Direction des Relations Européennes et Internationales (DREI)

Programme INRIA "Equipes Associées"

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I. DEFINITION

EQUIPE ASSOCIEE	CompuTumor
sélection	**2007**

Projet INRIA : ASCLEPIOS	Organisme étranger partenaire : HARVARD
Unité de recherche INRIA : INRIA SOPHIA ANTIPOLIS Thème INRIA : BIO	Pays : ETATS UNIS

	Coordinateurs français		Coordinateur étranger
Nom, prénom	Nicholas Ayache, PhD	Olivier Clatz, PhD	Simon Warfield, PhD
Grade/statut	Directeur de Recherche	Chargé de Recherche	Associate Professor
Organisme d'appartenance	INRIA Sophia Antipolis, Projet Asclepios		Harvard Medical School, Computational Radiology Laboratory
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In addition to the two aforementioned research teams, this proposals aims at grouping together the effort in neuro-oncology of different laboratories in Boston and Nice. Details about all concerned teams can be found in Table I and II.

American Institution	Brigham & Women's Hopital		Harvard	Mass General Hospital
Name	William Wells, PhD	Ron Kikinis, MD	Robert Howe, PhD	Thomas Deisboeck, MD
Academic Position	Associate Professor	Professor	Gordon McKay Professor of Engineering	Assistant Professor
Laboratory	BWH, Surgical Planning Laboratory.		Harvard, Biorobotics Laboratory	MGH, Complex Biosystems Modeling Laboratory
Mailing adress	Department of Radiology Brigham and Women's Hospital 75 Francis St. Boston, MA 02115 USA		Biorobotics Laboratory 323 Pierce Hall, 29 Oxford Street Cambridge, MA 02138, USA	Martinos Center for Biomedical Imaging, MGH-East, Room 2301 Building 149, 13th Street Charlestown, MA 02129 USA
URL	WELLS	KIKINIS	HOWE	DEISBOECK
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American Institution	MIT		CIMIT
Name	Eric Grimson, PhD	Polina Golland, PhD	Steven Dawson, MD
Academic Position	Bernard Gordon Professor of Medical Engineering	Assistant professor	Associate Professor
Laboratory	MIT- Computer Science and Artificial Intelligence Laboratory		CIMIT Simulation Group
Mailing adress	MIT CSAIL 32 Vassar Street 32-D470 Cambridge, MA 02139 USA		Simulation Group 65 Landsdowne Street Cambridge MA 02139-4232 USA
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Email	welg[at]csail.mit.edu	polina[at]csail.mit.edu	sdawson[at]partners.org
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Table I. American partners involved in the proposal.

French Institution	CHU Pasteur		Centre Antoine Lacassagne - Nice	
Name	Stéphane Litrico, MD	Philippe Paquis, MD	Marc Frenay, MD	Pierre-Yves Bondiau, MD, PhD
Academic Position	Chef de clinique, PH	Chef de service, PU PH	Oncologue	Radiothérapeute
Laboratory	CHU Pasteur, service de Neurochirurgie		Service d'Oncologie Médicale	CAL - Departement de Radiothérapie
Mailing adress	Service de Neurochirurgie - Hôpital Pasteur 30 avenue de la Voie Romaine 06000 Nice France		Service d'Oncologie Médicale Centre Antoine Lacassagne 33 avenue de valombrose 06189, Nice, France	Radiotherapy Department Centre Antoine Lacassagne 33 avenue de valombrose 06189, Nice, France
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Table II. French partners involved in the proposal.

