Activity Report 2013

Project-Team ATHENA

Computational Imaging of the Central Nervous System

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Neuroscience and Medecine

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Project-Team ATHENA

Keywords: Computational Neurosciences, Medical Images, Image Processing, Signal Processing, Inverse Problem, Brain Computer Interface

Creation of the Project-Team: 2010 July 01.

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2. Overall Objectives

2.1. Presentation

The main objective of ATHENA is to develop rigorous mathematical models and computational tools for analyzing and modeling the complex Central Nervous System (brain and spinal cord) anatomy and function. These models and tools will help to better understand the architecture and the functioning of human Central Nervous System (CNS) and address pressing and challenging clinical and neuroscience questions. Exploring new directions to solve these challenging problems will push forward the state-of-the-art in Anatomical and Functional Computational Imaging of the CNS.

The relationship between CNS structure and function is fundamental in neuroscience. Developing computational models and techniques that recover the anatomical connectivity and the function of the CNS in vivo is thus of utmost importance: it will definitely improve the understanding of the CNS and its mechanisms. On the basis of our expertise and contributions to the field of Computational Imaging of the CNS and in order to have an impact on this field, our research focusses mainly on the Anatomical and Functional Imaging of the CNS with a particular emphasis on signal and image recording from Diffusion Magnetic Resonance Imaging (dMRI), Magneto-Encephalography (MEG) and Electro-Encephalography (EEG).

In order to further increase the impact of our research, we also aim to push our contributions towards some applications related to CNS diseases with characteristic abnormalities in the micro-structure of brain tissues that are not apparent and cannot be revealed reliably by standard imaging techniques. Diffusion MRI, a recent imaging modality based on the measurement of the random thermal movement (diffusion) of water molecules within samples can make visible these co-lateral damages to the fibers of the CNS white matter that connect different brain regions. This is why in our research, Diffusion MRI is the major anatomical imaging modality that will be considered to recover the CNS connectivity.

Connectivity represents the network infrastructure of the CNS. Electric activity corresponds to communications over this network. MEG and EEG (jointly as M/EEG) reveal part of the cortical electric activity. M/EEG are also instrumental in diagnosing diseases linked to anomalous brain function - that in some cases anatomical or functional MR images do not reveal. In some CNS injuries (medullar injuries, strokes, AMS), the peripheral nervous system may not be able to execute commands that are issued by the brain.

Brain Computer Interfaces (BCI) is an application of EEG that has been proposed as a means to translate in real-time the electrical activity of the brain in commands to control devices. While BCI had been advocated as a means to communicate and help restore mobility or autonomy for very severe cases of disabled patients, it is more realistically a tool for a new interactive probing and training of the human brain.

These considerations support the need to do research on new models and computational tools to analyse CNS signals and imaging data. Our main objective is to push forward the state-of-the-art in our research domain to better understand the architecture and function of the CNS and help address pressing and challenging clinical and neuroscience questions. This better understanding of the CNS will help the development of new biomarkers related to the progression of certain types of neurodegenerative diseases and will also help improving BCI systems with the goal of better interactive probing and training of the human brain. These long term and ambitious applications, if successful, will help us make true our dream to effectively contribute reducing the number of people suffering from CNS diseases.

In order to tackle these challenging objectives, our strategy is based on the following road map:

- Develop rigorous mathematical and computational tools for the analysis and interpretation of Diffusion MRI and M/EEG data.
- Improve acquisition and processing techniques and push forward the state-of-the-art in Computational CNS imaging.
- Use our expertise to address with collaborators clinical and neuroscience questions.

This is implemented through:

- Publications in international conferences and journals dedicated to promoting advances in computational methods for Diffusion MRI and M/EEG analysis and/or use of Diffusion MRI and M/EEG in clinical and neuroscience applications.
- A dense network of collaborations with national as well as international neuroimaging laboratories through which we have access equipment and data and with whom we will jointly contribute to solve common crucial problems of interest.
- Software packages developed to be used in a first stage by our national and international collaborators and then made available to other partners.

2.2. Highlights of the Year

Rachid Deriche was awarded the 2013 French Academy of Sciences Grand Prize of the EADS CORPORATE FOUNDATION in Computer Science. This award recognizes the achievement of a scientist in a French laboratory who has made exceptional contributions to the vitality and influence of computer-science research while building outstanding cooperation with industry. It has been officially awarded at the Institut de France on October 15th, 2013.

Demian Wassermann has been recruited as junior research scientist (CR2 Inria). He joined the ATHENA project-team by the end of Decembre 2013.

4 PhD students have been recruited : Brahim Belaoucha, Kai Dang, Rutger Fick and Marco Pizzolato.

2 PhD students defended their thesis at Nice Sophia Antipolis University : Sylvain Merlet (Sept. 11) and Anne-Charlotte Philippe (Dec. 19).

2 ANR projects have been accepted : ANR Mosifah and ANR Vibrations (see the dedicated part in this report).

3. Research Program

3.1. Computational Diffusion MRI

Diffusion MRI (dMRI) provides a non-invasive way of estimating in-vivo CNS fiber structures using the average random thermal movement (diffusion) of water molecules as a probe. It's a recent field of research with a history of roughly three decades. It was introduced in the mid 80's by Le Bihan et al [60], Merboldt et al [64] and Taylor et al [71]. As of today, it is the unique non-invasive technique capable of describing the neural connectivity in vivo by quantifying the anisotropic diffusion of water molecules in biological tissues. The great success of dMRI comes from its ability to accurately describe the geometry of the underlying microstructure and probe the structure of the biological tissue at scales much smaller than the imaging resolution.

The diffusion of water molecules is Brownian in an isotropic medium and under normal unhindered conditions, but in fibrous structure such as white matter, the diffusion is very often directionally biased or anisotropic and water molecules tend to diffuse along fibers. For example, a molecule inside the axon of a neuron has a low probability to cross a myelin membrane. Therefore the molecule will move principally along the axis of the neural fiber. Conversely if we know that molecules locally diffuse principally in one direction, we can make the assumption that this corresponds to a set of fibers.

3.1.1. Diffusion Tensor Imaging

Shortly after the first acquisitions of diffusion-weighted images (DWI) were made in vivo [65], [66], Basser et al [43], [42] proposed the rigorous formalism of the second order Diffusion Tensor Imaging model (DTI). DTI describes the three-dimensional (3D) nature of anisotropy in tissues by assuming that the average diffusion of water molecules follows a Gaussian distribution. It encapsulates the diffusion properties of water molecules in biological tissues (inside a typical 1-3 mm^3 sized voxel) as an effective self-diffusion tensor given by a 3×3 symmetric positive definite tensor $\mathbf{D}$ [43], [42]. Diffusion tensor imaging (DTI) thus produces a

three-dimensional image containing, at each voxel, the estimated tensor $\mathbf{D}$. This requires the acquisition of at least six Diffusion Weighted Images (DWI) S_k in several non-coplanar encoding directions as well as an unweighted image S_0. Because of the signal attenuation, the image noise will affect the measurements and it is therefore important to take into account the nature and the strength of this noise in all the pre-processing steps. From the diffusion tensor $\mathbf{D}$, a neural fiber direction can be inferred from the tensor's main eigenvector while various diffusion anisotropy measures, such as the Fractional Anisotropy (FA), can be computed using the associated eigenvalues to quantify anisotropy, thus describing the inequality of diffusion values among particular directions.

DTI has now proved to be extremely useful to study the normal and pathological human brain [61], [54]. It has led to many applications in clinical diagnosis of neurological diseases and disorder, neurosciences applications in assessing connectivity of different brain regions, and more recently, therapeutic applications, primarily in neurosurgical planning. An important and very successful application of diffusion MRI has been brain ischemia, following the discovery that water diffusion drops immediately after the onset of an ischemic event, when brain cells undergo swelling through cytotoxic edema.

The increasing clinical importance of diffusion imaging has drived our interest to develop new processing tools for Diffusion MRI. Because of the complexity of the data, this imaging modality raises a large amount of mathematical and computational challenges. We have therefore started to develop original and efficient algorithms relying on Riemannian geometry, differential geometry, partial differential equations and front propagation techniques to correctly and efficiently estimate, regularize, segment and process Diffusion Tensor MRI (DT-MRI) (see [63], [9] and [62]).

3.1.2. High Angular Resolution Diffusion Imaging

In DTI, the Gaussian assumption over-simplifies the diffusion of water molecules. While it is adequate for voxels in which there is only a single fiber orientation (or none), it breaks for voxels in which there are more complex internal structures. This is an important limitation, since resolution of DTI acquisition is between 1mm^3 and 3mm^3 while the physical diameter of fibers can be between 1μm and 30 μm [68], [44]. Research groups currently agree that there is complex fiber architecture in most fiber regions of the brain [67]. In fact, it is currently thought that between one third to two thirds of imaging voxels in the human brain white matter contain multiple fiber bundle crossings [45]. This has led to the development of various High Angular Resolution Diffusion Imaging (HARDI) techniques [73] such as Q-Ball Imaging (QBI) or Diffusion Spectrum Imaging (DSI) [74], [75], [77] to explore more precisely the microstructure of biological tissues.

HARDI samples q-space along as many directions as possible in order to reconstruct estimates of the true diffusion probability density function (PDF) – also referred as the Ensemble Average Propagator (EAP) – of water molecules. This true diffusion PDF is model-free and can recover the diffusion of water molecules in any underlying fiber population. HARDI depends on the number of measurements N and the gradient strength (b-value), which will directly affect acquisition time and signal to noise ratio in the signal.

