. Rigid Registration of 3D Ultrasound with MR Images IEEE Tr. on Medical Imaging., 20(10):1038-1049, 2001. **146 citations**
5. T Vercauteren, X Pennec, A Perchant, and N Ayache. Diffeomorphic Demons: Efficient Non-parametric Image Registration. NeuroImage, 45(1, Supp.1):S61-S72, March 2009. **145 citations** including *81 citations* of previous MICCAI'07 conference paper.
6. G. Picinbono, H. Delingette, and N. Ayache. Non-Linear Anisotropic Elasticity for Real-Time Surgery Simulation. Graphical Models, 65(5):305-321, 2003. **123 citations** + **82 citations** of companion article in J. of Visualisation and Computer Animation 13(3):147-167, 2002.
7. P Cachier, E Bardinet, D Dormont, X Pennec, and N Ayache. Iconic Feature Based Nonrigid Registration: The PASHA Algor., Comp. Vis. and Image Und., 89(2-3):272-298, 2003. **118 citations**
8. O Clatz, H Delingette, I-F Talos, A J. Golby, R Kikinis, F Jolesz, N Ayache, and S Warfield. Robust Non-Rigid Registration to Capture Brain Shift from Intra-Operative MRI. IEEE Transactions on Medical Imaging, 24(11):1417-1427, 2005. **97 citations**
9. P Fillard, X Pennec, V Arsigny, and N Ayache. Clinical DT-MRI Estimation, Smoothing and Fiber Tracking with Log-Euclidean Metrics. IEEE TMI, 26(11):1472-1482, 2007. **96 citations**
10. A. Pitiot, H. Delingette, P. M. Thompson, and N. Ayache. Expert Knowledge Guided Segmentation System for Brain MRI. NeuroImage, 23(supplement 1):S85-S96, 2004. **76 citations**

Edited Books and Proceedings: (selection 2004 – present)
• N. Ayache, editor. Computational Models for the Human Body, Handbook of Numerical Analysis (Ph. Ciarlet series editor). Elsevier, 2004. Note: 670 pages.
• N. Paragios, J. Duncan, and N Ayache, editors. Biomedical Image Analysis: Methodologies And Applications. Springer, 1st edition, 2011. Note: ISBN: 978-0-387-09748-0, 590 pages.(in press)
• N Ayache, H Delingette, and M Sermesant, editors. Functional Imaging and Modeling of the Heart - FIMH 2009, volume 5528 of LNCS, Nice, France, June 2009. Note: 537 pages.
• N Ayache, S Ourselin, and A Maeder, editors. Medical Image Computing and Computer-Assisted Intervention - MICCAI 2007 - volumes 4791 + 4792 of LNCS, 2007. Springer (1001 + 977 pages).
• N. Ayache and H. Delingette, editors. International Symposium on Surgery Simulation and Soft Tissue Modeling, volume 2673 of Lecture Notes in Computer Science, Juan-les-Pins, France, June 2003. Springer. (386 pages)

Research monographs and chapters in collective volumes: (selection 2008–present)
• E Konukoglu, O Clatz, H Delingette, and N Ayache. Personalization of Reaction-Diffusion Tumor Growth Models in MR Images; Multiscale Cancer Modeling, CRC Press, 2010.

• N Ayache, O Clatz, H Delingette, G Malandain, X Pennec, and M Sermesant. Asclepios: a Research Project-Team at INRIA for the Analysis and Simulation of Biomedical Images. In From semantics to computer science: essays in honor of Gilles Kahn, pp. 415-436. Cambridge Univ. Press, 2009.
• T Mansi, B André, M Lynch, M Sermesant, H Delingette, Y Boudjemline, and N Ayache. Virtual Pulmonary Valve Replacement Interventions with a Personalised Cardiac Electromechanical Model. In Recent Advances in the 3D Physiological Human, pages 201-210. Springer, 2009.
• T Vercauteren, N Ayache, N Savoire, G Malandain, and A Perchant. Processing of In Vivo Fibered Confocal Microscopy Video Sequences. Microscopic Image Analysis for Life Science Applications, chapter 19, p 441-463. Artech House, 2008.

Patents:(selection 2001–present)
(1) Dispositif et méthode de traitement d'image pour détection de lésions évolutives. approche 1 & 2 (2001). (D. Rey, J. Stoeckel, G. Malandain, N. Ayache).FR: 0113192 & FR: 0115780 **(2)** Procédé et système de mesure de vitesse du flux sanguin, Mauna Kea technologies, (2005), FR 04 03519 (F. Lacombe, G. Le Gouahler, A. Perchant, N. Ayache). **(3)** A sophisticated device for the processing of raw images or DTI images, French Patent FR0503483, 2005. V. Arsigny, P. Fillard, X. Pennec, N. Ayache.2006 **(4)** Robust Mosaicing Method with Correction of Motion Distorsions and Tissue Deformations for In Vivo Fibered Microscopy. US Patent Application 2009/0041314, T. Vercauteren, A. Perchant, N. Ayache, X. Pennec, G. Malandain

Keynote presentations (selection 2005–2011 out of 47 plenary keynotes since 2000):
• *Fields Institute*, Toronto, CN, June 2011 • *Tata Institute*, Mumbai, India, Feb 2011 • *Royal Society*, London UK, Nov 2010 • *Oxford University* , Sept 2010 • *Tokyo University and MEXT*, Japan, Feb 2010 • *Osaka University*, Japan, Feb 2010 • *Isaac Newton Institute*, Cambridge UK, 2009 • *French Academy of Sciences*, Paris, 2009 • *Medical Imaging Conference*, 2009, Orlando, USA • *Molecular Imaging Summer School*, Lipari (I), 2009 • *Collège de France*, 2008 • *Mayo Clinic*, Rochester, USA, 2007 • *Brigham and Women's Hospital*,USA, 2007 • *French Academy of Sciences*, special session in Nice, 2006 • *Triangle Computer Science Distinguished Lecturer Series*, Chapell Hill, USA, 2006 • *Computational Physiological Fluids Conf.*, Bergamo Italy, 2006 • *Shun Hing Intitute, Distinguished Lecture*, Hong-Kong, 2005 • *First Robotics Science Conference*, MIT, Boston, 2005 • *Med. Image Underst. and Anal. Conf.*, Bristol, 2005 • *Computer Vision and Medicine Symp.*, Beijing, 2005 • *Computer-Aided Surgery, Medical Robotics, and Medical Imaging*, Tel Aviv, Israel, 2005.

Organisation of international conferences: (selection 2003-2012)
• Elected General chair, MICCAI 2012, Nice, France • General Chair, FIHM 2009, Nice, France • Program Chair MICCAI 2007, Brisbane, Australia • General co-Chair IS4TM 2003, Juan-les-Pins, France.

International prizes/awards/academy memberships: (selection 2006-2010)
• Grand Prize Microsoft 2008 for Science in Europe (Royal Society and French Academy of Sciences) • Grand Prize EADS 2006 (French Academy of Sciences) • Elected *Fellow of the MICCAI Society*, 2009, London. • Significant Researcher Award, awarded at the MICCAI conference, 2008, New-York. • Elected to *AIMBE* College (American Inst. for Med. & Biol. Eng.), NAS, 2008, Washington DC. • Designated *Best Researcher of the year* (PACA Region) by *Nouvel Economiste* Newspaper, 2007

Membership to editorial board of international journals: (selection 2005-2010)
• Co-Editor in Chief, Medical Image Analysis Journal, Elsevier. • Associate editor, IEEE Transactions on Medical Imaging • Editorial Board of Computer Assisted Surgery (Wiley) • Associate Editor of SIAM Journal on Imaging Sciences, Springer.

Biophysical Modeling & Analysis of Dynamic Medical Images

A Public Health Concern

During the past decades, tremendous progress was made with *in vivo* medical imaging technologies to capture the anatomical, structural and physiological properties of tissues and organs, with an ever increasing spatial and temporal resolution. The **quantity of information** provided by all the imaging techniques make their **interpretation** by the physician **extremely challenging**, especially when a **temporal component** is added to the already hard to integrate *3-D spatial*, *multimodal* and *multiscale* dimensions.