La proposition en bref

Titre de la thématique de collaboration : **Computational Brain Tumor - Modèles Algorithmiques de Croissance de Tumeurs**
Descriptif **:** The CompuTumor project is dedicated to the study of brain tumor models and their confrontation with medical images to better assist diagnosis and therapy. The project will strongly enhance the current collaborations between INRIA and a group of world leading teams with complementary technical and clinical expertise on these topics in Boston and Nice. The proposal is divided into 4 main themes of research, each theme involving at least 2 foreign partners. The first theme is dedicated to the brain tumor models, their evaluation and use in clinical applications. The second theme is dedicated to the develpment of new algorithms for real time image guided neurosurgery using 3D ultrasound imaging. The third theme is dedicated to the study of the variability of the white matter architecture and its influence on brain tumor growth. The objective of last theme of this proposal is the development of a neurosurgery simulator to train young surgeons to practice tumor resections. We believe that these four research themes nicely complement each other to bring significant advances in the future understanding, diagnosis and treatment of brain tumors. Le projet CompuTumor a pour objectif l'étude de modèles algorithmiques de croissance de tumeurs et leur confrontation à des images médicales pour mieux assister le diagnostic et la thérapie. Le projet doit permettre de renforcer de façon significative les collaborations actuelles entre l'INRIA et un ensemble d'équipes leaders disposant d'expertises complémentaires à la fois techniques et cliniques, à Boston et Nice. La proposition est divisée en quatre thèmes de recherche, chacun impliquant au moins 2 équipes de Boston. Le premier thème concerne les modèles de tumeurs cérébrales, leur évaluation et leur utilisation clinique. Le second thème est dédié au développement de nouveaux algorithmes pour l'utilisation per-opératoire des échographies 3-D en neurochirurgie. Le troisième thème est dédié à l'étude de la variabilité de l'architecture de la matière blanche et à son influence sur la croissance tumorale. L'objectif du quatrième et dernier thème est le développement d'un simulateur de neurochirurgie permettant l'entrainement des jeunes chirurgiens au geste de résection de tumeur. Nous pensons que ces quatre sujets de recherche sont complémentaires et participeront à des avancées importantes pour la compréhension, le diagnostic et le traitement des tumeurs cérébrales dans le futur.

Présentation de l'Équipe Associée

(environ 2 pages)

1. Présentation du coordinateur étranger

Dr. Warfield is the Director of the Computational Radiology Laboratory (CRL) in the Department of Radiology at Children's Hospital, a Research Associate in the Surgical Planning Laboratory, a Research Affiliate of the Artificial Intelligence Laboratory at the Massachusetts Institute of Technology and an Associate Professor of Radiology at Harvard Medical School.

Dr. Warfield founded the Computational Radiology Laboratory in 2001. The CRL was formed with the mission of improving our understanding of the structure and function of the brain and other organs of the human body, in order to improve our capacity to diagnose and treat disease. Members of the CRL achieve this by developing novel technologies and computational modeling strategies for understanding and interpreting radiological images.

His research in the field of medical image analysis has focused on methods for quantitative image analysis through novel segmentation and registration approaches, and in real-time image analysis, enabled by high performance computing technology, in support of surgery. A brief summary of Dr. Warfield's research interests is here.

Before joining Brigham and Women's Hospital in June 1996, he studied for a PhD at the School of Computer Science and Engineering of the University of New South Wales, in Sydney, Australia. His PhD in Computer Science and Engineering was awarded in April 1997.

Professional Experience:

- 1996-1998 Research Fellow, Dept. of Radiology, Brigham and Women's Hospital (BWH), Harvard Medical School
- 1998-2001 Instructor in Radiology, Harvard Medical School
- 2001- Assistant Professor of Radiology, Harvard Medical School
- 2004- Associate Professor of Radiology, Harvard Medical School
- 2004- Director, Computational Radiology Laboratory, Children's Hospital and BWH

Relevant Research Projects Ongoing or Completed During the Last 3 Years

- NIH R01 RR021885 - Bioinformatics Software for MRI of Brain Development
  Principal Investigator: Warfield, Simon K. Ph.D. 8/1/06-7/31/10
- Brigham Radiology Research and Education Foundation - Quantitative Assessment of Structural Neonate Brain Changes Associated with Periventricular Leukomalacia
  Principal Investigator: Warfield, Simon K, Ph.D. 1/1/03—12/31/06
- Whitaker Foundation - Characterization of Newborn Brain Development
  Principal Investigator: Warfield, Simon K, Ph.D. 1/1/02—06/30/06
- NIH NIMH R21 MH067054 - White Matter Architecture of Cognitive Dysfunction
  Principal Investigator: Warfield, Simon K. Ph.D. 12/01/03-11/30/06
- ITR: Collaborative Research - NSF 0426558 - ASE - DMC - DDDAS: A Novel Grid Architecture Integrating Real-Time Data and Intervention During Image Guided Therapy
  Principal Investigator: Warfield, Simon K. Ph.D. 10/1/04—09/30/06

A detailed version of Dr. Warfield's CV can be found here.