Typically, there are two strategies used in HARDI: 1) sampling of the whole q-space 3D Cartesian grid and estimation of the EAP by inverse Fourier transformation or 2) single shell spherical sampling and estimation of fiber distributions from the diffusion/fiber ODF (QBI), Persistent Angular Structure [59] or Diffusion Orientation Transform [80]. In the first case, a large number of q-space points are taken over the discrete grid ($N > 200$) and the inverse Fourier transform of the measured Diffusion Weighted Imaging (DWI) signal is taken to obtain an estimate of the diffusion PDF. This is Diffusion Spectrum Imaging (DSI) [77], [74], [75]. The method requires very strong imaging gradients ($500 \leq b \leq 20000$ s/mm^2) and a long time for acquisition (15-60 minutes) depending on the number of sampling directions. To infer fiber directions of the diffusion PDF at every voxel, people take an isosurface of the diffusion PDF for a certain radius. Alternatively, they can use the second strategy known as Q-Ball imaging (QBI) i.e just a single shell HARDI acquisition to compute the diffusion orientation distribution function (ODF). With QBI, model-free mathematical approaches can be developed to reconstruct the angular profile of the diffusion displacement probability density function (PDF) of water molecules such as the ODF function which is fundamental in tractography due to the fact that it

contains the full angular information of the diffusion PDF and has its maxima aligned with the underlying fiber directions at every voxel.

QBI and the diffusion ODF play a central role in our work related to the development of a robust and linear spherical harmonic estimation of the HARDI signal and to our development of a regularized, fast and robust analytical QBI solution that outperforms the state-of-the-art ODF numerical technique available. Those contributions are fundamental and have already started to impact on the Diffusion MRI, HARDI and Q-Ball Imaging community [53]. They are at the core of our probabilistic and deterministic tractography algorithms devised to best exploit the full distribution of the fiber ODF (see [51], [4] and [52],[5]).

3.1.3. High Order Tensors

Other High Order Tensors (HOT) models to estimate the diffusion function while overcoming the shortcomings of the 2nd order tensor model have also been recently proposed such as the Generalized Diffusion Tensor Imaging (G-DTI) model developed by Ozarslan et al [78], [81] or 4th order Tensor Model [41]. For more details, we refer the reader to our articles in [55], [70] where we review HOT models and to our articles in [8], co-authored with some of our close collaborators, where we review recent mathematical models and computational methods for the processing of Diffusion Magnetic Resonance Images, including state-of-the-art reconstruction of diffusion models, cerebral white matter connectivity analysis, and segmentation techniques. Recently, we started to work on Diffusion Kurtosis Imaging (DKI), of great interest for the company OLEA MEDICAL. Indeed, DKI is fast gaining popularity in the domain for characterizing the diffusion propagator or EAP by its deviation from Gaussianity. Hence it is an important tool in the clinic for characterizing the white-matter's integrity with biomarkers derived from the 3D 4th order kurtosis tensor (KT) [18].

All these powerful techniques are of utmost importance to acquire a better understanding of the CNS mechanisms and have helped to efficiently tackle and solve a number of important and challenging problems. They have also opened up a landscape of extremely exciting research fields for medicine and neuroscience. Hence, due to the complexity of the CNS data and as the magnetic field strength of scanners increase, as the strength and speed of gradients increase and as new acquisition techniques appear [3], [2], these imaging modalities raise a large amount of mathematical and computational challenges at the core of the research we develop at ATHENA [56], [39].

3.1.4. Improving dMRI Acquisitions and Modeling

One of the most important challenges in diffusion imaging is to improve acquisition schemes and analyse approaches to optimally acquire and accurately represent diffusion profiles in a clinically feasible scanning time. Indeed, a very important and open problem in Diffusion MRI is related to the fact that HARDI scans generally require many times more diffusion gradient than traditional diffusion MRI scan times. This comes at the price of longer scans, which can be problematic for children and people with certain diseases. Patients are usually unable to tolerate long scans and excessive motion of the patient during the acquisition process can force a scan to be aborted or produce useless diffusion MRI images.

Recently, we have developed novel methods for the acquisition and the processing of diffusion magnetic resonance images, to efficiently provide, with just few measurements, new insights into the structure and anatomy of the brain white matter in vivo.

First, we contributed developing real-time reconstruction algorithm based on the Kalman filter [3]. Then, and more recently, we started to explore the utility of Compressive Sensing methods to enable faster acquisition of dMRI data by reducing the number of measurements, while maintaining a high quality for the results. Compressed Sensing (CS) is a recent technique which has been proved to accurately reconstruct sparse signals from undersampled measurements acquired below the Shannon-Nyquist rate [11].

We have contributed to the reconstruction of the diffusion signal and its important features as the orientation distribution function and the ensemble average propagator, with a special focus on clinical setting in particular for single and multiple Q-shell experiments [11] [47], [48]. Compressive sensing as well as the parametric reconstruction of the diffusion signal in a continuous basis of functions such as the Spherical Polar Fourier basis, have been proved through our recent contributions to be very useful for deriving simple and analytical

closed formulae for many important dMRI features, which can be estimated via a reduced number of measurements [11] [47], [48].

We have also contributed to design optimal acquisition schemes for single and multiple q-shell experiments. In particular, the method proposed in [2] helps generate sampling schemes with optimal angular coverage for multi-shell acquisitions. The cost function we proposed is an extension of the electrostatic repulsion to multi-shell and can be used to create acquisition schemes with incremental angular distribution, compatible with prematurely stopped scans. Compared to more commonly used radial sampling, our method improves the angular resolution, as well as fiber crossing discrimination. The optimal sampling schemes, freely available for download [1], have been selected for use in the HCP (Human Connectome Project) [2].

We think that such kind of contributions open new perspectives for dMRI applications including, for example, tractography where the improved characterization of the fiber orientations is likely to greatly and quickly help tracking through regions with and/or without crossing fibers [38]

3.2. MEG and EEG

Electroencephalography (EEG) and Magnetoencephalography (MEG) are two non-invasive techniques for measuring (part of) the electrical activity of the brain. While EEG is an old technique (Hans Berger, a German neuropsychiatrist, measured the first human EEG in 1929), MEG is a rather new one: the first measurements of the magnetic field generated by the electrophysiological activity of the brain were made in 1968 at MIT by D. Cohen. Nowadays, EEG is relatively inexpensive and is routinely used to detect and qualify neural activities (epilepsy detection and characterisation, neural disorder qualification, BCI, ...). MEG is, comparatively, much more expensive as SQUIDS only operate under very challenging conditions (at liquid helium temperature) and as a specially shielded room must be used to separate the signal of interest from the ambient noise. However, as it reveals a complementary vision to that of EEG and as it is less sensitive to the head structure, it also bears great hopes and an increasing number of MEG machines are being installed throughout the world. Inria and ODYSSÉE/ATHENA have participated in the acquisition of one such machine installed in the hospital "La Timone" in Marseille.

MEG and EEG can be measured simultaneously (M/EEG) and reveal complementary properties of the electrical fields. The two techniques have temporal resolutions of about the millisecond, which is the typical granularity of the measurable electrical phenomena that arise within the brain. This high temporal resolution makes MEG and EEG attractive for the functional study of the brain. The spatial resolution, on the contrary, is somewhat poor as only a few hundred data points can be acquired simultaneously (about 300-400 for MEG and up to 256 for EEG). MEG and EEG are somewhat complementary with fMRI and SPECT in that those provide a very good spatial resolution but a rather poor temporal resolution (of the order of a second for fMRI and a minute for SPECT). Also, contrarily to fMRI, which “only” measures an haemodynamic response linked to the metabolic demand, MEG and EEG measure a direct consequence of the electrical activity of the brain: it is acknowledged that the signals measured by MEG and EEG correspond to the variations of the post-synaptic potentials of the pyramidal cells in the cortex. Pyramidal neurons compose approximately 80% of the neurons of the cortex, and it requires at least about 50,000 active such neurons to generate some measurable signal.

While the few hundred temporal curves obtained using M/EEG have a clear clinical interest, they only provide partial information on the localisation of the sources of the activity (as the measurements are made on or outside of the head). Thus the practical use of M/EEG data raises various problems that are at the core of the ATHENA research in this topic:

- First, as acquisition is continuous and is run at a rate up to 1kHz, the amount of data generated by each experiment is huge. Data selection and reduction (finding relevant time blocks or frequency bands) and pre-processing (removing artifacts, enhancing the signal to noise ratio, ...) are largely done manually at present. Making a better and more systematic use of the measurements is an important step to optimally exploit the M/EEG data [1].

[1] http://www.emmanuelcaruyer.com/
[2] http://humanconnectome.org/documentation/Q1/imaging-protocols.html

- With a proper model of the head and of the sources of brain electromagnetic activity, it is possible to simulate the electrical propagation and reconstruct sources that can explain the measured signal. Proposing better models [7], [10] and means to calibrate them [76] so as to have better reconstructions are other important aims of our work.
- Finally, we wish to exploit the temporal resolution of M/EEG and to apply the various methods we have developed to better understand some aspects of the brain functioning, and/or to extract more subtle information out of the measurements. This is of interest not only as a cognitive goal, but it also serves the purpose of validating our algorithms and can lead to the use of such methods in the field of Brain Computer Interfaces. To be able to conduct such kind of experiments, an EEG lab has been set up at ATHENA.