For instance, in cancer imaging, as discussed in a recently published book on Multiscale Cancer Modeling [Deisboeck and Stamatakos, 2010][1], patients with gliomas (brain tumors) are followed with multimodal MR images involving multiple parameter sequences (T1, T2, Flair, Gadolinium enhanced T1, diffusion tensor images, etc.). This makes the visual analysis by the physician extremely cumbersome. The quantitative effect (or absence of effect) of a chemotherapy typically requires several weeks or more to be visually assessed, while automated tools could quantify earlier the evolution, and help adjust or change the therapy protocol. For radiotherapy or surgery, a constant margin of security of 2 cm is applied uniformly around the apparent tumor boundary, neglecting the fact that gliomas can infiltrate the tissues beyond the visible boundary in a very anisotropic and specific manner which depends on their dynamics and on the local anatomy of the patient.

For cardiovascular diseases, a recent Nature paper on the role of cardiac MRI and nuclear imaging in cardiac resynchronization therapy (CRT) [Aggarwal et al., 2009] recalled that up to 40% of patients who receive CRT (with a costly pacemaker implantation) do not benefit from this treatment. This happens despite a thorough analysis of the cardiac images and a set of other biosignals.

Similar examples can be found, for instance, in the follow-up of patients with other neurological diseases such as Multiple Sclerosis (MS) [Geremia et al., 2010] or Alzhheimer's disease [Cuingnet et al., 2010], where subtle measurements of the disease evolution are necessary to quantify the impact of a therapy. This is also the case in other cardiovascular diseases, such as arrhythmia, where a therapeutic strategy of radiofrequency ablation (RFA) of tissues must be decided after the analysis of medical images and other biosignals. Even after this careful analysis, there is a great deal of uncertainty regarding the expected benefit for the patient [Relan et al., 2010, Cochet et al., 2011].

Finally, the analysis of images is even more difficult in pediatric and gerontological cases where a significant and natural evolution of the organs must be "subtracted" from the time series of observations to reveal abnormal deviations from a normal evolution [Gerig et al., 2010].

Image Analysis Bottlenecks

All the previous examples clearly raise the problem of the **optimal exploitation of time series of medical images** to model both the current condition of the patients and the potential effect of the therapy. Many research efforts have been devoted worldwide to medical image processing during the past decades to accompany the advances in image acquisition. A good vision of the evolution of the state-of-the-art is provided for example by the archived proceedings of the recent editions of the flagship MICCAI conference [Ayache et al., 2007, Metaxas et al., 2008, Yang et al., 2009, Jiang et al., 2010], the last FIMH conference [Ayache et al., 2009], by a recent book [Paragios et al., 2011], and by the recent issues of top level journals like IEEE Trans. on Medical Imaging, Medical Image Analysis, and NeuroImage, to cite a few leading publications.

Despite remarkable advances in the domain of image acquisition and image processing, it remains extremely difficult to interpret and quantify the **dynamics** of the **underlying living processes**

[1] The complete list of references is at the end of part B2, while a few are duplicated at the end of part B1.

from time series of medical images. This comes from a number of specific difficulties like **(1)** the large range of **time intervals** between successive images, which can vary between tens of milliseconds (e.g., in cardiac imagery) up to months and years (e.g., in oncology); **(2)** the **normal evolution** of the patient between two exams, which is particularly important in pediatric imaging (growth of the organs between two exams) and in gerontology (normal atrophy due to aging for instance). Also, the shape of some organs like the heart or liver can change significantly during the months following a therapy, or as a consequence of a pathology (heart remodeling, liver growth); and **(3)** the **anatomical** and **physiological** nature of the information that the physicians need to extract from the images is very specific to improve the diagnosis, prognosis, as well as the therapy planning and monitoring. This information is usually not directly accessible with classical image processing tools and requires an appropriate **biophysical modeling** of the observed tissues or organs.

First Challenge: a new generation of models

To change this situation, it is therefore essential to introduce a biophysical level of modeling taking into account explicitly the dynamics of the underlying processes of life [Noble, 2002] [Ayache, 2004]. To achieve this goal, we will revisit, improve and/or redesign computational models of brain and cardiac diseases (e.g., [Konukoglu et al., 2010, Clatz et al., 2005, Chapelle et al., 2011, Sermesant et al., 2008], etc.):

• These models will all include a **generative** component able to simulate a dynamic evolution of the organ *and* of the disease at a scale compatible with the resolution of the medical images.

• The generative component will be based on **biological** and **physical** principles simulating the evolving processes of interest. For instance, for a brain tumor, the model will reproduce proliferation and infiltration of tumor cells as well as brain deformation due to tumor progression. For Alzheimer's disease, it will simulate a local transformation producing a local and global modification of the brain shape [Singh et al., 2009]. For a cardiac disease, it will simulate the electrical, mechanical and hemodynamic activity of the organ, etc.

• The models will **simulate** the **aging** of the patient as well as **remodeling** of tissues whenever necessary [Lefevre and Mangin, 2010, Szczerba et al., 2009].

• The models will have a **limited** number of **parameters** to be identified from images.

• The parameter selection and the range of possible values will be constrained by the **statistical** knowledge on anatomy and physiology acquired on **large populations** of patients and controls [Pennec and Joshi, 2008, Young and Frangi, 2009].

Second Challenge: producing databases of synthetic images

We will use the previous generative models in combination with physical models of image formation [Aubert-Broche et al., 2006], [Benoit-Cattin et al., 2005], [Prastawa et al., 2009] and limited databases of real patients, to create new databases of synthetic, realistic medical images (e.g., CT, US, MRI, Pet or Scan) of evolving organs and diseases **with ground-truth values**. These ground-truth values will include not only the precise localization of the anatomy and pathology at different time points (without the huge cost of manual segmentation and interpretation by experts), but also important local biological and physical values (e.g., for brain models : the simulated density of tumoral, quiescent, necrotic, or oedema cells in each volume element, and/or a local atrophy measure in white or grey matter, etc.; for cardiac models: a local conductivity or contractility parameter per vascular territory, etc.). Many of these values are not directly accessible in patient images, and only a subset can be physically acquired on real patients at the cost of additional and usually invasive and possibly hazardous *in vivo* measurements (e.g., cardiac endovascular electrical mapping or pressure measurements, brain physical or optical biopsies, etc.). On the opposite, our simulations will produce this additional ground-truth at no extra cost. Moreover, this approach will allow not only the generation of dynamic

images of standard healthy and pathological cases, but also the simulation of rare but important cases that could be rarely visible in databases of real patient images.

Such synthetic but realistic databases will be an **exceptionally precious new resource** to **train** and **benchmark** new personalization strategies for statistical and biophysical models of image evolution. They will also permit to qualitatively and quantitatively assess the realism of the proposed statistical and biophysical generative models, by presenting the simulated images of evolving anatomy and physiology to the critical eyes of expert physicians. When realistic enough, these images could even serve for the training of young physicians, in particular for the visualization of rare situations. By making these databases available to the scientific community of medical image analysis, it will help the development and comparison of new and competing image analysis techniques, and help producing consensus agreements on the best retained solutions.

Third Challenge : Personalization of Models

To become patient-specific, the models must be personalized, i.e., their parameters must be identified to reproduce through simulation the image observations. Such a personalization is still a difficult challenge. In effect, if the geometric part of the personalization is fairly mature (creation of computational meshes from the patient's images), personalization of the biophysical parameters is still in its infancy. There is a difficult trade-off between realism and identifiability [Fink and Noble, 2009]. Current personalization methods are mathematically complex [Delingette et al., 2007], very demanding in terms of computational resources and mostly borrowed from other fields (control theory, weather forecast, oceanography, mechanics...). Moreover, they often do not take into account uncertainty in the information extracted from images and do not provide uncertainty on the estimated parameters. On top of the previous issues, there is a dramatic lack of clinical images with ground-truth values to train and benchmark personalization methods, despite recent efforts like the STACOM workshop organized at MICCAI'2010 [Camara et al., 2010].