2. Historique de la collaboration

2.1. entre les équipes :

There is a long history of collaboration and shared research interests between the different teams. In the past, these collaborations mainly consisted in exchange or visit of researcher and PhD students between the Epidaure team and the American partners. We listed below the main interactions between the involved teams for the past 5 years:

- In 2003, Simon Warfield Director of the Computational Radiology Laboratory was invited to give a lecture entitled "Capturing Brain Deformation" at the IS4TM Symposium in Juan les Pins organized by Nicholas Ayache and Hervé Delingette.
- In 2004, Robert Howe Director of the Biorobotics Laboratory of Harvard, took a sabbatical in the Epidaure Research Project.
- In 2004, Olivier Clatz was a research assistant at the Surgical Planning Laboratory. During his time spent at the SPL, Olivier worked on 2 research subjects:
  - The estimation of intraoperative brain deformation during brain tumor resection for real-time surgical planning update.[1], [2], [3]
  - Modeling the growth of gliomas in the brain including the fiber direction information and the biomechanical effect.[4], [5]
- In 2004 Olivier Clatz was a visiting scientist at the Biorobotics Laboratory of Harvard. He worked on real time integration of a tactile display with a finite element model [6].
- In 2004, Marius Linguraru shared a Postdoctoral Fellow position between Epidaure Research Project and Harvard Biorobotics Laboratory. Marius developed algorithms for the robust segmentation and tracking of instruments and tissue as part of a common work in echocardiography for computer-assisted minimally invasive surgery and image-guided robotics surgery.
- Until the end of 2006 Olivier Clatz will be a Research Associate at the Computational Radiology Laboratory. Olivier works on studying the sensitivity of Diffusion Tensor Imaging for multiple sclerosis diagnosis.
- In 2006, INRIA and CIMIT created the Simulation Open Framework Architecture (SOFA). This objective of this consortium including different INRIA teams (Alcove, Epidaure, Evasion) is to develop a flexible kernel for simulation software.
- In the past, several PhD students from Epidaure Research Project did a post-doc at SPL and CRL: Alexandre Guimond 2000-2003 [7] [8] [9] [10], Karl Krissian 2001-2005 [11], Julien Dauguet 2005-2006 [12].

2.2. entre l'INRIA et l'organisme partenaire :

The collaborations between INRIA, MIT and Harvard are numerous. Bellow are only listed the collaboration in the specific field of medical imaging.
Geographic area : United States (see the INRIA DREI website)
In 2006, Jean-Jacques E. Slotine, professor at MIT took a sabbatical at Odyssee - INRIA
In 2006, Pierre Jannin (INRIA - Visages team) and Simon Warfield (Harvard medical School, CRL) were guest editors of a special Issue on Validation in Medical Image Processing in IEEE Transactions on Medical Imaging.
In 2003, Florent Ségonne (MIT - CSAIL) was a visiting research fellow at Odyssee - INRIA, leading to a joint publication [13].
In 2002, Lilla Zollei (MIT - CSAIL) was a visiting research fellow at Odyssee - INRIA
In 2002, Simon Warfield (Harvard medical School, CRL) co-authored a book chapter with Alexandre Guimond and Alexis Roche (PhDs from Epidaure - INRIA) [14]
In 1998, Liana Iorigo (MIT - CSAIL) was a visiting research fellow at Odyssee - INRIA
For many years, Olivier Faugeras was an Adjunct Professor of Electrical Engineering and Computer Science at MIT.

3. Impact :

- **3.1.** *sur la collaboration déjà existante avec votre partenaire*

This research proposal is a unique opportunity of acknowledging the collaboration record between the French and the American institutions.
It is a chance to strengthen the link between partners through an official established partnership. Sharing data will be made easyer through the formalism of this proposal.

- **3.2.** *sur la collaboration avec d'autres projets INRIA*

Different research teams at INRIA could benefit from such a collaboration.
The Odyssee team shares a common interest with MIT, CRL and SPL on level-set methods for registration and segmentation in medical imaging, as well as for the analysis of diffusion tensor MR images.
The SPL has a world leading expertise in image guided therapy, with several on-going project. Connection with INRIA team Visage could be possible.
The CRL and SPL are also interested in EEG and MEG inverse problems for epilepsy treatment. This topis is one of the research themes of Odyssee. Such problems are also closely related to numerical methods and mesh generation, addressed in the INRIA ARC HeadExp. Potential collaborations could then follow with research teams Geometrica and Caiman.
Thomas Deisboeck, Director of the Complex Biosystems Modeling Laboratory created a consortium dedicated to tumor growth modeling: the Center for the Development of a Virtual Tumor (CVIT). The Asclepios Team recently joined this consortium. This collaboration could be extended to the INRIA teams Bang and Comore.