4. Application Domains

4.1. Applications of Diffusion MRI

Various examples of CNS diseases as Alzheimer's and Parkinson's diseases and others like multiple sclerosis, traumatic brain injury and schizophrenia have characteristic abnormalities in the micro-structure of brain tissues that are not apparent and cannot be revealed reliably by standard imaging techniques. Diffusion MRI can make visible these co-lateral damages to the fibers of the CNS white matter that connect different brain regions. This is why in our research, Diffusion MRI is the major anatomical imaging modality that will be considered to recover the CNS connectivity.

Clinical domain: Diagnosis of neurological disorder

- *Parkinson's and Alzheimer's diseases* are among the most important CNS diseases. Six million patients (among which 850.000 in France) are suffering from Alzheimer's, making it the most important neurodegenerative disease in Europe. Over 85 years of age, 1 woman in 4 and 1 man in 5 are affected in Europe. In France, the number of Alzheimer's patients is expected to reach at least 2 million in 2025 and will probably double in 2050, with the increasing age of the population. Parkinson's disease is the second most important neurodegenerative disease. There are six and a half million patients in the world and roughly 150.000 patients in France, among which 10% are under 40 and 50% over 58. Together with our partners from NeuroSpin (Saclay), Inserm U678 and CENIR (CHUPS, Paris), we are involved in the ANR project NucleiPark which is about high field MRI of the braintem, the deep nuclei and their connections in the Parkinsonian syndromes.
- *Spinal Cord Injury* (SCI) has a significant impact on the quality of life since it can lead to motor deficits (paralysis) and sensory deficits. In the world, about 2.5 million people live with SCI (http://www.campaignforcure.org). To date, there is no consensus for full rehabilitative cure in SCI, although many therapeutic approaches have shown benefits [69], [72]. It is thus of great importance to develop tools that will improve the characterization of spinal lesions as well as the integrity of remaining spinal tracts to eventually establish better prognosis after spinal injury. We have already started to be active in this domain with our collaborators at Inserm U678 (H. Benali) and CRSN/Faculté de médecine Université de Montréal (Pr. S. Rossignol).

4.2. Applications of M/EEG

Applications of EEG and MEG cover: **Clinical domain: diagnosis of neurological disorders**
The dream of all M/EEG researchers is to alleviate the need for invasive recordings (electrocorticograms or intracerebral electrodes), which are often necessary prior to brain surgery, in order to precisely locate both pathological and vital functional areas. We are involved in this quest, particularly through our collaborations with the La Timone hospital in Marseille.

Subtopics include:

- Diagnosis of neurological disorders such as epilepsy, schizophrenia, tinnitus, ...
- Presurgical planning of brain surgery.

Cognitive research

- Aims at better understanding the brain spatio-temporal organisation.
- Collaboration with the *Laboratory for Neurobiology of Cognition* in order to develop methods that suit their needs for sophisticated data analysis.

Brain Computer Interfaces look at allowing a direct control of the world using brain signal such as EEG signals. Those can be considered both as an application of EEG processing techniques and as a tool for fundamental and applied research as it opens the way for more dynamical and active brain cognitive protocols.

We are developing research collaborations with the Neurelec company in Sophia Antipolis (subsidiary of Oticon Medical) and with the leading EEG software company BESA based in Munich. We are conducting a feasibility study with the Nice University Hospital on the usage of BCI-based communication for ALS [3] patients.

5. Software and Platforms

5.1. OpenMEEG

Participants: Théodore Papadopoulo, Maureen Clerc, Alexandre Gramfort [Telecom ParisTech].

OpenMEEG provides state-of-the art tools for low-frequency bio-electromagnetism, notably solving forward problems related to EEG and MEG [57], [58]. It implements the symmetric BEM which provides excellent accuracy and versatility. OpenMEEG is a free open software written in C++. It can be accessed either through a command line interface or through Python/Matlab interfaces. The first release has been directly downloaded about 600 times since October 2008. Our last release (in September 2011) has been downloaded more than 2000 times to this date. OpenMEEG has been integrated in the neuro-debian distribution (http://neuro.debian.net/) and matlab suites (such as BrainStorm, FieldTrip or SPM) which may represent several more indirect downloads. Work is under progress to integrate it in a commercial package (BESA).

See also the web page http://openmeeg.gforge.inria.fr.

- Version: 2.2
- License: French opensource license CeCILL-B
- Multiplatform: Windows - Linux - MacOSX
- Programming language: C++
- 17 000 lines of code.
- 1800 downloads in 2012-2013.
- Web: http://openmeeg.gforge.inria.fr

5.2. Diffusion MRI

Participants: Aurobrata Ghosh, Théodore Papadopoulo, Rachid Deriche.

[3] Nice University Hospital hosts a regional reference center for patients suffering from Amyotrophic Lateral Syndrome.

We have been closely involved in pushing the frontiers of the diffusion MRI (dMRI) in the recent years, especially in the mathematical modelling and processing of the dMRI signal and have developed state-of-the-art software implementations in the form of a C++ library that can be effectively used to infer the complex microstructure of the cerebral white matter. These algorithms and software fall into four categories : (i) local tissue modelling, which includes both popular 2nd order models and advanced higher than 2nd order models such as DTI, higher order Cartesian tensors (HOTs), ODF, FOD, EAP, maxima extraction, regularization and segmentation; (ii) generation of scalar indices (or biomarkers), which include DTI biomarkers, Diffusion Kurtosis Imaging (DKI) and invariants of 4th order tensors; (iii) global structure estimation, which includes deterministic and probabilistic tractography; and (iv) data visualisation for scalar indices, local models and global structures.

So far, ODF estimation from the ATHENA-dMRI C++ library has been successfully included in medInria 1.9, and in the process to be re-adapted for medInria 2.1. Otherwise, the ATHENA-dMRI C++ library has been mostly used internally for research purposes. However, this is now changing with a fresh restructuring of the entire library so that it can be successfully ported and used externally – primarily to be included in parts with the cutting-edge software developed by OLEA MEDICAL.

- License: French opensource license CeCILL-B - To change when it is to be sourced to OLEA MEDICAL.
- Platform: Linux and (medInria platforms)
- Programming language: C++

5.3. medInria

Participants: Jaime Garcia Guevara, Théodore Papadopoulo.

The ATHENA team is heavily involved in the development of medInria 2.0 along with the ASCLEPIOS, PARIETAL and VISAGES research teams. medInria is a free software platform dedicated to medical data visualization and processing. medInria 2.0, it is a complete re-write of the first version of medInria in order to be modular and allow a distributed development. It aims at providing an integrative platform for medical image processing and to be a framework for disseminating various research tools not only to other researchers but also to clinicians. New algorithms or data formats can be added as plugins.

It aims at providing to clinicians and researchers state-of-the-art algorithms developed at Inria and elsewhere (for the future), through an intuitive user interface. medInria offers from standard to cutting-edge processing functionalities for medical images such as 2D/3D/4D image visualization, image registration, diffusion MR processing and tractography.

ATHENA's contributions so far consist in various improvements on the infrastructure, the core application as well as several plugins which are already available with version 2.1 (ODF vizualization) or in future ones: advanced dMRI processing, M/EEG signal visualisation (by integrating code from the software AnyWave developed by Bruno Colombet and J.-M. Badier INSERM U1106 and Aix-Marseille University).

In 2013, the source code of the core of medInria was made public. Regular releases and bug fixes are provided on a large number of Linux, Windows and Mac versions, thanks to the Continuous Integration platform proposed at Inria.

After 4 years of important development, medInria is now rather mature and can be used as a basis for collaborations and projects. We now receive regular feedback through the forum and the mailing list, from both academic and clinical users.

- Version: 2.1
- Keywords: Medical Image Processing and Visualization
- License: BSD 4
- Multiplatform: Windows - Linux - MacOSX
- Programming language: C++
- 250 000 lines of code.
- 5000 downloads on 2012-2013.
- Web: http://med.inria.fr.

5.4. FindSources3D

Participants: Maureen Clerc, Juliette Leblond [APICS project-team], Jean-Paul Marmorat [APICS project-team], Théodore Papadopoulo.

FindSources3D is a Matlab software program dedicated to solving inverse source localization problems in electroencephalography (EEG), and in the future, magnetoencephalography (MEG). FindSources3D implements a new formalism for source localization, based on rational approximations in the complex plane. It is able to estimate, with high precision, and with no a priori on the number of sources, pointwise dipolar current sources within the brain. The head model used is a spherical model with concentric layers of homogenous conductivity.

Contributors: APICS and ATHENA Project Teams, Inria Sophia-Antipolis Méditerranée, Centre de Mathématiques Appliquées (CMA), Ecole des Mines de Paris.

- Version: 1.0
- Keywords: Medical Image Processing and Visualization
- License: CeCILL
- Multiplatform: Windows - Linux - MacOSX
- Programming language: Matlab
- Web: http://www-sop.inria.fr/apics/FindSources3D/fr/index.html

5.5. ImplicitFEM

Participants: Théodore Papadopoulo, Sylvain Vallaghé.

ImplicitFEM is a software to simulate the forward EEG/MEG problem. It uses a volumic finite element approach (FEM) that allows the modeling of anisotropic conductivities (which OpenMEEG cannot). Its main originality is to avoid the need of meshes that can be very complicated to build for the head. Instead, it uses directly representations of tissue interfaces as levelsets (that can be provided directly by some segmentation program based on levelsets or can be generated from other representations). It also uses non-differentiable elements so as to properly model continuity of both potential and normal current across the tissues interfaces (which correspond to conductivity discontinuities). This tool is currently used only internally by students and researchers.