To overcome these limitations we will take full advantage of the large datasets of the previously described simulated images with ground-truth to explore the **best personalization strategies** for various biophysical models, and benchmark them quantitatively. We will use these databases to explore **model reduction** strategies, and quantify their impact on the final personalization and image interpretation. We will include uncertainty in the personalization methods by propagating uncertainty from the images to the estimated parameters. Finally, we will design new biophysical personalization methods fast and robust enough to be clinically useful. To this aim, we will focus on some very promising **machine learning** [Zheng et al., 2009, Criminisi et al., 2010] and **variational methods**, possibly combined together. We will constrain the parameter values with prior distributions provided by the literature and/or from a previous statistical analysis on the anatomy and physiology [Pennec and Joshi, 2008, Young and Frangi, 2009].

High Impact and Representative Clinical Applications

For a chosen set of clinical applications (brain tumors, Alzheimer's disease, heart failure and cardiac rhythm disorders), we will show how the personalized biophysical models can be projected back on the dynamic images for a better interpretation, and how they can allow the introduction of **new image biomarkers** useful for **diagnosis, prognosis, therapy planning** and therapy **monitoring**. We will also explore how the parameters of those personalized models can be used to **index and search** databases of synthetic and real images to retrieve similar time series of evolving images, useful to provide the physician with the patient's history of similar cases.

From a clinical point of view, the chosen applications cover a set of diseases where any progress in the diagnosis, prognosis and therapy delivery can have a **huge societal impact**. From a technical point of view, they cover a sufficiently well representative set of dynamic images, including long

term and short term dynamics. The proposed methodology will remain similar across the set of selected applications, namely the development of adapted generative models, simulated databases, personalization techniques, and the development of new image biomarkers and indexing methods. Moreover, some of the components of the biophysical models will be similar for several applications, such as the use of reaction-diffusion models for the proliferation-infiltration component of brain tumors, the electro-physiological component of the heart, and possibly the simulation of brain or cardiac tissue growth or atrophy.

High Risk but High Gain, an Opportunity for Europe

There is a large number of computational models able to simulate biological processes in the human body. They operate within a large range of scales, from nanoscopic (molecular) to microscopic (cells), mesoscopic (tissues), and macroscopic (organs) scales. Many of these models have been developed in the framework of the Physiome project [Hunter et al., 2006] and more recently of the Virtual Physiological Human (VPH) European initiative http://en.wikipedia.org/wiki/Virtual_Physiological_Human.

Despite these efforts, it remains quite difficult to find models that can be fitted to medical images and signals to describe their dynamic evolution. This is because most of the designed models operate at scales that are not compatible with clinical images, and have consequently many parameters which cannot be identified from the observations. Moreover, even when dynamic models operate at the right scale, the observations in the images are in general not directly linked to the variables or parameters of the model.

Hopefully, some useful progress was achieved recently, in particular in the projects Health-e-Child (completed) Passport (ending June 2011) and euHeart (June 2012) in which our team was involved. Preliminary results were obtained for the quantitative analysis and simulation of brain, cardiac and liver diseases. Although these results were obtained on a small set of patients, with necessarily oversimplified models and often interactive personalization methods, they are extremely promising.

In part thanks to this VPH initiative, our team has acquired a remarkable joint expertise in the modeling and analysis of cardiac, brain and liver images. It has helped us tighten **collaborations** with **world class research teams** in Europe in **academic, clinical** and **industria**l environments (e.g., Pitié-Salpêtrière Hospital (Paris), Ircad (Strasbourg), Bordeaux CHU, Neurospin (Saclay), Nice CHU & CAL, KCL and UCL (London), Oxford Univ., Univ. Pompeu Fabra (Barcelona), KIT (Karlsruhe), Siemens (Erlangen and Princeton), Philips (Hamburg, Suresnes), GE (Buc), Microsoft Research (Cambridge), MKT (Paris), Dosisoft, etc.). This has also given us the opportunity to get access to large databases of dynamic images (e.g., KCL Database in cardiac pediatrics, Cardiac Atlas project database (NZ), ADNI database and CATI initiative (for Alzheimer's disease), MICCAI Challenge SEP database (for multiple sclerosis), DKFZ database (Heidelberg, brain tumors), IRCAD (CT Liver), etc.). These precious collaborations will highly contribute to the success of this challenging proposal.

Methodology

The proposal is structured into 5 workpackages (WP) corresponding to 5 research axes (4 methodological and 1 experimental) with logical interactions between all of them.

• **WP1** and bfWP2 describe the generative models we will explore for the analysis of brain and cardiac images. They share common properties like the integration of several levels of modeling, including geometry, statistics, biophysics up to various physiological properties.

• **WP3** is built on top of the previous ones to simulate synthetic time series images of controls and patients. The previous biophysical models of anatomy and physiology are used in combination with physical models of image formation or with a limited number of real images of patients to create larger databases of synthetic images with various forms of ground-truth.

• **WP4** describes the strategies we will develop to personalize the previous biophysical models by confronting simulation results with image analysis. It also describes how to retrieve similar time series of images in a large database of dynamic images. The previous synthetic databases play a crucial role in the quantitative evaluation of the various strategies, providing a dramatic help before the evaluation of the methods on real databases of patients.
• **WP5** describes concrete clinical applications on at least three important databases of patients covering brain gliomas, Alzheimer's diseases, heart failure and cardiac rhythm disorders.

The Right Team

I will dedicate 70% of my time to this research project, and **I will dedicate all my expertise and efforts** to conduct and supervise the research work as well as the necessary academic, clinical and industrial collaborations for this project. To this end, I will receive the precious help of three permanent researchers of the current Asclepios team: **Hervé Delingette**, **Xavier Pennec**, and **Maxime Sermesant**. They will devote 20% of their time to this project, to co-supervise with me the research work of the 4 PhD students and of 2 research engineers and 1 post-doc student to be engaged in this research for 5 years. Hervé is a world expert in Computational Physiology, and an expert in inverse problems, which will be crucial for the development of brain tumor and cardiac models as well as for the personalization challenge. Xavier is a world expert in Computational Anatomy, and his help will be essential to bring statistical constraints based on population analyses in the modeling and personalization components. His expertise in brain imaging will be crucial for the Alzheimer's disease modeling and applications. Maxime has developed an international expertise in Computational Cardiology, as well as exceptional clinical collaborations with world expert physicians in London (where he has a part-time appointment at St Thomas Hospital) and in Bordeaux (University Hospital). This will be priceless for the success of the clinical applications in cardiology. In addition, the research work of the whole Asclepios team will contribute to the success of MedYMA.

We will also invite for short periods and on a regular basis a number of world leader scientists and clinicians from collaborating groups in France and abroad to contribute to this study and promote European leadership in the computational analysis and simulation of dynamic medical images.

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European Research Council

ERC Advanced Grant 2011 research proposal (PART B2)

Biophysical Modeling & Analysis of Dynamic Medical Images

This proposal introduces a new generation of biophysical and statistical computational models for the simulation and analysis of dynamic medical images. Thanks to their generative *nature, they will allow the construction of databases of synthetic, realistic medical image sequences simulating various evolving diseases, producing an invaluable new resource for training and benchmarking. Leveraging on their* biophysical *and* statistical foundations*, these new models will bring a remarkable clinical added value after they are personalized with innovative methods to fit the medical images of any specific patient.*

By explicitly revealing the underlying evolving biophysical processes observable in the images, this approach will yield new groundbreaking image processing tools to correctly interpret the patient's condition (computer aided diagnosis*), to accurately predict the future evolution (computer aided* prognosis*), and to precisely simulate and monitor an optimal and personalized therapeutic strategy (computer aided* therapy*). First applications will concern high impact diseases including brain tumors, Alzheimer's disease, heart failure and cardiac arrhythmia and will open new horizons in computational medical imaging.*

2. The project proposal

2a. state-of-the-art and objectives

The analysis of medical images has undergone huge progress during the past 30 years and a good evolution of the state-of-the-art is provided by the archived proceedings of the flagship MICCAI conference every year [Ayache et al., 2007, Metaxas et al., 2008, Yang et al., 2009, Jiang et al., 2010], the last FIMH conference [Ayache et al., 2009], by a recent book [Paragios et al., 2011], and by the recent issues of top level journals like IEEE Trans. on Medical Imaging, Medical Image Analysis, and NeuroImage, to cite a few leading publications.