- **3.3.** *sur la collaboration avec d'autres équipes de l'organisme étranger partenaire.*

Through the three coordinators of the project, Nicholas Ayache, Olivier Clatz and Simon Warfield, this proposal aims at supporting existing collaborations with the Surgical Planning Laboratory (Ron Kikinis, William Wells) and Harvard Biorobotics Laboratory (Robert Howe), as well as intensifying more recent collaborations with MIT (Polina Golland) and MGH (Thomas Deisboeck).

II. PREVISIONS 2007

Programme de travail

The CompuTumor project is dedicated to the study and development of brain tumor models for improved therapy. This project aims at expanding the work of Asclepios in computational brain tumor through the collaboration with world class leaders showing expertise in complementary research domains. This proposal is divided into 3 main themes of research, each of which involving at least 2 American partners. The first theme is the development of the tumor model, its evaluation and use for clinical applications. The second theme aims at developing new algorithms for real time image guided neurosurgery using 3D ultrasound. The third theme objective is to study the variability of the white matter architecture and its influence on brain tumor growth. The last theme of this proposal is dedicated to the development of a neurosurgery simulator.

1. Brain Tumor Growth Modeling.

We proposed in [4] a new model to simulate the 3D growth of gliomas. This model describes at a macroscopic scale the growth of the tumor in the brain parenchyma with an anisotropic partial differential equation. This equation is composed of a diffusion term describing the invasion of the tumor in the brain tissue, and the logistic law as a reaction term. We recently proposed a new formulation to estimate the invasion margin of a tumor by extrapolating low tumor densities in MRIs [19]. Our formulation is based on the Fisher-Kolmogorov equation that is been widely used to model the growth of brain tumors. This work is among the first ones to propose an evaluation of computational tumor models with medical images. The results we obtained were promising, although their impact was limited because of the small number of cases. This proposal will contribute to evaluate the model on larger datasets, develop algorithms to characterize the tumor in medical images, and enrich the model with new concepts. The specific aims are:

- Simulate the tumor growth on larger dataset available at the Brigham and Women's Hospital. Through this series of experiments, we want:
  - to demonstrate the relevance of the model for the simulation of various diffusive tumors. The objective is to show that different tumor behaviors can be simulated by the proposed equation.
  - to evaluate the predictive power of the model. Based on 3 times steps evolution of the tumor on the same patient, we want to show that parameters that fit 2 times points could be used to predict the evolution of the tumor measured at the 3rd time point.
- Develop new algorithms for the evaluation of model parameters using multiple images. The idea here is to solve the inverse problem consisting in finding the optimal parameters that best match the growth observed in the data. Such algorithms could then be used to make statistics on the distribution of parameters among patients.

The long term aims consist in correlating such parameters estimated with inverse methods and genetic analysis to allow for a better understanding and evaluation of the tumor microscopic invasion.

This subject will involve the following researchers:
P.Y. Bondiau (CAL), Olivier Clatz (INRIA), Thomas Deisboeck (MGH), Herve Delingette (INRIA), Ender Konuko□lu (INRIA), Kilian Pohl (SPL), William Wells (SPL)

2. 3D Ultrasound for Image Guided Neurosurgery.

As a consequence of a joint effort between SPL, CRL and Asclepios, we developed in 2004 an algorithm to register 3D preoperative Magnetic Resonance (MR) images to intra-operative MR images of the brain which have undergone brain shift due to tumor resection [1][2][3]. A patient-specific model was used to ensure a realistic mechanical behavior of the brain and tumor tissue. To meet the clinical time constraint, the algorithm was parallelized so that we could perform a full 3D image registration in 35 seconds on a cluster of 15 PCs. More recently, this algorithm was used during 10 cases of neurosurgery for real time update of the preoperative planning [20].
The MRI intraoperative scanner is however not a technology widely available in hospitals around the world. We propose in this proposal to bring together (i) the expertise of Asclepios, SPL and CRL in MRI registration and (ii) of the Biorobotics Laboratory of Harvard in 3D ultrasound registration (best paper award at last MICCAI conference [21]) to develop a new nonrigid registration algorithm for 3D ultrasound. The specific aims of this project are:

- To develop a registration algorithm that uses 3D ultrasound to deform MR images. We propose to use the mechanical model to enforce the realism of the computed displacement field. The idea is to precompute realistic modes of deformation with the model that will depend on a few parameters (gravity, extent of tumor resection, use of drugs during surgery, CSF leakage). During surgery, a first displacement field will be estimated with the real-time tracking method based on 3D ultrasound developed in [21]. Then, a minimization algorithm will be used to find the precomputed mode of deformation that minimizes the error with respect to the estimated displacements.
- To validate the previous algorithm using both 3D ultrasound and MR imaging during surgery. The algorithm will be used to deform the preoperative MR image based on the 3D ultrasound information. This new image will be compared to the MR image that could be acquired during surgery at the Brigham and Women's Hospital.

This subject will involve the following researchers:
Nicholas Ayache (INRIA), Olivier Clatz (INRIA), Herve Delingette (INRIA), Rob Howe (Harvard Biorobotics Lab), Petr Jordan (Harvard Biorobotics Lab), Ron Kikinis (SPL), Stephane Litrico (CHU Pasteur), Simon Warfield (CRL)

3. Statistics on White Matter Architecture Using DTI

One of the contribution of the model proposed by Olivier Clatz in his Ph.D. thesis [18] was the use of Diffusion Tensor Imaging (DTI) to simulate the preferential growth of the tumor in the white mater fibers. The DTI however is usually not acquired in standard imaging protocols for the treatment of gliomas. In addition, the tumor disturbs the DTI signal in the invaded area, whereas the structure of the fibers still guides the diffusion of the tumor in the underlying tissue. Imaging techniques thus have to compensate for the lack of information. We proposed in [4] to use non-rigid registration algorithms to match the DTI of a healthy subject on the patient. In the first year of this collaboration, we will study the variability of the DTI among healthy subjects and its influence on the tumor growth. The specific aims are:

- Study the normal variability of the brain DTI. This problem is twofold:
  - the geometric variability. It consists in studying the variability of the deformation field that matches the DTIs of a given group of subject. In the first year, we will develop new algorithms for computing the deformation between two DTIs. We will adapt the method proposed in the "demons" algorithm [15] to the specific nature of tensor using the log-Euclidean metric introduced by V. Arsigny of Asclepios research [16].
  - the tensor variability. It consists in studying the local variability of the diffusion tensor given a set of aligned subjects. During the first year, this variability will be studied using state of the art non-rigid registration algorithms (demons, splines, poly-affines)
- Building a DTI brain Atlas. The log-Euclidean distance allows for simple computation on tensors. Based on this framework, the method proposed by Zollei [17] can be extended to tensor computation to build an average DTI atlas. This atlas will be based on multiple acquisitions of the same healthy subject acquired at Harvard Medical School, as well as multiple healthy subject acquired for NIH R21 MH067054.

The long term aims consist in studying the influence of the aforementioned variability on the growth of the tumor. We plan to use Monte-Carlo methods to study the influence of the DTI variability on the extension of the tumor diffusion in the brain.

This subject will involve the following researchers:
Nicholas Ayache (INRIA), Olivier Clatz (INRIA), Pierre Fillard (INRIA), Polina Golland (MIT), Xavier Pennec (INRIA), Simon Warfield (CRL), Williams Wells (SPL)

4. Tumor Resection Simulation

The last objective of this proposal is to develop a neurosurgery simulator to train surgeons on tumor resection procedures. Asclepios research project acquired, through the Ph.D. thesis of S. Cotin [22], G. Picimbono [23] and C. Forest [24] a valuable experience in the development of surgery simulator. More recently, they developed new models of the brain tissue and its interaction with cerebrospinal fluid [25]for the purpose of neurosurgery simulation. The new consortium created with the CIMIT allows for the integration of the existing algorithms in a flexible platform. Through the collaboration with the CIMIT and the SPL, we want to take advantage of the new SOFA architecture to develop a powerful neurosurgery simulator to train new surgeons to practice tumor resections. The specific aims are:

- The development of new brain constitutive equations taking into account the mechanical influence of blood vessels and the auto-regulation of blood pressure. We also want to study the influence of diuretics agents like Mannitol on the rheology of the brain tissue.
- The implementation of new resection method, taking advantage of the SOFA architecture to uncouple the mechanical computation from the visualization computation.