- Version: 0.5
- Programming language: C++

5.6. External Stimulator for OpenViBE

Participants: Maureen Clerc, Loïc Mahé, Dieter Devlaminck.

In the domain of Brain Computer Interfaces, extracting relevant features requires a precise timing of all events occurring in the system. In particular, when dealing with evoked responses as in the P300 speller, the timing of the visual stimulations must be well controlled. To alleviate some timing issues with the P300 speller initially provided with OpenViBE, we have implemented an external visual stimulator that allows to flash the visual targets, in a time-robust manner.

- Version: 1.0
- Keywords: Brain Computer Interfaces
- Multiplatform: Windows - Linux - MacOSX
- Programming language: C++

6. New Results

6.1. Improving Diffusion MRI Signal and Acquisition

6.1.1. Design of multishell sampling schemes with uniform coverage in diffusion MRI

Participants: Emmanuel Caruyer [SBIA, University of Pennsylvania Medical School,USA], Christophe Lenglet [CMRR, Department of Radiology, University of Minnesota,USA], Guillermo Sapiro [Electrical & Computer Engineering Dept, Duke University,USA], Rachid Deriche.

In diffusion MRI, a technique known as diffusion spectrum imaging reconstructs the propagator with a discrete Fourier transform, from a Cartesian sampling of the diffusion signal. Alternatively, it is possible to directly reconstruct the orientation distribution function in q-ball imaging, providing so-called high angular resolution diffusion imaging. In between these two techniques, acquisitions on several spheres in q-space offer an interesting trade-off between the angular resolution and the radial information gathered in diffusion MRI. A careful design is central in the success of multishell acquisition and reconstruction techniques.

The design of acquisition in multishell is still an open and active field of research, however. In this work, we provide a general method to design multishell acquisition with uniform angular coverage. This method is based on a generalization of electrostatic repulsion to multishell.

The impact of our method on the angular resolution in one and two bundles of fiber configurations is evaluated using simulations. Compared to more commonly used radial sampling, we show that our method improves the angular resolution, as well as fiber crossing discrimination.

This work has been published in [14].

6.1.2. Motion detection in diffusion MRI via online ODF estimation

Participants: Emmanuel Caruyer [SBIA, University of Pennsylvania Medical School,USA], Iman Aganj [Martinos Center for Biomedical Imaging, MGH, Harvard Medical School,USA], Christophe Lenglet [CMRR, Department of Radiology, University of Minnesota,USA], Guillermo Sapiro [Electrical & Computer Engineering Dept, Duke University,USA], Rachid Deriche.

The acquisition of high angular resolution diffusion MRI is particularly long and subject motion can become an issue. The orientation distribution function (ODF) can be reconstructed online incrementally from diffusion-weighted MRI with a Kalman filtering framework. This online reconstruction provides real-time feedback throughout the acquisition process. In this work, the Kalman filter is first adapted to the reconstruction of the ODF in constant solid angle. Then, a method called STAR (STatistical Analysis of Residuals) is presented and applied to the online detection of motion in high angular resolution diffusion images. Compared to existing techniques, this method is image based and is built on top of a Kalman filter. Therefore, it introduces no additional scan time and does not require additional hardware. The performance of STAR is tested on simulated and real data and compared to the classical generalized likelihood ratio test. Successful detection of small motion is reported (rotation under 2 degrees) with no delay and robustness to noise.

This work has been published in [13].

6.1.3. A Robust variational approach for simultaneous smoothing and estimation of DTI

Participants: Rachid Deriche, Meizhu Liu [Department of CISE, University of Florida, Gainesville, USA], Baba C. Vemuri [Department of CISE, University of Florida, Gainesville, USA].

Estimating diffusion tensors is an essential step in many applications — such as diffusion tensor image (DTI) registration, segmentation and fiber tractography. Most of the methods proposed in the literature for this task are not simultaneously statistically robust and feature preserving techniques. In this work, we propose a novel and robust variational framework for simultaneous smoothing and estimation of diffusion tensors from diffusion MRI. Our variational principle makes use of a recently introduced total Kullback–Leibler (tKL) divergence for DTI regularization. tKL is a statistically robust dissimilarity measure for diffusion tensors, and regularization by using tKL ensures the symmetric positive definiteness of tensors automatically. Further, the regularization is weighted by a non-local factor adapted from the conventional non-local means filters. Finally, for the data fidelity, we use the nonlinear least-squares term derived from the Stejskal–Tanner model. We present experimental results depicting the positive performance of our method in comparison to competing methods on synthetic and real data examples.

This work has been published in [20].

6.1.4. Tensor estimation and visualization using dMRI

Participants: Dalila Cherifi [University of Boumerdes, Algeria], Ali Chellouche [University of Boumerdes, Algeria], Amazigh Ait-Ouakli [University of Boumerdes, Algeria], Youcef Benamara [University of Boumerdes, Algeria], Rachid Deriche.

Diffusion tensor imaging in a non-invasive in vivo image modality that allows us to measure molecular diffusion of water in tissues. We characterize diffusion transport of water by an effective diffusion tensor D. The practical importance of the effective diffusion tensor is that it contains new and useful structural and physiological informations about tissues that were previously unobtainable. In this work, we present a software implementation of the estimation of these tensors and their visualization in order to extract these informations.

This work has been published in [28]

6.2. Modeling in Diffusion MRI

6.2.1. A computational diffusion MRI and parametric dictionary learning framework for modeling the diffusion signal and its features

Participants: Sylvain Merlet, Emmanuel Caruyer [SBIA, University of Pennsylvania Medical School,USA], Aurobrata Ghosh, Rachid Deriche.

In this work, we first propose an original and efficient computational framework to model continuous diffusion MRI (dMRI) signals and analytically recover important diffusion features such as the Ensemble Average Propagator (EAP) and the Orientation Distribution Function (ODF). Then, we develop an efficient parametric dictionary learning algorithm and exploit the sparse property of a well-designed dictionary to recover the diffusion signal and its features with a reduced number of measurements. The properties and potentials of the technique are demonstrated using various simulations on synthetic data and on human brain data acquired from 7T and 3T scanners. It is shown that the technique can clearly recover the dMRI signal and its features with a much better accuracy compared to state-of-the-art approaches, even with a small and reduced number of measurements. In particular, we can accurately recover the ODF in regions of multiple fiber crossing, which could open new perspectives for some dMRI applications such as fiber tractography.

This work has been published in Medical Image Analysis [21]. It is part of Merlet's PhD thesis defended on Sept. 11th, 2013 [11].

6.2.2. Continuous diffusion signal, EAP and ODF estimation via compressive sensing in diffusion MRI

Participants: Sylvain Merlet, Rachid Deriche.

In this work, we exploit the ability of Compressed Sensing (CS) to recover the whole 3D Diffusion MRI (dMRI) signal from a limited number of samples while efficiently recovering important diffusion features such as the Ensemble Average Propagator (EAP) and the Orientation Distribution Function (ODF). Some attempts to use CS in estimating diffusion signals have been done recently. However, this was mainly an experimental insight of CS capabilities in dMRI and the CS theory has not been fully exploited. In this work, we also propose to study the impact of the sparsity, the incoherence and the RIP property on the reconstruction of diffusion signals. We show that an efficient use of the CS theory enables to drastically reduce the number of measurements commonly used in dMRI acquisitions. Only 20–30 measurements, optimally spread on several b-value shells, are shown to be necessary, which is less than previous attempts to recover the diffusion signal using CS. This opens an attractive perspective to measure the diffusion signals in white matter within a reduced acquisition time and shows that CS holds great promise and opens new and exciting perspectives in diffusion MRI (dMRI).

This work has been published in Medical Image Analysis [22]. It is part of Merlet's PhD thesis defended on Sept. 11th, 2013 [11].

6.2.3. Constrained diffusion kurtosis imaging using ternary quartics & MLE

Participants: Aurobrata Ghosh, Tristan Milne, Rachid Deriche.

Diffusion kurtosis imaging (DKI) is a recent improvement over diffusion tensor imaging that characterizes tissue by quantifying non-gaussian diffusion using a 3D fourth-order kurtosis tensor. DKI needs to consider three constraints to be physically relevant. Further, it can be improved by considering the Rician signal noise model. A DKI estimation method is proposed that considers all three constraints correctly, accounts for the signal noise and incorporates efficient gradient-based optimization to improve over existing methods.

In this work, the ternary quartic parameterization is utilized to elegantly impose the positivity of the kurtosis tensor implicitly. Sequential quadratic programming with analytical gradients is employed to solve nonlinear constrained optimization efficiently. Finally, a maximum likelihood estimator based on Rician distribution is considered to account for signal noise.

Extensive experiments conducted on synthetic data verify a MATLAB implementation by showing dramatically improved performance in terms of estimation time and quality. Experiments on in vivo cerebral data confirm that in practice the proposed method can obtain improved results.

This work has been published in [18].

6.2.4. Compressive Sensing DSI

Participants: Sylvain Merlet, Michael Paquette [Sherbrooke Connectivity Imaging Laboratory, Computer Science Departement, Université de Sherbrooke, Québec, Canada], Maxime Descoteaux [Sherbrooke Connectivity Imaging Laboratory, Computer Science Departement, Université de Sherbrooke, Québec, Canada], Rachid Deriche.