Despite these advances, even world leading hospitals have immense difficulties in exploiting the highly complex multimodal image sequences acquired for patients followed with various diseases. This is because the quantity of information provided by modern imaging techniques make the interpretation of images by the physician extremely challenging, especially when a **temporal component** is added to the already hard to integrate *3-D spatial*, *multimodal* and *multiscale* dimensions.

In cancer imaging, as discussed in a very recent book [Deisboeck and Stamatakos, 2010] on Multiscale Cancer Modeling patients with gliomas (brain tumors) are followed with multimodal MR images involving multiple parameter sequences (T1, T2, Flair, Gadolinium enhanced T1, diffusion tensor images, etc.), which makes their visual analysis by the physician extremely cumbersome. The quantitative effect (or absence of effect) of a chemotherapy requires typically several weeks or more to be visually assessed, while automated tools could quantify earlier the evolution, and help adjust or change the therapy protocol. For radiotherapy or surgery, a constant margin of security of 2 cm is applied uniformly around the apparent tumor boundary, neglecting the fact that gliomas can infiltrate the tissues beyond the visible boundary in a very anisotropic and specific manner which depends on their dynamics and on the local anatomy of the patient.

For cardiovascular diseases, a recent Nature paper on the role of cardiac MRI and nuclear imaging in cardiac resynchronization therapy (CRT) [Aggarwal et al., 2009] recalled that up to 40% of patients

who receive CRT (i.e. a pacemaker implantation) do not benefit for this treatment. This happens despite a thorough analysis before the intervention of the cardiac images and a set of other biosignals.

Many similar examples can be found in the follow-up of patients with other neurological diseases such as Multiple Sclerosis (MS) [Geremia et al., 2010] or Alzhheimer's disease [Cuingnet et al., 2010], where subtle measurements of the disease evolution are necessary to quantify for instance the impact of a therapy, or in other cardiovascular diseases like arrhythmia, where a therapeutic strategy of radiofrequency ablation (RFA) of tissues must be decided after the analysis of medical images and other biosignals. Even after this careful analysis, there is a great deal of uncertainty regarding the expected benefit for the patient[Relan et al., 2010, Cochet et al., 2011].

Finally, the analysis of images is even more difficult in pediatric and gerontological cases where a significant and natural evolution of the organs must be "subtracted" from the time series of observations to reveal abnormal deviations from a normal evolution [Gerig et al., 2010].

To change this situation, we propose to introduce specific computational models able to simulate and analyze the evolution of the continuous biophysical processes observed at discrete times points in any dynamic series of images.

There is a large number of computational models able to simulate biological processes [Noble, 2002] [Ayache, 2004]. They operate within a large range of scales, from nanoscopic (molecular) to microscopic (cells), mesoscopic (tissues) and macroscopic (organs) scales. Many of these models have been developed in the framework of the Physiome project [Hunter et al., 2006] and more recently of the Virtual Physiological Human (VPH) European initiative http://en.wikipedia.org/wiki/Virtual_Physiological_Human.

Despite these efforts, it remains quite difficult to find models that can be fitted to medical images and signals to explain their dynamic evolution. This is because most of the designed models operate at scales which are much below the scale of clinically available images, and have consequently many parameters which cannot be identified from the observations. Moreover, even when dynamic models operate at a macroscopic scale, the observations in the images are in general not directly linked to the variables or parameters of the model. We showed, for example, [Konukoglu et al., 2010] that it was better to approximate the well established reaction-diffusion models of brain tumors [Chakraborty et al., 2010] by front-propagation models to identify their parameters, because the concentration of cancerous cells modeled by reaction-diffusion models was not directly observable in clinical brain images, whereas the evolution of the tumor boundary is. Similar choices are made in cardiac electrophysiology to relate the activation maps recorded on cardiac ventricles to depolarization times simulated by the model [Relan et al., 2010].

An article was published this year on the vision and strategy for the VPH in 2010 and beyond [Hunter et al., 2010]. This article lists all the current ongoing projects, including the projects EuHeart and Passport in which we are involved, and the progress made so far. It also points out important current bottlenecks and the research efforts required to overcome them, stressing, for instance, the challenge of models reduction, the necessary introduction of uncertainty in the models, and the need for an explicit modeling of the development and aging processes.

In this proposal, we want to take advantage of the expertise we have acquired in the modeling and analysis of brain and cardiac diseases with oversimplified models, to address the above mentioned issues. This will be done by designing **more realistic** but still **identifiable models**, and by exploring **more powerful personalization** techniques. To this end, a very important milestone will be the use of these models to create **new databases of synthetic images** of evolving diseases for training and benchmarking of any model personalization with quantitative measurements. This will allow us to introduce **groundbreaking new medical image analysis tools** for diagnosis, prognosis and therapy delivery on databases of real patients for at least 4 types of high impact brain and cardiac diseases, including brain tumors, Alzheimer's disease, heart failure and cardiac arrhythmia. **This will open new horizons** for the analysis of dynamic medical images for many other diseases.

2b. Methodology

The proposal is structured into 5 workpackages (methodological and experimental): **WP1 and WP2***: Brain and Cardiac Models* describe the type of generative models we want to design for the analysis of brain and cardiac images. **WP3***: Image Simulation* is built on top of the previous worpackages to simulate synthetic time series of images of controls and patients. **WP4***: Model Personalization* explores promising strategies to identify the parameters of the previous biophysical models from medical images. **WP5:** *Clinical Applications* addresses concrete applications on several high impact clinical diseases. We now describe in more details each of these workpackages.

WP1: Brain Generative Models

The brain models must simulate dynamic MR images of patients with brain tumors or Alzheimer's disease. They are structured into levels. The **first level** consists in a geometrical model of the patient's anatomy, including the definition of all the structures of interest that are visible in a clinical MRI. These structures will include the grey matter (GM), white matter (WM), the cerebrospinal fluid (CSF), the skull, and as many additional structures as needed (the falx, the hippocampus, etc.). Various state-of-the-art methods will be available or refined to achieve the best possible geometrical description at this stage. The use of diffusion tensor images (DTI) will be necessary to include additional structural information such as the main bundles of white matter fibers, which play an important role in the migration of tumoral cells for instance. When DTI is not readily available for a patient, computational atlases will be used to infer this missing structural information. The **second level** is a biomechanical model of the brain, implementing for instance a linear inhomogeneous anisotropic behavior. This level is necessary to reproduce the displacement of brain tissues due to the progression of a tumor, or to reproduce the loss of white and grey matter. The **third level** is the pathophysiology level, which can be modeled differently for *i) brain tumors* and *ii) Alzheimer's disease.*

i) Brain tumors: we will build on top of the previous brain models a set of new generative models derived from the reaction diffusion equations now well established as reasonably good macroscopic descriptors of the evolution of the local tumoral cell concentration [Angelini et al., 2007, Menze et al., 2011, Chakraborty et al., 2010]:

$$\begin{cases} \partial_t u = \nabla.\ (D(x)\nabla u) + \rho u(1-u) \\ D\nabla u.\ n_{\partial\Omega} = 0 \end{cases} \tag{1}$$

where u represents the normalized tumor cell density ranging between 0 and 1, ∇ denotes the spatial gradient, ρ is the proliferation rate, D denotes the tumor diffusion tensor defined as a definite, positive and symmetric 3×3 matrix, Ω is the brain domain, and $n_{\partial\Omega}$ is the normal direction to the brain boundary $\partial\Omega$.

We want to explore radical improvements of these models that will allow these models to reach the level where they become clinically useful.

- Gliomas are highly **heterogeneous**, this means that we should introduce locally varying proliferation and infiltration parameters. We will explore various approaches (e.g., [Kelly et al., 2007]), including the definition of zones where these parameters are constant or stochastic approaches where these parameters have a random spatial evolution [Marzouk and Najm, 2009].
- Infiltration is highly **anisotropic**, as was demonstrated by many observations. It is crucial to preserve this anisotropy in the generative model. However, the acquisition of diffusion tensor images (DTI) is costly in a clinical setting, and currently hampers a wider use of this reaction diffusion models. We want to study the possibility to replace the patient's DTI by an atlas DTI,

as was originally proposed by [Clatz et al., 2005] by comparing simulation results based on the 2 approaches on an available clinical database of patients with DTIs.