This subject will involve the following researchers:
Olivier Clatz (INRIA), Steven Dawson (CIMIT), Stephane Litrico (CHU Pasteur), Philippe Paquis (CHU Pasteur), Simon Warfield (CRL)

Budget prévisionnel 2007

1. Co-financement

The Computational Radiology Laboratory will share its dataset of 12 high resolution Diffusion Tensor Images of healthy subject with the Asclepios Research Project. Each DTI represents an actual charge of $2556.00 plus a physicist fee of $452.00, which is a total of $36096.
The housing expenses of Olivier Clatz during his 2 months visit in 2007 will be covered by the CRL up to $4000. Facilities and administrative costs will be covered by the CRL up to $3000.
The facilities and administrative costs associated with the visit of Nicholas Ayache will be shared between the SPL, the MIT CSAIL, and Harvard Biorobotics Laboratory.
The cost of data acquisition with the 3D ultrasound device ($200 K) will be supported by the Harvard Biorobotics Laboratory.
William Wells is applying for a Fullbright travel fellowship to finance part of his travel expenses.

2. Echanges

In 2007, Olivier Clatz Researcher at Asclepios will be a visiting scientist in the Computational Radiology Laboratory for 2 months.
In 2007, Nicholas Ayache Researcher at Asclepios will take a 5 months extended scientific visit in Boston. He will spend his time between the MIT Computer Science and Artificial Intelligence Laboratory, the Surgical Planning Laboratory of the Brigham & Women's Hospital and the Biorobotics Laboratory of Harvard. Nicholas will partly take over scientific supervision of the "computation core" group.
In 2007, William Wells Researcher at the Surgical Planning Laboratory will visit the Asclepios Research Project. William Wells will work at Asclepios project on extending his work on mutual information and non-rigid regstration algorithms [26;27] to diffusion tensor images.
In 2007, Kilian Pohl, Post-Doc at SPL will be a visiting scientist in the Asclepios Research Project for 4 weeks.
In 2007, Ender Konuko□lu, Ph.D. student at the Asclepios Research Project will be a visiting scientist in the Complex Biosystems Modeling Laboratory for 2 months.
In 2007, Petr Jordan, Ph.D. student at the Biorobotics Laboratory of Harvard will be a visiting scientist at Asclepios for 1 month.

The detailed travel expenses for year 2007 are as follow:

- 2 Round trips of Willian Wells, researcher at SPL.
- 1 Round trip for Killian Pohl, Post-Doc. at MIT.
- 2 Round trips of Nicholas Ayache, researcher at Asclepios - INRIA
- 1 Round trip for Olivier Clatz, researcher at Asclepios - INRIA
- 1 Round trip for Ender Konuko□lu, Ph.D. student at Asclepios - INRIA
- 1 Round trip for Petr Jordan, PhD. Student at the Biorobotics Laboratory of Harvard

ESTIMATION DES DÉPENSES POUR 2007	Montant			
	Nombre	Accueil	Missions	Total
Chercheurs confirmés	5	Wells (2)	Ayache (2) Clatz (1)	20 000
Post-doctorants	1	Pohl (1)		1 000
Doctorants	2	Jordan (1)	Konuko□lu (1)	2 000
Total				23 000
		- total des co-financements		See paragraph above
	Financement "Équipe Associée" demandé			23 000

ESTIMATION DES DÉPENSES POUR 2008-2009	Montant			
	Nombre	Accueil	Missions	Total
Chercheurs confirmés	5	Warfield (1)	Ayache (1) Clatz (2) Delingette (1)	20 000
Post-doctorants	3	Commowick (1)	To be defined (2)	3 000
Doctorants	7	To be defined (2)	Fillard (1) Konuko□lu (2) Litrico (2)	7 000
Total				30 000
		- total des co-financements		See paragraph above
	Financement "Équipe Associée" demandé			30 000

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[2] O. Clatz, H. Delingette, I.-F. Talos, A. J. Golby, N. Ayache, R. Kikinis, F. Jolesz, and S. K. Warfield. Hybrid Formulation of the Model-Based Non-Rigid Registration Problem to Improve Accuracy and Robustness. In J. Duncan and G. Gerig, editors, Proceedings of MICCAI'05, volume 3750 of LNCS, pages 295-302, October 2005. Springer Verlag.
[3] O. Clatz, H. Delingette, I.F. Talos, A. Golby, N. Ayache, R. Kikinis, F. Jolesz, and S. Warfield. Robust Nonrigid Registration to Capture Brain Shift from Intraoperative MRI. In 5th Interventional MRI Symposium, Cambridge, MA. USA, October 2004.
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Children's Hospital Boston
The Hospital for Children

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Dear Dr. Ayache,

I am writing this letter to express my strong support for the application for an "Equipes Associees" proposal.