Compressive Sensing (CS) offers an efficient way to decrease the number of measurements required in Diffusion Spectrum Imaging (DSI). This method aims to reconstruct the Ensemble Average Propagator (EAP) and, for the purpose of this contest, we compute the numerical Orientation Distribution Function (ODF) by integrating the EAP over a solid angle. In this abstract, we briefly describe three important points underlying the CS technique in order to accelerate DSI, namely the sparsity, the Restricted Isometry Property (RIP) and the L1 reconstruction scheme. Due to the high b-values required in the sampling protocol, our approach enters the heavyweight sampling category. Nevertheless, only 64 measurements are used for the reconstruction.

This work has been published in [31]. It is part of Merlet's PhD thesis defended on Sept. 11th, 2013 [11].

6.2.5. 4th Order symmetric tensors and positive ADC modelling

Participants: Aurobrata Ghosh, Rachid Deriche.

High Order Cartesian Tensors (HOTs) were introduced in Generalized DTI (GDTI) to overcome the limitations of DTI. HOTs can model the apparent diffusion coefficient (ADC) with greater accuracy than DTI in regions with fiber heterogeneity. Although GDTI HOTs were designed to model positive diffusion, the straightforward least square (LS) estimation of HOTs doesn't guarantee positivity. In this work, we address the problem of estimating 4th order tensors with positive diffusion profiles. Two known methods exist that broach this problem, namely a Riemannian approach based on the algebra of 4th order tensors, and a polynomial approach based on Hilbert's theorem on non-negative ternary quartics. In this work, we review the technicalities of these two approaches, compare them theoretically to show their pros and cons, and compare them against the Euclidean LS estimation on synthetic, phantom and real data to motivate the relevance of the positive diffusion profile constraint.

This work has been published in [37].

6.2.6. Higher-Order tensors in diffusion imaging: A survey

Participants: Thomas Schultz [MPI for Intelligent Systems, Tubingen, Germany], Andrea Fuster [Eindhoven University of Technology, The Netherlands], Aurobrata Ghosh, Luc Florack [Eindhoven University of Technology, The Netherlands], Rachid Deriche, Lek-Heng Lim [University of Chicago, USA].

Diffusion imaging is a noninvasive tool for probing the microstructure of fibrous nerve and muscle tissue. Higher-order tensors provide a powerful mathematical language to model and analyze the large and complex data that is generated by its modern variants such as High Angular Resolution Diffusion Imaging (HARDI) or Diffusional Kurtosis Imaging. This survey gives a careful introduction to the foundations of higher-order tensor algebra, and explains how some concepts from linear algebra generalize to the higher-order case. From the application side, it reviews a variety of distinct higher-order tensor models that arise in the context of diffusion imaging, such as higher-order diffusion tensors, q-ball or fiber Orientation Distribution Functions (ODFs), and fourth-order covariance and kurtosis tensors. By bridging the gap between mathematical foundations and application, it provides an introduction that is suitable for practitioners and applied mathematicians alike, and propels the field by stimulating further exchange between the two.

This work has been published in [39].

6.2.7. Regularized spherical polar fourier diffusion MRI with optimal dictionary learning

Participants: Jian Cheng [University of North Carolina at Chapel Hill,USA], Tianzi Jiang [LIAMA, China], Rachid Deriche, Shen Dinggang [University of North Carolina at Chapel Hill,USA], Yap Pew-Thian [University of North Carolina at Chapel Hill,USA].

One important problem in diffusion MRI (dMRI) is to recover the diffusion weighted signal from only a limited number of samples in q-space. An ideal framework for solving this problem is Compressed Sensing (CS), which takes advantage of the signal's sparseness or compressibility, allowing the entire signal to be reconstructed from relatively few measurements. CS theory requires a suitable dictionary that sparsely represents the signal. To date in dMRI there are two kinds of Dictionary Learning (DL) methods: 1) discrete representation based DL (DR-DL), and 2) continuous representation based DL (CR-DL). Due to the discretization in q-space, DR-DL suffers from the numerical errors in interpolation and regridding. By considering a continuous representation using Spherical Polar Fourier (SPF) basis, this work proposes a novel CR-DL based Spherical Polar Fourier Imaging, called DL-SPFI, to recover the diffusion signal as well as the Ensemble Average Propagator (EAP) in continuous 3D space with closed form. DL-SPFI learns an optimal dictionary from the space of Gaussian diffusion signals. Then the learned dictionary is adaptively applied for different voxels in a weighted LASSO framework to robustly recover the di ffusion signal and the EAP. Compared with the start-of-the-art CR-DL method by Merlet et al. and DRDL by Bilgic et al., DL-SPFI has several advantages. First, the learned dictionary, which is proved to be optimal in the space of Gaussian diffusion signal, can be applied adaptively for different voxels. To our knowledge, this is the first work to learn a voxel-adaptive dictionary. The importance of this will be shown theoretically and empirically in the context of EAP estimation. Second, based on the theoretical analysis of SPF basis, we devise an efficient learning process in a small subspace of SPF coefficients, not directly in q-space as done by Merlet et al.. Third, DL-SPFI also devises different regularization for different atoms in the learned dictionary for robust estimation,

by considering the structural prior in the space of signal exemplars. We evaluate DL-SPFI in comparison to L1-norm regularized SPFI (L1-SPFI) with fixed SPF basis, and the DR-DL by Bilgic et al. The experiments on synthetic data and real data demonstrate that the learned dictionary is sparser than SPF basis and yields lower reconstruction error than Bilgic's method, even though only simple synthetic Gaussian signals were used for training in DL-SPFI in contrast to real data used by Bilgic et al.

This work has been published in [27].

6.2.8. Fiber orientation distribution from non-negative sparse recovery

Participants: Aurobrata Ghosh, Thinhinane Megherbi [USTHB, Algeria], Linda Oulebsir-Boumghar [USTHB, Algeria], Rachid Deriche.

We revisit the theory of spherical deconvolution and propose a new fiber orientation distribution (FOD) model that can efficiently reconstruct extremely narrow fiber-crossings from limited number of acquisitions. First, we show how to physically model fiber-orientations as rank-1 tensors. Then, we parameterize the FODs with tensors that are decomposable into non-negative sums of rank-1 tensors and finally, we propose a non-negative sparse recovery scheme to estimate FODs of any tensor order from limited acquisitions. Our method features three important advantages: (1) it estimates non-negative FODs, (2) it estimates the number of fiber-compartments, which need not be predefined and (3) it computes the fiber-directions directly, rendering maxima detection superfluous. We test for various SNRs on synthetic, phantom and real data and find our method accurate and robust to signal-noise: fibers crossing up to 23° are recovered from just 21 acquisitions. This opens new and exciting perspectives in diffusion MRI (dMRI), where our improved characterization of the FOD can be of great help for applications such as tractography.

This work has been published in [29].

6.2.9. A polynomial approach for extracting the extrema of a spherical function and its application in diffusion MRI

Participants: Aurobrata Ghosh, Elias Tsigaridas [PolSys Project-Team, Inria, Paris Rocquencourt, France], Bernard Mourrain [Galaad Project-Team, Inria, Sophia Antipolis, Méditerranée, France], Rachid Deriche.

This work has been partially supported by the ANR project NucleiPark and the France-Parkinson Association.

Antipodally symmetric spherical functions play a pivotal role in diffusion MRI in representing sub-voxel-resolution microstructural information of the underlying tissue. This information is described by the geometry of the spherical function. In this work we propose a method to automatically compute all the extrema of a spherical function. We then classify the extrema as maxima, minima and saddle-points to identify the maxima. We take advantage of the fact that a spherical function can be described equivalently in the spherical harmonic (SH) basis, in the symmetric tensor (ST) basis constrained to the sphere, and in the homogeneous polynomial (HP) basis constrained to the sphere. We extract the extrema of the spherical function by computing the stationary points of its constrained HP representation. Instead of using traditional optimization approaches, which are inherently local and require exhaustive search or re-initializations to locate multiple extrema, we use a novel polynomial system solver which analytically brackets all the extrema and refines them numerically, thus missing none and achieving high precision.

To illustrate our approach we consider the Orientation Distribution Function (ODF). In diffusion MRI the ODF is a spherical function which represents a state-of-the-art reconstruction algorithm whose maxima are aligned with the dominant fiber bundles. It is, therefore, vital to correctly compute these maxima to detect the fiber bundle directions. To demonstrate the potential of the proposed polynomial approach we compute the extrema of the ODF to extract all its maxima. This polynomial approach is, however, not dependent on the ODF and the framework presented in this work can be applied to any spherical function described in either the SH basis, ST basis or the HP basis.

This work has been published in [19].

6.2.10. ODF maxima computation using hill climbing algorithm

Participants: Thinhinane Megherbi [USTHB, Algeria], Makhlouf Laouchedi [EMP, Algeria], Houssem Khabatti [EMP, Algeria], Linda Oulebsir-Boumghar [USTHB, Algeria], Ishak Serrat [EMP, Algeria], Vincent Perlbarg [LIF, UMRS 678, INSERM, UPMC - Paris 6], Rachid Deriche.

Diffusion MRI (dMRI) is the only technique to probe in-vivo and non-invasively fiber structure of white matter. Diffusion was first modeled using the classical Second Order Diffusion Tensor model. However, this model is limited in regions of multiple fiber crossings and this has motivated the development of many approaches to extract crossing fibers. Methods like Diffusion Spectrum Imaging (DSI), High Angular Resolution Diffusion Imaging (HARDI) and the High Order Tensor techniques have been proposed to reconstruct specific functions like the Orientation Distribution Function (ODF) whose maxima do correspond to the directions of the multiple fibers.