- It is rare to have time series of patients having gliomas with no therapy delivered to the patient between two successive exams (radiotherapy, chemotherapy, or surgery). Since surgery is very difficult to simulate at this stage, we want to refine the previous equations to account for the effect of **radiotherapy** and/or **chemotherapy** on the proliferation and diffusion rate.
- The progression of the tumor usually creates a deformation of the brain parenchyma (called mass effect), which can be modeled by introducing a local increase of pressure related to the local increase of tumoral cells, as was demontrated by [Clatz et al., 2005]. We want to explore more advanced biomechanical models including for instance an advection term in the previous equations to improve the realism of the **mass effect** [Hogea et al., 2007].
- We want to introduce a larger number of cell categories, including quiescent, necrotic, oedema cells, as well as a simplified description of the local **vasculature** which plays an important role in the development of the tumor [Hirsch et al., 2010, Lloyd et al., 2007].
- It is crucial to model the **uncertainty** of the model parameters. We will study several strategies, including a sensitivity analysis on multiple simulations, to attach a measure of uncertainty to each parameter of the model, which will be taken into account during the simulation and personalization stages.

ii) Alzheimer's Disease: the current modeling of the progression of the Alzheimer's disease is not as advanced as for brain tumors. At the macroscopic level, it is known that there is an increasing global atrophy with the progression of the disease. This atrophy has been measured through the cortex thickness and on limbic structures, such as the hippocampus, with a displacement of these structures in time [Singh et al., 2009]. For example, a significant increase of the atrophy rate was observed for the hippocampus in presymptomatic, mildly affected patients, in temporal lobes for mildly or moderately affected patients, in medial parietal lobe at all stages and in frontal lobes in later stages of the disease [Scahill et al., 2002].

For a long time, the changes of the white matter were not found significant, probably because they could not be observed sufficiently well with standard anatomical MRIs. Recent results actually show that the structure of the white matter is also affected with an increased value of the mean diffusivity and a reduction of the fractional anisotropy in many limbic and extra-limbic areas [Sexton et al., 2010, Ito, 2008]. This suggests that fiber bundle modifications may play an important role in the pattern of atrophy and can possibly be driving its temporal evolution. However, the underlying action mechanism is still unknown.

To understand and model this process, we intend to establish first a **statistical model** of the **deformation** of the brain along the course of the disease at a population level. Such a model should be established from classical longitudinal anatomical (T1) images, but also from longitudinal DTI in order to capture the patterns of grey and white matter changes. Then, we intend to describe these patterns with a small number of local components (e.g., local sinks to model **matter loss**) with simple interactions. Such a model could then be combined with the previous geometrical and biomechanical models of levels 1 and 2 to simulate the shape evolution of the organ under various assumptions.

WP2: Cardiac Generative Models

Our cardiac models must be able to reproduce the contractions visible in the cardiac images, acquired with any of the classical clinical imaging modalities: MR, CT, US or Nuclear Medicine images. Again, the **first level** of modeling is geometric, and we plan to adjust an average geometric model

[Peyrat et al., 2007] of the heart, which includes the information on the average direction of the main cardiac fibers, to the clinical images of the patient. This is currently done very efficiently with state-of-the-art segmentation and registration tools available in our team.

The **second level** of modeling is the electrical activity of the heart or electrophysiology (EP). We plan to investigate the use of several models of limited complexity, in particular the following Michell Schaeffer (MS) model [Mitchell and Schaeffer, 2003], which is a 2-variable simplified biophysical model derived from the 3-variable Fenton Karma (FK) ionic model [Fenton and Karma, 1998]. It models the transmembrane potential as the sum of a passive diffusive current and several active reactive currents including a fast sodium ion (influx) current, and a slow potassium ion (outflux) current. Unlike FK model, it does not model the calcium ion current. The MS model is described by the following system of Partial Differential Equations:

$$\left\{ \begin{array}{rcl} \partial_t u & = & div(D\nabla u) + \frac{zu^2(1-u)}{\tau_{in}} - \frac{u}{\tau_{out}} + J_{stim}(t) \\ \partial_t z & = & \left\{ \begin{array}{ll} \frac{(1-z)}{\tau_{open}} & if \quad z < z_{gate} \\ \frac{-z}{\tau_{close}} & if \quad z > z_{gate} \end{array} \right. \end{array} \right. \tag{2}$$

where u is a normalised transmembrane potential variable, and z is a gating variable for sodium ion influx which makes the gate open and close, thus describing the depolarisation and repolarisation phase. $J_{in} = (zu^2(1-u))/\tau_{in}$ represents the inward sodium ion current which raises the action potential voltage and $J_{out} = -u/\tau_{out}$ represents the outward potassium ion current that decreases the action potential voltage describing repolarisation. J_{stim} is the stimulation current, at the pacing location. The diffusion term in the model is also controlled by the anisotropic tensor D, as was the case in the previous brain model (cf. Equation 1).

The **third level** of modeling is biomechanical, and must simulate the contraction of the cardiac fibers triggered by the previous electrical model. We plan to investigate several possible models to describe this electro-mechanical coupling, in particular the Bestel-Clement-Sorine model recently revisited by [Chapelle et al., 2011]:

$$\left\{ \begin{array}{l} \dot{k_c} = -(|u| + \alpha|\dot{e}_c|)k_c + k_0|u|_+ \\ \dot{\tau}_c = -(|u| + \alpha|\dot{e}_c|)\tau_c + \dot{e}_c k_c + \sigma_0|u|_+ \\ \sigma_c = \tau_c + \mu\dot{e}_c \end{array} \right. \tag{3}$$

where u is the action potential (electrical activity) described by the previous model (cf. Equation 2), and where k_c, $\dot{e}_c$, τ_c and k_0 are respectively the equivalent stiffness, strain rate, active stress, and maximum stiffness of the sarcomere, σ_c is the total stress and σ_0 maximum value of the active stress. These partial differential equations can be solved for the right and left ventricles with boundary conditions imposing a volume invariance of the ventricle cavities when their valves are closed.

Our current experience [Sermesant et al., 2008] demonstrates that these models produce quite realistic simulations of the electrical conductivity and of the cardiac motion, both for normal and pathological hearts, reproducing for instance the occurrence of re-entry currents due to the presence of scars and inducing a ventricular tachycardia with the risk of a ventricular fibrillation (sudden death). However, these models still suffer from a number of excessive simplifications, and we want to explore a number of drastic improvements that will make them clinically powerful:

- **Hemodynamics** is currently modeled by static pressure fields applied to the boudaries of the cardiac cavities, and by specific Windkessel models in the aortic and pulmonary arteries. We wish to introduce higher level models of the blood motion to produce much more realistic global simulation of the cardiac activity. We plan to collaborate with the group of Dorin Comaniciu in Princeton [Mihalef et al., 2010] to introduce an advanced hemodynamic model.

- Parameters of local **conductivity** and local **contractility** must be personalized for each patient, taking into account the geometry of the vascular territories delimited by the coronary arteries, or more simply, by the conventions of the AHA (American Heart Association). We want to explore the possibility to make these parameters vary within each zone along various constraints to refine the quality of the personalization (e.g., stochastic variations based on the observations).
- The actual **orientation** of the cardiac fibers plays an important role in the electrical and mechanical activity of the heart. For example, the velocity of the depolarisation wave is several times faster in the direction of the cardiac fibers than in the transverse plane. To model the direction of the cardiac fibers, we currently map onto the anatomical images of the patient the average diffusion tensor image obtained from a statistical study of DT images acquired on canine and human hearts [Lombaert et al., 2011]. However, through a joint work in collaboration with the King's College London, we will have access to *in vivo* DT images of patients during the course of this project, and we want to explore the potential improvements this could bring to the simulation of both the electrical and mechanical activity [Toussaint et al., 2010].
- **Remodeling** of the heart is a modification of the shape of the organ and possibly of the orientation of the cardiac fibers, which occur over a period of time due to various pathologies or the action of the therapy. This is a highly complex process that we need to introduce to better predict the longer term effects of therapy (e.g., resynchronization), and we want to explore the development of recent models to our cardiac simulations [Lefevre and Mangin, 2010, Szczerba et al., 2009]. Aging of the patient must be also modeled: this is essential in pediatric cardiology, as already studied in [Mansi et al., 2009].
- **Uncertainty** on the cardiac parameters will be modeled explicity, to better quantify the assesments induced from the simulation, and to better constrain the personalization of the parameters.