I am the Director of the Computational Radiology Laboratory (CRL), which was founded in 2001 with the mission of improving our understanding of the structure and function of the brain and other organs of the human body, and improving our capacity to diagnose and treat disease. Members of the CRL achieve this by developing novel technologies and computational modeling strategies for understanding and interpreting radiological images. My research interests focus on methods for quantitative and real-time image analysis, enabled by high performance computing strategies. I am the principal investigator of research grants from both the National Institutes of Health and from the National Science Foundation.

I am delighted to act as coordinator for this proposal. It will be a pleasure to coordinate this study between INRIA, Massachusetts General Hospital, Brigham and Women's Hospital, MIT, CIMIT and Harvard, all of whom we have worked closely and successfully in the past. The CRL in Children's Hospital, Department of Radiology, has a very active research program developing medical image computing technologies for improved diagnosis and treatment of pediatric brain tumor patients. We currently utilize structural MRI and diffusion tensor MRI to visualize the brain tumor and critical white matter structures for preoperative surgical planning. Patients are also followed longitudinally, and we are interested in functional measures of tumor progression, derived from multimodality fusion of MRI and PET scans.

Children's Hospital has recently installed a 1.5T MRI scanner in a neurosurgical operating room, and we utilize real-time ultrasound imaging to guide intraoperative navigation. The simultaneous display of preoperatively acquired MRI with intraoperative ultrasound is expected to dramatically enhance the capacity of the neurosurgeons to resect brain tumor while avoiding postoperative neurological deficits. The technology development proposed in this proposal will be key in enabling these advances.

I am strongly convinced your proposed research will have a major impact upon our understanding of the early appearance and diagnosis of brain tumors, and will lead to objective assessment of improved interventions which will lead to enhanced quality of life for brain tumor patients.

Yours sincerely,

Simon K. Warfield, Ph.D.

BRIGHAM AND
WOMEN'S HOSPITAL

HARVARD
MEDICAL SCHOOL

75 Francis Street
Boston, Massachusetts 02115

Department of Radiology

October 12, 2006

Dear Sir or Madam:

Based on recent conversations with Nicholas Ayache I am enthusiastic to participate in the proposed "equipes associees" to facilitate an academic collaboration among Inria, MIT, Harvard University and Harvard Medical School Hospitals.

I currently direct the *computation core* of the NIH funded National Center for Image Guided Therapy (NCIGT) at Brigham and Women's Hospital (one of the Harvard hospitals). The core is concerned with the image processing, navigation, and informatics aspects of our research activities in image-guided neurosurgery, liver tumor ablation, prostate brachytherapy and other applications. I also actively supervise MIT graduate students and postdoctoral fellows in research related to our clinical applications.

I am especially keen to collaborate with Asclepios in the areas of modeling tumor growth, developing statistical models on tensors, and simulating the electrical currents in the brain that are caused by intraoperative electro-cortical stimulation.

About ten years ago I spent a three month sabbatical visit to the Epidaure project at Sophia Antipolis. This visit was scientifically very rewarding, and I think that grant funding to support interchange among faculty, postdoctoral fellows, and students would be a very effective way to establish strong

collaborations among the institutions.

Sincerely,

William M. Wells III

Associate Professor of Radiology
Harvard Medical School and Brigham
and Women's Hospital

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Dr. Nicholas AYACHE
Asclepios Research Project
INRIA Sophia Antipolis
2004 route des Lucioles - BP 93
06902 Sophia Antipolis Cedex
FRANCE

20 October 2006

Dear Nicholas:

It is a pleasure to write in support of the proposed INRIA Equipes Associées Project, "CompuTumor: Computational Brain Tumor." This project promises to advance the state-of-the-art in brain tumor modeling, and its application to image-guided procedures.