In this work, we are interested to extract all the crossing fibers characterized as the maxima of the Orientation Distribution Function (ODF). A Hill Climbing algorithm based approach has been developed and implemented to efficiently and accurately extract all the fibers. Promising experimental results obtained with synthetic and real data illustrate the potential of the technique.

This work has been submitted to ISBI'2014 and accepted for presentation and publication.

6.2.11. On SHORE and SPF bases

Participants: Elodie Pozzi, Gonzalo Sanguinetti, Rachid Deriche.

The 3D Simple Harmonic Oscillation Reconstruction and Estimation (SHORE) basis and the Spherical Polar Fourier (SPF) basis were introduced recently to represent the dMRI signal in the full 3D Q-space. SPF presents some continuity problems at the origin which led to our development of the modified SPF basis we introduced to overcome this issue. These bases can be written with radial and angular functions. The radial part of the decomposition is a family of orthogonal functions (the Gauss-Laguerre functions) and the angular component are the spherical harmonic functions. Even though they look similar, they have different properties. The first objective of this work has been to analyse and clarify the differences between those bases. This has been accomplished by describing the spanned spaces. The second goal has been to classify the bases according to their continuity and differentiability and thus draw a more focused comparison between.

This on-going work will be submitted to a journal.

6.3. From DW-MRI to Fiber Pathways and Microstructures Recovery

6.3.1. Mapping Average axon diameters under long diffusion time

Participants: Gonzalo Sanguinetti, Rachid Deriche.

This work proposes an original method to recover axon diameter distribution (ADD) parameters using nuclear magnetic resonance. White matter (WM) is modelled as a bi-compartmental medium composed of an intra axonal space where the diffusion is restricted and an extra axonal space where diffusion is hindered. Under the assumption of long diffusion time, we provide a novel and efficient model for the component of the signal due to the restricted part. This technique might be interpreted as an interesting simplification of the AxCaliber framework, which leads to a simpler model and an extremely faster acquisition protocol. To test and validate our method, we use the open-source toolkit Camino for computing Monte-Carlo simulations of NMR data and model the WM as 3D cubic environments, formed by parallel cylinders with gamma distributed radii. Promising experimental results illustrate the potential of the proposed method.

This work has been submitted to ISBI'2014 and accepted for presentation and publication.

6.3.2. NMR characterization of cylinder radii distribution using a SHORE-based regularization method.

Participants: Gonzalo Sanguinetti, Daniel Alexander [Centre for Medical Image Computing, Dept. Computer Science, UCL], Matt Hall [Centre for Medical Image Computing, Dept. Computer Science, UCL], Rachid Deriche.

In this work, we extend the framework presented by Ozarslan et al [79] by adding a regularization term for better measuring the moments of a cylinder radii distribution by means of NMR acquisitions. The added value of the regularization term is tested and validated using Monte Carlo simulations of NMR signals from complex white matter-like environment. The open source toolkit CAMINO [50] is used for computing the simulations and an excellent agreement is obtained between the ground truth and the estimated moments.

This work has been submitted to ISMRM'2014.

6.3.3. Quantitative comparison of reconstruction methods for intra-voxel fiber recovery from diffusion MRI

Participants: Emmanuel Caruyer [SBIA, University of Pennsylvania Medical School, USA], Sylvain Merlet, Rachid Deriche.

In diffusion MRI, a technique known as diffusion spectrum imaging reconstructs the propagator with a discrete Fourier transform, from a Cartesian sampling of the diffusion signal. Alternatively, it is possible to directly reconstruct the orientation distribution function in q-ball imaging, providing so-called high angular resolution diffusion imaging. In between these two techniques, acquisitions on several spheres in q-space offer an interesting trade-off between the angular resolution and the radial information gathered in diffusion MRI. A careful design is central in the success of multishell acquisition and reconstruction techniques and the design of acquisition in multishell is still an open and active field of research.

In this work, we propose a novel method to design sampling schemes with optimal angular coverage and show the positive impact on angular resolution in diffusion MRI. Our method is based on a generalization of electrostatic repulsion to multishell and allows to design multishell acquisition with uniform angular coverage.

We evaluated the impact of our method using simulations, on the angular resolution in one and two bundles of fiber configurations. Compared to more commonly used radial sampling, we show that our method improves the angular resolution, as well as fiber crossing discrimination.

This work has been published in [16].

6.3.4. Choosing tractography parameters to improve connectivity mapping

Participants: Gabriel Girard [SCIL Lab., Sherbrooke University], Kevin Whittingstall [SCIL Lab., Sherbrooke University], Kevin Whittingstall [SCIL Lab., Sherbrooke University], Rachid Deriche.

Diffusion-weighted imaging (DWI) is often used as a starting point for in vivo white matter (WM) connectivity to reconstruct potential WM pathways between brain areas. Tractography algorithms have many parameters which can influence reconstruction and connectivity. Various choices of parameters have been proposed. But how does one choose the best set of parameters ? In this study, we varied three critical parameters while monitoring connectivity score using the Tractometer evaluation system on the International Symposium on Biomedical Imaging (ISBI) Challenge synthetic dataset. The three parameters were: The maximum deviation angle between two consecutive tractography steps (this addresses the hypothesis of smoothness of the WM pathways), the spherical function (SF) threshold (this aims at removing noisy propagation directions during the tractography process) and the initial SF threshold (this aims at removing initial noise at the seeds and to start tractography in a good tangent direction to the WM bundle).

This work has been submitted to ISMRM'2014.

6.3.5. Improved tractography using structural priors

Participants: Gabriel Girard [SCIL Lab., Sherbrooke University], Maxime Descoteaux [SCIL Lab., Sherbrooke University], Kevin Whittingstall [SCIL Lab., Sherbrooke University], Rachid Deriche.

In this work, we propose better tractography parameters in term of global connectivity and a novel tractography stopping criterion based on partial volume estimation maps, calculated from a T1-weighted image. We also propose a particle filtering method using anatomical information as prior for tractography to enforce streamlines connecting gray matter regions and reducing the proportion of erroneous streamlines. Results show streamlines more uniformly distributed among long and short, and small and large white matter bundles. This provides connectivity estimation not underestimated for bundles having higher complexity. Quantitative analysis is done on synthetic datasets and qualitative results are shown on real data. The proposed method takes advantage of prior information on the brain to change the dMRI-based tracking direction and help providing streamlines that can quantify the brain structure.

This on-going work will be submitted to NeuroImage.

6.3.6. From diffusion MRI to brain connectomics

Participants: Aurobrata Ghosh, Rachid Deriche.

Diffusion MRI (dMRI) is a unique modality of MRI which allows one to indirectly examine the microstructure and integrity of the cerebral white matter in vivo and non-invasively. Its success lies in its capacity to reconstruct the axonal connectivity of the neurons, albeit at a coarser resolution, without having to operate on the patient, which can cause radical alterations to the patient's cognition. Thus dMRI is beginning to assume a central role in studying and diagnosing important pathologies of the cerebral white matter, such as Alzheimer's and Parkinson's diseases, as well as in studying its physical structure in vivo. In this work, we present an overview of the mathematical tools that form the framework of dMRI – from modelling the MRI signal and measuring diffusion properties, to reconstructing the axonal connectivity of the cerebral white matter, i.e., from Diffusion Weighted Images (DWIs) to the human connectome.

This work has been published in [38].

6.4. Forward and Inverse Problems in MEEG

6.4.1. Source localization using rational approximation on plane sections

Participants: Maureen Clerc [Athena Project-Team, Inria, Sophia Antipolis, Méditerranée, France], Théodore Papadopoulo [Athena Project-Team, Inria, Sophia Antipolis, Méditerranée, France], Juliette Leblond [Apics Project-Team, Inria, Sophia Antipolis, Méditerranée, France], Jean-Paul Marmorat [CMA, Ecole des Mines Paristech, Sophia Antipolis, France].

In functional neuroimaging, a crucial problem is to localize active sources within the brain non-invasively, from knowledge of electromagnetic measurements outside the head. Identification of point sources from boundary measurements is an ill-posed inverse problem. In the case of electroencephalography (EEG), measurements are only available at electrode positions, the number of sources is not known in advance and the medium within the head is inhomogeneous. We have presented [49] a new method for EEG source localization, based on rational approximation techniques in the complex plane. The method is used in the context of a nested sphere head model, in combination with a cortical mapping procedure. Results on simulated data prove the applicability of the method in the context of realistic measurement configurations. In the continuation of this work, we are in discussion with an industrial partner (BESA, Munich) for a scientific partnership.

6.4.2. Dictionary learning for multitrial datasets

Participants: Maureen Clerc, Sebastian Hitziger, Théodore Papadopoulo.

Following the path opened with the Consensus matching Pursuit method (CMP) [46], we continue our endeavour to avoid signal averaging using directly the raw signal with the assumption that events of interest are those that repeat in each trial [36]. Towards such a goal, and to improve the simple dictionary used in CMP, we have adapted dictionary learning methods to multitrial bio-electric signals, by explicitly implementing jitter invariance [30]. This allows for a much more detailed data-driven description of events. For example, using local field potential signals of chemically induced spikes (in a rat model), we have been able to distinguish several spike shapes which show some coherence in time. The method has been recently extended to detect spike events in continuous signals (i.e. not organized in epochs). While it requires a good signal to noise ratio, the method is very general and has also been used for various other signal types (see section 6.5).

6.5. Coupling functional and structural models

6.5.1. Cortex parcellation via diffusion data as prior knowledge for the MEG inverse problem

Participants: Anne-Charlotte Philippe, Maureen Clerc, Théodore Papadopoulo, Rachid Deriche.