WP3: Image Simulation

The previous models simulate the evolution of the anatomy and physiology of the brain and the heart under various conditions. This workpackage will explore how to exploit these new generative models of organs and pathologies to create realistic and multimodal dynamic images of virtual healthy controls and patients, with the remarkable advantage that all the parameters of the generative models will be readily available along with any image of the database. This advantage will be exploited extensively in the next *personalization* workpackage, (WP4).

- **Brain models:** the strategy will be to use a physical model of image formation, exploiting a number of simulators which are made available to our scientific community, e.g., the MRI simulator developed at the McConnell Brain Imaging Centre in Montreal around the Brainweb environment [Aubert-Broche et al., 2006], the multimodal image simulator developed by the Creatis group in Lyon (Fr) [Benoit-Cattin et al., 2005], or the MR simulator for brain tumors of University of Utah [Prastawa et al., 2009]. Based on the parameters and variables of our brain tumor models, we will generate time series of MR images corresponding to the typical or advanced image sequences used in the clinic. For brain tumors we will simulate, for instance, T1 and T2 weighted images, Flair sequences, Gadolinium enhanced T1 images, based on the knowledge of the geometry of the patient's anatomy (white matter, grey matter, CSF, skull, etc.) as well as the knowledge of the tumoral cell density in each voxel. More advanced tumor models, including quiescent cells, necrotic cells, edema cells, etc., can easily be introduced to refine further the simulated images. Simulation of dynamic images of patients with Alzheimer's disease will be simulated with a similar strategy, taking advantage of the knowledge of the decay rate of white or grey matter in each region, and having simulated the resulting local apparent

deformation field. Simulation of other modalities like MR Spectroscopy, or CT or US or PET will also be explored in this workpackage whenever necessary.

- **Cardiac models:** we will explore mainly another strategy, motivated by the fact that our models do not describe completely the upper shape of the organ nor the neighboring anatomical structures. Therefore we plan to exploit our currently available large databases of patients, like the ones of the cardiac atlas project www.cardiacatlas.org or of the St. Thomas Hospital London to create new time series of realistic images with the following method. We select a patient or a healthy control, and adjust the first image of the patient to the geometry of our model at a reference time of the cardiac cycle (e.g., end of diastole, or mid-diastole). Then, we create a dynamic time series of cardiac images corresponding to the simulated motion of our model by simply deforming the original images of the patient so that they correspond to the motion predicted by the model. With this approach, we can produce new databases of extremely realistic images of controls and patients with cardiac pathologies for which we will know perfectly the parameters of the underlying cardiac model.

WP4: Model Personalization

This workpackage explores the best strategy to personalize the previous models (i.e. identify their parameters) from dynamic medical images, so that they correspond to a specific patient.

The model personalization includes geometric and biophysical personalization. While geometric personalization is fairly mature (creating computational meshes from images), biophysical personalization from medical images is still in its infancy. Current approaches have limitations: a) There is still a debate about which biophysical models are most suitable for personalization: trade-off between versatility and identifiability [Fink and Noble, 2009]. b) Personalization methods are mathematically rather complex, very demanding in terms of computational resources and are mostly borrowed from other fields (control theory, weather forecast, oceanography, mechanics...). c) Current approaches often do not take into account the uncertainty in the information extracted from images and do not provide uncertainty on the estimated parameters. d) On top of the previous issues, there is often a lack of clinical images with ground-truth values to train and benchmark personalization methods.

To overcome these limitations, **first**, we will use the large datasets of realistic simulated images with the ground-truth values of WP3 to explore various personalization methods and benchmark them quantitatively. We will also use the databases of simulated images to train supervised machine learning algorithms to predict various combinations of biophysical parameters of the generative models from various combination of visual geometric and kinetic (motion) features extracted from the images. **Second** we will include uncertainty in the personalization methods by propagating uncertainty from the images to the estimated parameters. **Third** we will develop new biophysical personalization methods based on *dedicated i) machine learning and ii) variational methods.*

i) Machine Learning Methods: The relationship between medical images and biophysical parameters can be learned from a training set consisting in sets of simulated images (see WP3) along with the biophysical parameters used to produce the simulations. This requires to define and select invariant iconic and motion features (such as local or regional distances, displacements or strains) as an input to machine learning methods such as kernel ridge regression [Prakosa et al., 2010], support-vector-machine regression, manifold learning, marginal space learning [Zheng et al., 2009], or random forests[Criminisi et al., 2010] [Geremia et al., 2010]. As output, these machine learning algorithms can provide density probability function for each parameter or the most likely set of parameters with a confidence measure. This approach may not only be used to estimate biophysical parameters (e.g., conductivity, contractility, diffusivity) from images and signals but also initial conditions (e.g. location of an ectopic focus in electrophysiology, initial source point of a brain tumor) and any physical

quantity that results from biophysical simulations (e.g. active stress in the myocardium, depolarization times). We believe that the key for success is to produce a large number of realistic simulated images that cover a broad number of pathologies and geometries, corresponding to a large population of patients and involving stochastic processes [Marzouk and Najm, 2009]. This large production of simulated images can be performed through clusters of PCs or grid computing [Xiu, 2009].

ii) Variational Methods: The parameters can be estimated directly through the minimization of a functional, which measures the discrepancy between simulated quantities and observed ones and possibly additional terms capturing the prior knowledge on the parameters. There are numerous ways to optimize those functionals among which are the Adjoint method used for instance by [Sundar et al., 2009], or derivation-free optimization methods [Zaslavski and Powell, 2006]. We are specially interested in the latter type of methods but with radically new approaches : for instance combining machine learning to initialize the set of parameters (see previous paragraph) and parallel computing to quickly explore the functional close to the optimal set of parameters. To ensure robustness and efficiency we will apply a coarse to fine strategy, starting with the most important parameters first and then refining (sensitivity analysis will be used to estimate the most important parameters). We will constrain the parameter values to be within a range provided from the literature and/or from a previous statistical analysis [Pennec and Joshi, 2008, Young and Frangi, 2009]. We will also add a regularization term in the energy that corresponds to some *a priori* or acquired knowledge on the statistical distribution of the parameters.

WP5: Clinical Applications

We plan to evaluate the power of the tools developed in this proposal on a number of clinical databases of patients and in close collaboration with world leading physicians and clinical centers.

i) Brain tumors: The clinical evaluations will be done in close collaboration with the German Cancer Research Center (Heidelberg) on a large database of MR images of patients followed for brain tumors in longitudinal studies of several years. Each exam includes multiple MR sequences (T1, T2, Flair, GdT1, etc.) as well as diffusion tensor images (DTI) and possibly spectroscopic MRIs. We also plan a close collaboration with Emmanuel Mandonnet (Neurosurgeon in Lariboisiere Hospital, Paris) who has also collected an important database of longitudinal studies of brain tumors.

We will adjust our biophysical models of brain tumors to time series of MR images of patients with gliomas of varying types (from low grade to high grade gliomas), and evaluate the clinical value of the estimated proliferation and diffusion parameters for the diagnosis and prognosis. This will be done retrospectively on the available databases, using for instance the first time points of a time series to predict the evolution at the next time points.