As Gordon McKay Professor of Engineering and Director of the BioRobotics Laboratory at Harvard University, I look forward continuing our productive collaboration in this new project. I chose your group at INRIA for my sabbatical stay in 2004 because of its world-leading expertise in medical image processing. I am pleased that my visit led to our successful, ongoing collaboration. Our joint work on combining haptic feedback methodologies with fast FEM modeling resulted in the unprecedented ability to realistically reproduce the sensations of finger tip contact with soft tissues. The image processing capabilities we attained through our mutual postdoctoral fellow, Dr. Marius Linguraru, has enabled new cardiac surgical procedures based on 3-D ultrasound guidance, including image-based robot control. Both our haptics and ultrasound capabilities will be immediately applicable to the proposed project.

I am certain that this project will provide new insights into tumor growth, cancer imaging, and effective surgical interventions. You have my full support.

Sincerely,

Robert D. Howe
Gordon McKay Professor of Engineering

MIT COMPUTER SCIENCE AND ARTIFICIAL INTELLIGENCE LABORATORY

October 19, 2006

To: Nicholas Ayache

INRIA Sophia Antipolis
Asclepios Research Project
2004 route des Lucioles - BP 93
06902 Sophia Antipolis Cedex
France

Dear Nicholas,

I am delighted to support your INRIA - Boston equips associees proposal. We share many research interests in the biomedical image analysis, including statistical shape modeling, image registration, diffusion tensor image analysis and microscopy image analysis. I am confident your stay here will lead to great interactions between our groups and will allow us to boostrap collaborative projects. Given our close ties with Brigham and Women's Hospital, we are particularly interested in jointly developing methods for detection and monitoring of tumors during treatment. Your extensive expertise in the mathematical methods for image analysis will be a great asset for our students during your visit.

I am looking forward your visit and the fruitful research resulting from it.

Sincerely,

Polina Golland

Polina Golland
Assistant Professor
MIT EECS/CSAIL

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October 19, 2006

Nicholas Ayache, PhD
Asclepios Project
INRIA – BP 93
06902 Sophia-Antipolis Cedex
France

Dear Professor Ayache:

I write to express my strong support for your effort to begin a joint collaboration between the INRIA SOPHIA laboratories and the Boston medical academic community, especially as it relates to the concepts of surgical simulation. The work my group has been doing with members of the INRIA community in creating a Simulation Open Framework Architecture (SOFA) is potentially a critical element in making these developments widely accessible to the medical community. The chance to partner with INRIA to make this breakthrough come sooner is a welcome offer and I pledge my full support to seeing it to a successful end.

Respectfully,

/s/

Steven Dawson, MD

Program Lead, Medical Simulation
MGH – CIMIT
Interventional Radiologist
Massachusetts General Hospital
Associate Professor, Harvard Medical School

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NMR Research Laboratories
MGH Imaging Center
MR Education

October 17, 2006

To:
Prof. Nicholas Ayache, Ph.D.
INRIA -- BP 93
06902 Sophia-Antipolis Cedex
France

RE: EU Grant Application, entitled "Equipes Associees"

Dear Professor Ayache,

I am delighted to participate in this exciting EU-US research network that promises to combine biomedical imaging, cutting edge image analysis and innovative computational modeling and simulation.

As you know, I am the founder and Principal Investigator of MGH's Center for the Development of a Virtual Tumor, CViT (http://www.cvit.org). I hold appointments as Assistant Professor of Radiology at Massachusetts General Hospital and Harvard Medical School. My group, the Complex Biosystems Modeling Laboratory, is part of Harvard-MIT's (HST) Martinos Center for Biomedical Imaging here at MGH.

As I understand, the focus of this EU project is exchange of research personnel and expertise with the teams located in the US and CViT seems to be ideally suited to play a significant role in this. That is, CViT, one of NIH/NCI's currently only nine Integrative Cancer Biology Programs (http://icbp.nci.nih.gov/), it is charged with developing the first online community dedicated to cancer modeling, and the innovative IT infrastructure to support it, en route to a modeling tool kit for *in silico* cancer research. Currently, CViT.org includes some 100 participating investigators from more than 50 institutions around the globe. Establishing scientific collaborations that yield valuable data for these modeling efforts as well as promoting teaching and educational outreach is a main focus of ICBP in general and of CViT in particular and as such I enthusiastically support this application and hope it will receive funding.

With best regards,

Thomas S. Deisboeck, M.D.
Massachusetts General Hospital
Harvard Medical School