In this work, a new approach is presented for the recovery of dipole magnitudes in a distributed source model for magnetoencephalographic (MEG) imaging. This method consists in introducing prior knowledge regarding the anatomical connectivity in the brain to this ill-posed inverse problem. Towards this goal, a cortex parcellation is performed using structural information coming from diffusion MRI (dMRI), the only non-invasive modality allowing to have access to the structure of the WM tissues. Then, sources in the same diffusion parcel are constrained, in the MEG inverse problem, to have close magnitude values. Results of our method on MEG simulations are presented and favorably compared with classical source reconstruction methods.

This work has been published in [32], and is part of A.C. Philippe's Ph.D thesis [12].

6.5.2. Diffusion-Weighted Imaging tractography-based parcellation of the human cortex as regularization term for the MEG inverse problem

Participants: Anne-Charlotte Philippe, Maureen Clerc, Théodore Papadopoulo, Rachid Deriche.

The purpose of this work is to advocate the use of structural connectivity information to regularize the ill-posed MEG inverse problem. Diffusion MRI being the only non invasive modality allowing to have access to the connectivity profile of cortical sources, the proposed method called Diff-MNE consists in the introduction of a cortex parcellation based on diffusion data regularization term to the MEG inverse problem. Our method is tested on synthetic and real human brain data and compared to the classical minimum-norm method. Results show that a diffusion-based cortex parcellation as a regularization term for the MEG inversion process improves the source reconstruction. This proves the interest of merging diffusion MRI and MEG data.

This work is under submission to a Neuroimage and is part of A.C. Philippe's Ph.D thesis [12]

6.5.3. Propagation of epileptic spikes revealed by diffusion-based constrained MEG source reconstruction

Participants: Anne-Charlotte Philippe, Maureen Clerc, Théodore Papadopoulo, Rachid Deriche.

In this work, we study the propagation of an epileptic spike (from single event data). As in the two previous sections, a cortex parcellation is performed using structural information coming from diffusion MRI Then, a MEG inverse problem is defined on a parcellated source space which imposes constant activity on each parcel. This inverse problem is applied separately for measurements obtained in a given time range. The most active parcels over the time range are located and their time course are displayed. This allowed the study of the propagation of an epileptic spike via those active parcels. Results on real data shows varying spatial propagations of an epileptic spike for the same subject.

This work has been published in [40], and is part of A.C. Philippe's Ph.D thesis [12].

6.6. Brain Computer Interfaces

6.6.1. Combining ERD and ERS features to create a system-paced BCI

Participants: Maureen Clerc, Joan Fruitet, Théodore Papadopoulo, Eoin Thomas.

An important factor in the usability of a brain computer interface (BCI) is the setup and calibration time required for the interface to function accurately. Recently, brain-switches based on the rebound following motor imagery of a single limb effector have been investigated as basic BCIs due to their good performance with limited electrodes, and brief training session requirements. In this work, a BCI is proposed which expands the methodology of brain-switches to design an interface composed of multiple brain-buttons. The algorithm is designed as a system paced interface which can recognise 2 intentional-control tasks and a no-control state based on the activity during and following motor imagery in only 3 electroencephalogram channels. An online experiment was performed over 6 subjects to validate the algorithm, and the results show that a working BCI can be trained from a single calibration session and that the post motor imagery features are both informative and robust over multiple sessions.

This work has been published in [24].

6.6.2. An analysis of performance evaluation for motor-imagery based BCI

Participants: Maureen Clerc, Matthew Dyson [Laboratoire de Neurosciences Cognitives, Marseille], Eoin Thomas.

In recent years, numerous brain–computer interfaces (BCIs) based on motor-imagery have been proposed which incorporate features such as adaptive classification, error detection and correction, fusion with auxiliary signals and shared control capabilities. Due to the added complexity of such algorithms, the evaluation strategy and metrics used for analysis must be carefully chosen to accurately represent the performance of the BCI. In this work, metrics are reviewed and contrasted using both simulated examples and experimental data. Furthermore, a review of the recent literature is presented to determine how BCIs are evaluated, in particular, focusing on the relationship between how the data are used relative to the BCI subcomponent under investigation. From the analysis performed in this study, valuable guidelines are presented regarding the choice of metrics and evaluation strategy dependent upon any chosen BCI paradigm.

This work has been published in [23].

6.6.3. Bandit algorithms for faster task selection in BCI

Participants: Maureen Clerc, Aurélien Emmanuel, Joan Fruitet [former Athena PhD student], Alexandra Carpentier [Sequel Project-Team, Inria Lille], Rémi Munos [Sequel Project-Team, Inria Lille].

Brain–computer interfaces (BCIs) based on sensorimotor rhythms use a variety of motor tasks, such as imagining moving the right or left hand, the feet or the tongue. Finding the tasks that yield best performance, specifically to each user, is a time-consuming preliminary phase to a BCI experiment. This study presents a new adaptive procedure to automatically select (online) the most promising motor task for an asynchronous brain-controlled button. We have developed for this purpose an adaptive algorithm UCB-classif based on the stochastic bandit theory and design an EEG experiment to test our method. We compare (offline) the adaptive algorithm to a naïve selection strategy which uses uniformly distributed samples from each task. We also run the adaptive algorithm online to fully validate the approach. By not wasting time on inefficient tasks, and focusing on the most promising ones, this algorithm results in a faster task selection and a more efficient use of the BCI training session. More precisely, the offline analysis reveals that the use of this algorithm can reduce the time needed to select the most appropriate task by almost half without loss in precision, or alternatively, allow us to investigate twice the number of tasks within a similar time span. Online tests confirm that the method leads to an optimal task selection. This study is the first one to optimize the task selection phase by an adaptive procedure. By increasing the number of tasks that can be tested in a given time span, the proposed method could contribute to reducing 'BCI illiteracy'.

This work has been published in [17].

6.6.4. Enhancing visuospatial attention performance with brain-computer interfaces

Participants: Thomas Brochier [Institut des Neurosciences de La Timone, Marseille], Maureen Clerc, Romain Trachel.

Brain-Computer Interfaces (BCI) can provide innovative solutions beyond the medical domain. In human research, visuospatial attention is often assessed from shifts in head or gaze orientation. However in some critical situations, these behavioral features can be dissociated from covert attention processes and brain features may indicate more reliably the spatial focus of attention. In this context, we investigate whether EEG signals could be used to enhance the behavioral performance of human subjects in a visuospatial attention task. Our results demonstrate that a BCI protocol based on adaptive or warning displays can be developed to shorten the reaction time and improve the accuracy of responses to complex visual targets. We performed offline and online tests demonstrating the validity of this type of approach.

This work was presented at conferences in the HCI community [35] and in the Neural Engineering community [34].

6.6.5. Verbal communication through brain computer interfaces

Participants: Maureen Clerc, Dieter Devlaminck, Claude Desnuelle [CHU de Nice l'Archet], Violaine Guy [CHU de Nice l'Archet], Manu Maby [Centre de Recherche Neurologique de Lyon], Jérémie Mattout [Centre de Recherche Neurologique de Lyon], Théodore Papadopoulo.

Brain Computer Interfaces (BCI) provide a way of communicating directly from brain activity, bypassing muscular control. We report some recent advances in a BCI communication system called the P300 speller, which is a virtual brain-operated keyboard. This system relies on electroencephalographic activity time-locked to the flashing of the desired letters. It requires calibration of the system, but very little training from the user. Clinical tests are being conducted on a target population of patients suffering from Amyotrophic Lateral Sclerosis, in order to confirm the usability of the P300 speller for reliable communication.

This work has been published in [26]. It is also the object of an intensive clinical study on 20 patients which we are currently conducting at Nice University Hospital.

7. Bilateral Contracts and Grants with Industry

7.1. Patent

Participants: Maureen Clerc, Thomas Brochier, Romain Trachel.

A French patent (number 13 60563) was filed on 29 october 2013. It describes a Brain Computer Interface to enhance human performance in visuo-spatial attention tasks.

7.2. CIFRE PhD contract with Neurelec

Participants: Maureen Clerc, Kai Dang, Théodore Papadopoulo, Jonathan Laudanski [Neurelec].

Title: Modeling and characterizing electrical conductivity for the placement of cochlear implants.
Neurostimulation consists in applying an electrical current close to a nerve to trigger its activation. This is the principle of cochlear implants, which aim to stimulate the auditory nerve via an electrode coil inserted in the cochlea. The interplay between the stimulating electrodes and the bioelectrical medium is modeled by a partial differential equation whose main parameters are the electrical conductivity and geometry of the tissues. This equation also links active sources and electric potential measurements by electroencephalography. The objective of this PhD thesis is to propose models for efficiently representing tissues and their electrical conductivity within the auditory system (bone, cochlea, ganglia, auditory cortex). This will make it possible to optimize the stimulating current, thanks to a better knowledge of the current diffusion due to the anatomical conformation of the cochlea.

7.3. PACA PhD contract with Olea Medical

Participants: Marco Pizzolato, Rachid Deriche.

Title: Diffusion & Perfusion MRI : From bench to bedside

The objectives of this PhD thesis are to develop innovative techniques in diffusion and perfusion MRI in close collaboration with OLEA MEDICAL. A certain number of important issues related to dMRI and pMRI signal processing and modeling have been identified by ATHENA and OLEA MEDICAL. These technical issues will be tackled within the framework of this PhD thesis fully granted by the Region PACA and by OLEA MEDICAL.

7.4. dMRI@Olea-Medical

Participants: Aurobrata Ghosh, Théodore Papadopoulo, Rachid Deriche.