We will also investigate the prediction of the infiltration of the tumor beyond the visible boundary at a given time point based on the adjustment of the biophysical model on the time series images until this time point. We will try to evaluate the actual extension of the tumor with the one predicted by the model with two strategies. The first one will be to study the location of tumor recurrences for patients undergoing a radiotherapy or a surgery with a margin of security of 2 cm around a tumor, which is the current practice, and to correlate retrospectively the location of such recurrences with the predicted extension of the tumor infiltration. The second strategy would be to exploit *in vivo microscopic images* like the ones provided by the Cellvizio www.maunakeatech.com, to explore during neurosurgery the cell architecture around the visible boundary of the tumor. Such an approach was demonstrated recently with a prototype imaging systems [Lerch et al., 2008], and it is likely that clinical solutions will become available during the course of this project. As N. Ayache has a longstanding collaboration

with the company MKT producing the Cellvizio and he will be informed of the availability of such images during the course of this project.

ii) Alzheimer's disease: The clinical evaluation will be done in collaboration with Pitie Salpetriere (Didier Dormont and Olivier Colliot), NeuroSpin (J.F. Mangin), UCL (Nick Fox and Sebastien Ourselin), and Univ. of Brescia (G. Frisoni) to exploit databases of longitudinal MR images of patients (with or without DT images) acquired at these centers or with the publicly available ADNI database http://adni.loni.ucla.edu. We will combine our new biophysical model with our current geometrical models [Lorenzi et al., 2010] to better detect and quantify local atrophy of the brain. We will also use the new model to simulate a future evolution, and we will compare retrospectively the estimated prognosis with the actual evolution of the patients. We will produce databases with simulated time series of patients with various forms of brain atrophy. If realistic enough, these databases will be made publicly available, and will be used to to benchmark competing medical image analysis methods.

iii) Cardiac application: The clinical evaluation will be done in collaboration with KCL and St Thomas Hospital (Reza Razavi, Philipp Beerbaum), and with Bordeaux Hospital (Michel Haissaguerre, Pierre Jais), where large databases of cardiac images with electrophysiology data are available. We will also have access to a large database of cardiac MR Images from the cardiac atlas project (www.cardiacatlas.org) thanks to a collaboration with Alistair Young in New Zealand.

First, we will adjust the electrical model on the cardiac images and EP signals of patients with arrhythmia to simulate clinical ventricular tachycardia procedures (VT-Stim) on virtual anatomical models. These simulations will be compared to the actual VT-Stim procedure delivered on the same patients, to assess the quality of the model personalization and the predictive power. We will produce maps showing the potential risk of inducing a VT from every point in the ventricular cardiac tissues, both endocardia, epicardia, and in between. These maps will be compared retrospectively to clinical data to assess their predictive potential [Relan et al., 2010, Cochet et al., 2011].

We will also adjust the electro-mechanical models on cardiac images and EP signals of patients. Will will study the biophysical parameters of the model in collaboration with the physician to better understand and quantify a number of cardiac dysfunctions, in particular the asynchrony between left and right ventricles. We will simulate cardiac resynchronization therapy with various positions of the pacemaker leads, and various delays between the stimulation signals, to optimize the cardiac function on the virtual cardiac model. We will compare the simulations with real implantations of pacemakers on patients to assess the predictive power of the models.

Finally, we will use the biophysical parameters of our personalized models to index images in large databases of cardiac images, with the objective of retrieving similar time series of images with the patient history attached to these images. We will compare the performances of this image retrieval strategy with other strategies based on the use of shape and motion parameters extracted on each time series of images.

Conclusion

This study will introduce **pioneering** and **influential methodologies** for the analysis of dynamic medical images. It will bring methodological **breakthroughs** and will be applied to several **high impact clinical applications** for which it will provide prototypes of new image analysis tools, new synthetic databases, new biomarkers and new indexing techniques. It will allow an accurate detection and quantification of the selected diseases, a precise planning and delivery of therapy, thus supporting medicine to move from reactive to **predictive** and **personalized**. These results will stimulate further development and validation with several of our world class clinical and industrial partners to promote Europe as a world leader in the computational exploitation of dynamic medical images.

Acknowledgments

The MedYMA proposal owes a lot to a number of colleagues, in particular the permanent researchers of Asclepios, O. Clatz, H. Delingette, G. Malandain, X. Pennec, M. Sermesant, our project assistant I. Strobant, and our PhD students, postdoctoral students and research engineers. Special thanks to F. Lavirotte and J.-P. Banatre for their help while preparing this document. The proposal also owes a lot to the support of our clinical, industrial and academic partners from all around the world.

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2c. Resources

(i) The team members

The team members are the PI (N. Ayache) and the other members of the Asclepios team, including currently 5 more permanent researchers (O. Clatz, H. Delingette, G. Malandain, X. Pennec and M. Sermesant), about 14 PhD students, 5 research engineers and 2 post-docs. All team members will directly or indirectly contribute to the ideas and expertise of MedYMA.

N. Ayache will be directly involved for at least 70% of his time, to conduct and supervise the research activities of MedYMA. He will receive the precious help of H. Delingette, M. Sermesant and X. Pennec on the computational anatomy and computational physiology components of this proposal, for at least 20% of their time. (cf. page 11 of part B1, "The Right Team"). The research activities of G. Malandain, world expert in biomedical image analysis, will also contribute to this proposal.

Olivier Clatz is currently working on the creation of a spin-off company around the MedINRIA software library with most of the research engineers of the team. The actual creation is likely to happen in 2012. Olivier and the involved engineers will stay close to INRIA and to our team, and this spin-off can be a strong asset for the dissemination of the new tools emerging from this proposal.

We will also invite for short periods and on a regular basis a number of world leader scientists and clinicians from collaborating groups in France and abroad to contribute to this study and promote European leadership in the computational analysis and simulation of dynamic medical images.

(ii)Available resources

In 2012, among our current European projects, only Care4me, Euheart and VPH will still be active, for a maximum remaining amount of 570Keuros. These projects will stop before the end of year 2012.

The funding of projects Neurolog and Karametria, from the French funding agency (ANR), will also end in 2012.

For the period 2011-2014, we obtained a new funding from Microsoft Research (MSR) Cambridge (UK), and from the MSR-INRIA research center of Saclay, for a total amount of 360Keuros.

All this funding will provide additional resources for the Asclepios activities in medical image analysis, and will be in synergy with the MedYMA proposal.

The Asclepios team is equipped with numerous PCs and has access to a large PC cluster owned by INRIA Sophia Antipolis.

(iii) Requested resources and project costs.

Personnel costs:

- 70% of PI's salary over 5 years with a 70% commitment of his time.
- 20% of 3 PI's close collaborators over 5 years with a 20% commitment of their time.
- Full-time post-doctoral researcher during last 2 years
- 2 full-time research engineers during 2.5 years covering the 5 years of the project
- 2 full time PhD students during years 1,2,3
- 1 full time PhD student during years 2,3,4
- 1 full time PhD student during years 3,4,5
- 4 men-months of invited professors in years 1, 2,3,4 plus 2 men-months in year 5 (total 18MM)

Other direct costs:
• 30KEuros of travel per year for 5 years to visit our partners and attend international conferences.
• 25KEuros during years 1 to 3 to upgrade our PCs and contribute to the upgrade of the common INRIA cluster in Sophia Antipolis.
The rest of the costs consists of eligible indirect costs, at the rate of 20% of the direct costs. The grand total amounts to 2,498,327Euros over a period of 5 years, as detailed in the table below. Please note that the first 4 lines correspond respectively to 70% of PI's salary, followed by 20% of the salaries of H. Delingette, X. Pennec and M. Sermesant.

	Cost Category	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Direct Costs:	*Personnel:*						
	PI[1] Research Director- DR0	117 823	119 268	120 748	122 240	123 253	603 332
	Research Director- DR1	28 477	28 902	29 337	29 776	30 075	146 567
	Research Director- DR2	21 286	21 607	21 932	22 260	22 484	109 569
	Qualified Scientist- CR1	16 157	16 401	16 646	16 896	17 067	83 167
	Post Doc 1	0	0	0	48 278	48 762	97 040
	Engineer 1	56 639	57 205	28 888	0	0	142 732
	Engineer 2	0	0	28 888	58 355	58 938	146 181
	PhD Student 1	41 541	41 956	42 376	0	0	125 873
	PhD Student 2	41 541	41 956	42 376	0	0	125 873
	PhD Student 3	0	41 956	42 376	42 800	0	127 132
	PhD Student 4	0	0	42 376	42 800	43 228	128 404
	Invited Professor 1	12 240	0	0	0	0	12 240
	Invited Professor 2	0	12 362	0	0	0	12 362
	Invited Professor 3	0	0	12 486	0	0	12 486
	Invited Professor 4	0	0	0	12 611	0	12 611
	Invited Professor 5	0	0	0	0	6 370	6 370
	Total Personnel :	**335 704**	**381 613**	**428 429**	**396 016**	**350 177**	**1 891 939**
	Other Direct						
	Equipment (Cluster)	8 400	8 300	8 300	0	0	25 000
	Travel	30 000	30 000	30 000	30 000	30 000	150 000
	Workshop	0	15 000	0	0	0	15 000
	Total Other Direct Costs:	**38 400**	**53 300**	**38 300**	**30 000**	**30 000**	**190 000**
	Total Direct Costs:	**374 104**	**434 913**	**466 729**	**426 016**	**380 177**	**2 081 939**
Indirect Costs (overheads):	**Max 20 % of Direct Costs**	**74 821**	**86 983**	**93 346**	**85 203**	**76 035**	**416 388**
Subcontracting Costs:		0	0	0	0	0	0
Total Costs of project:	**(by year and total)**	**448 925**	**521 896**	**560 075**	**511 219**	**456 212**	**2 498 327**
Requested Grant:	**(by year and total)**	**448 925**	**521 896**	**560 075**	**511 219**	**456 212**	**2 498 327**

For the above cost table, please indicate the % of working time the PI dedicates to the project over the period of the grant:	**70%**

The funded **4 PhD students** will have their research devoted to the design of the biophysical and statistical models required to address the 4 main brain and cardiac diseases of this proposal. There will be a lot of synergy between their works, in particular in the design of innovative image simulation and model personalization methods. The funded **research engineers** and **post-doc** will help stabilize the software modules designed for the personalization of models and the simulation of images, as well as for the construction of new databases of images to be made available to the scientific community.

We expect several researchers among our current partners (clinical, academic, industrial) to visit us each year and participate to MedYMA. We will also welcome talents from new groups who could bring a complementary expertise to the success of MedYMA. These visits will be funded in part by the "invited professors" budget above, and in part by INRIA and other resources.

We will also organize a workshop early after the beginning of MedYMA to make it known to the international community, and to help attracting talented scientists for the success of MedYMA.

2d. Ethical issues

Please see the Ethical Issues Tables **and the uploaded Annex** for an explanation of the ethical issues involved with medical imaging datasets, and how they will be dealt with appropriately.

N. Ayache Part B2 MedYMA

d. Ethical issues

ETHICS ISSUES TABLE

Areas Excluded From Funding Under FP7 *(Art. 6)*

(i) Research activity aiming at human cloning for reproductive purposes;

(ii) Research activity intended to modify the genetic heritage of human beings which could make such changes heritable (Research relating to cancer treatment of the gonads can be financed);

(iii) Research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer;

All FP7 funded research shall comply with the relevant national, EU and international ethics-related rules and professional codes of conduct. Where necessary, the beneficiary(ies) shall provide the responsible Commission services with a written confirmation that it has received (a) favourable opinion(s) of the relevant ethics committee(s) and, if applicable, the regulatory approval(s) of the competent national or local authority(ies) in the country in which the research is to be carried out, before beginning any Commission approved research requiring such opinions or approvals. The copy of the official approval from the relevant national or local ethics committees must also be provided to the responsible Commission services.

	Research on Human Embryo/ Foetus	YES	Page
	Does the proposed research involve human Embryos?		
	Does the proposed research involve human Foetal Tissues/ Cells?		
	Does the proposed research involve human Embryonic Stem Cells (hESCs)?		
	Does the proposed research on human Embryonic Stem Cells involve cells in culture?		
	Does the proposed research on Human Embryonic Stem Cells involve the derivation of cells from Embryos?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	x	

	Research on Humans	YES	Page
	Does the proposed research involve children?	x	WP5-p20
	Does the proposed research involve patients?	x	WP5-p20
	Does the proposed research involve persons not able to give consent?		
	Does the proposed research involve adult healthy volunteers?	x	WP5-p20
	Does the proposed research involve Human genetic material?		
	Does the proposed research involve Human biological samples?		
	Does the proposed research involve Human data collection?	x	WP5-p20
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL		

N. Ayache Part B2 MedYMA

	Privacy	YES	Page
	Does the proposed research involve processing of genetic information or personal data (e.g. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?		
	Does the proposed research involve tracking the location or observation of people?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	x	

	Research on Animals[1]	YES	Page
	Does the proposed research involve research on animals?		
	Are those animals transgenic small laboratory animals?		
	Are those animals transgenic farm animals?		
	Are those animals non-human primates?		
	Are those animals cloned farm animals?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Research Involving non-EU Countries (ICPC Countries[2]) [3]	YES	Page
	Is the proposed research (or parts of it) going to take place in one or more of the ICPC Countries?		
	Is any material used in the research (e.g. personal data, animal and/or human tissue samples, genetic material, live animals, etc) : a) Collected in any of the ICPC countries?		
	b) Exported to any other country (including ICPC and EU Member States)?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Dual Use	YES	Page
	Research having direct military use		
	Research having the potential for terrorist abuse		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

If any of the above issues apply to your proposal, you are required to complete and upload the "B2_Ethical Issues Annex" (template provided).

Without this Annex, your application cannot be properly evaluated and even if successful the granting process will not proceed.
Please see the Guide for Applicants for the Advanced Grant 2011 Call for further details and CORDIS http://cordis.europa.eu/fp7/ethics_en.html for further information on how to deal with Ethical Issues in your proposal.

[1] The type of animals involved in the research that fall under the scope of the Commission's Ethical Scrutiny procedures are defined in the Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes Official Journal L 358 , 18/12/1986 p. 0001 - 0028
[2] In accordance with Article 12(1) of the Rules for Participation in FP7, 'International Cooperation Partner Country (ICPC) means a third country which the Commission classifies as a low-income (L), lower-middle-income (LM) or upper-middle-income (UM) country. Countries associated to the Seventh EC Framework Programme do not qualify as ICP Countries and therefore do not appear in this list.
[3] A guidance note on how to deal with ethical issues arising out of the involvement of non-EU countries is available at:
ftp://ftp.cordis.europa.eu/pub/fp7/docs/developing-countries_en.pdf

ERC Advanced Grant
Research proposal (B2 Ethical Issues Annex)[1]

Ethical Annex (max 2 pages of text[2]):

If the answer to any of the questions of the Ethical Issues Table (in part B2) is YES, you must provide a brief explanation of the ethical issue involved and how it will be dealt with appropriately.

Please specify as well any authorization or permission you already have for the proposed work and include copies (the copies do not count towards the page limit).

Please upload this Ethical Issues Annex and any related documents in the 'Extra Annexes Upload' section included in the EPSS tab 'Part B & Annexes'.

Please see the Guide for Applicants and CORDIS http://cordis.europa.eu/fp7/ethics_en.html for further information on how deal with Ethical Issues in your proposal.

The MedYMA proposal describes research on the automated simulation and analysis of medical images. It has 4 methodological packages and 1 experimental workpackage, called WP5, in which we plan to experiment the image processing software tools designed and developed in the previous workpackages on databases of medical images of patients and healthy volonteers.

We are convinced that this proposal should not raise any ethical problem for the following reasons:

1. We do not intend to acquire any clinical data in the proposal; we will be acting as user on it.
2. We already have a longstanding experience in our research team Asclepios with medical images of real patients. All the databases mentioned in the proposal are already accessible and used by our team, except the database from the Cardiac Atlas Project for which we are just currently finalizing an authorization protocol to start during the first half of year 2011.
3. All the databases of images mentioned in the proposal were acquired by accredited hospitals following strict ethical rules applied in occidental countries like France, UK, Germany, and USA. In such a context, acquisitions either refer to standard clinical practices or to specific research protocols being approved from an appropriate ethics committee. In the latter case, subjects have provided their explicit consent for multiple uses of their anonymized data. The proposal MedYMA aims at developing and testing new image analysis tools on those already acquired and available databases of Medical Images.
4. All these databases were anonymized by the accredited hospitals before they were made available to us, so we do not have access to the identity of the persons, only to anonymous data like the age, gender, disease, etc

We sincerely believe that these explanations will reinsure the ethical committee, and we will stay at the disposal of the committee to provide any additional details upon request.

[1] Instructions for completing Part B2 can be found in the Guide for Applicants on ERC Grant Schemes
[2] This Ethical Annex does not count towards 15 page limit