The ongoing collaboration with OLEA MEDICAL has allowed us to form a crucial link between academic research at ATHENA and the medical imaging industry, via OLEA MEDICAL. Since Auro's recruitment in May and following a planned road-map, we have been developing a generic and templated C++ core library comprised of the expert algorithms researched at ATHENA in the domain of diffusion MRI. This library and its functionalities are being integrated into OLEA MEDICAL's flagship product Olea Sphere. So far the following non-exhaustive list of estimation modules have been implemented – DTI (least squares (LS), weighted least squares (WLS) & Cholesky, which provides positivity constraint); Generalized DTI using tensors of order 4 (LS, WLS & Ternary Quartics (TQ) which provides positivity constraint) and DKI (LS, WLS, Cholesky + TQ for positivity). Further a number of biomarkers or scalar strains for each of these models have also been implemented, such as FA, MD, VR, RA, MK, etc. The external tools used consist of well known standard libraries and softwares such as C++ STL, LAPACK, NLOpt, CMake, Git, etc. Finally an externally callable C-interface is provided to wrap the core C++ library, which makes it useable from C++ and C programs.

The next milestones on the road-map includes higher order models such as ODFs, FODs, EAPs, etc. This will be followed up by tractography algorithms – both deterministic and probabilistic.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

8.1.1.1. ANR ViMAGINE

Participants: Maureen Clerc, Rachid Deriche, Alexandre Gramfort [Parietal project-team, ENST since september 2012], Emmanuel Olivi [Former member of the Athena Project-Team], Théodore Papadopoulo, Anne-Charlotte Philippe.

Duration: *July 2008 to July 2013*

The partners of this project are ATHENA, the LENA (CHU Pitié-Salpétrière), and the Parietal project-team at Inria Futurs and Neurospin-Saclay.

This project takes a new challenge on the non invasive exploration of the Human visual system in vivo. Beyond the basic mechanisms of visual perception – which have already been investigated at multiple scales and through a large variety of modalities – we are primarily interested in proposing and exploring innovative solutions to the investigation of dynamic neural activations and interactions at the systems level. Bridging the elements involved in this endeavour requires that we are capable of observing, modelling and predicting the interplay between the anatomical/functional architecture of the brain systems and some identified timing properties of neural processes. The overall framework in which this project will be conducted is a federation of partners who will be bringing complementary expertise to this multidisciplinary research. The collaborators include experts in (1) electromagnetic and magnetic resonance brain imaging methods, (2) computational models of neural systems and (3) the neuroscience of vision. A central asset of our group is the easy access to state-of-the-art imaging platforms (e.g. high-density MEG and EEG arrays; 3T and 7T MR scanners) that will ensure the acquisition of quality experimental data.

8.1.1.2. ANR CO-ADAPT

Participants: Maureen Clerc, Dieter Devlaminck, Sebastian Hitziger, Loïc Mahé, Théodore Papadopoulo, Eoin Thomas, Romain Trachel.

Duration: *December 2009 to April 2014*

The partners of this projects are the INSERM U821 laboratory of Bron, the "laboratoire de Neurologie de la cognition" UMR6155 CNRS of Marseille, The Inria Lille Sequel project-team and the "Laboratoire d'Analyse Topologie et Probabilités" UMR6632/CNRS of Université de Provence, Marseille.

Brain Computer Interfaces (BCI) provide a direct communication channel from the brain to a computer, bypassing traditional interfaces such as keyboard or mouse, and also providing a feedback to the user, through a sensory modality (visual, auditory or haptic). A target application of BCI is to restore mobility or autonomy to severely disabled patients, but more generally BCI opens up many new opportunities for better understanding the brain at work, for enhancing Human Computer Interaction, and for developing new therapies for mental illnesses.

In BCI, new modes of perception and interaction come into play, and a new user must learn to operate a BCI, as an infant learns to explore his/her sensorimotor system. Central to BCI operation are the notions of feedback and of reward, which we believe should hold a more central position in BCI research.

The goal of this project is to study the co-adaptation between a user and a BCI system in the course of training and operation. The quality of the interface will be judged according to several criteria (reliability, learning curve, error correction, bit rate). BCI will be considered under a joint perspective: the user's and the system's. From the user's brain activity, features must be extracted, and translated into commands to drive the BCI system. Feature extraction from data, and classification issues, are very active research topics in BCI. However, additional markers may also be extracted to modulate the system's behavior. It is for instance possible to monitor the brain's reaction to the BCI outcome, compared to the user's expectations. This type of information we refer to as meta-data because it is not directly related to the command, and it may be qualitative rather than quantitative. To our knowledge, there is so far no BCI system that integrates such meta-data from the user's brain. From the point of view of the system, it is important to devise adaptive learning strategies, because the brain activity is not stable in time. How to adapt the features in the course of BCI operation is a difficult and important topic of research. A Machine Learning method known as Reinforcement Learning (RL) may prove very relevant to address the above questions. Indeed, it is an adaptive learning method that explicitly incorporates a reward signal, which may be qualitative (hence allowing meta-data integration). The aim of CO-ADAPT is to propose new directions for BCI design, by modeling explicitly the co-adaptation taking place between the user and the system (web site http://coadapt.inria.fr).

8.1.1.3. ANR NucleiPark

Participants: Rachid Deriche, Aurobrata Ghosh, Anne-Charlotte Philippe, Antoine Wolfermann.

Duration: *September 2009 to December 2013*

This project is about High field MR imaging (7T and 3T) of the brainstem, the deep nuclei and their connections in the parkinsonian syndromes with applications to prognosis, pathophysiology and improvement of therapeutic strategies. It involves three partners: The NeuroSpin team including C. Poupon and D. Le Bihan, the Inria with our project as well as the VISAGES project-team and the UPMC (University Pierre and Marie Curie, Paris) including INSERM U678 (H. Benali) and the CENIR (S. Lehericy).

The goal of the project is to find new neuroimaging markers of deep brain nuclei in neurodegenerative diseases that can be used for the diagnosis of Parkinsonian syndromes at the early stage. In addition, the goal is the characterization of lesions of deep brain structures and the detection of biomarkers of neuronal lesions in PD that can be related to clinical signs, such as gait disorders. Biomarkers of Parkinsonian syndromes could be used to create a diagnostic tool of the pathology and to correlate the identified markers with clinical signs. We will perform tractography of small fibre bundles using our HARDI techniques and Diffusion markers (anisotropy, apparent diffusion coefficient, fibre density, curvature, average diameter) will be collected along the reconstructed bundles.

Complementary parts of these objectives directly related to the acquisitions protocols have been accepted within the framework of another proposal submitted by the same partners and accepted for grant for two years (2009 & 2010) by the *France-Parkinson Association*

8.1.1.4. ANR Mosifah

Participants: Rachid Deriche, Maureen Clerc, Théodore Papadopoulo, Gonzalo Sanguinetti.

Duration: *October 2013 to September 2017*

This ANR Numerical Models 2013 project is about multimodal and multiscale modelling and simulation of the fiber architecture of the human heart. It started on October 2013 and involves three partners : Creatis Team, INSA, Lyon (I. Magnin, Y. Zhu); TIMC-IMAG, CNRS, Grenoble (Y. Uson) and the ATHENA project team.

It consists in modelling and simulating the ex vivo and in vivo 3D fiber architectures at various scales using multiphysical data from different imaging modalities working at different spatial resolutions. To this end, the myocardium of the human heart will be imaged using respectively Polarized Light Imaging (PLI) and dMRI.

Appropriate diffusion models will be explored including second and fourth order DTI models as well as HARDI models such as the single shell Q-Ball Imaging (QBI). These various types of images will be processed within the right Riemannian mathematical framework to provide tensor as well as Ensemble Average Propagator (EAP) and Orientation Distribution Function (ODF) fields. Virtual cardiac fiber structure (VCFS) will then be modelled using myocardial fiber information derived from each of these imaging modalities. Finally, diffusion behavior of water molecules in these VCFSs will be simulated by means of quantum spin theory, which allows computing ex vivo and in vivo virtual diffusion magnetic resonance (MR) images at various scales ranging from a few microns to a few millimeters. From the obtained virtual diffusion MR images, multiscale and probabilistic atlas describing the 3D fiber architecture of the heart ex vivo and in vivo will be constructed. Meanwhile, the simulation involving a large number of water molecules, grid computing will be used to cope with huge computation resource requirement.

We expect to construct a complete database containing a very wide range of simulated (noise and artifact-free) diffusion images that can be used as benchmarks or ground-truth for evaluating or validating diffusion image processing algorithms and create new virtual fiber models allowing mimicking and better understanding the heart muscle structures. Ultimately, the proposed research can open a completely novel way to approach the whole field of heart diseases including the fundamental understanding of heart physiology and pathology, and new diagnosis, monitoring and treatment of patients.

8.1.1.5. ANR MULTIMODEL

Participants: Théodore Papadopoulo, Maureen Clerc, Sebastian Hitziger, Emmanuel Olivi.

Duration: *December 2010 to May 2014*

The MULTIMODEL project stems from a conjoint INSERM-Inria scientific initiative launched in December 2008 and ended in 2010. It involves 5 partners (Inserm U751 in Marseille, U678 in Paris, U836 in Grenoble, U642 in Rennes and Inria ATHENA project-team).

The general objectives of the MULTIMODEL project are :

- To develop computational models at the level of neuronal systems that will help interpreting neuroimaging data in terms of excitation-, inhibition- and synchronization-related processes.
- To acquire multimodal datasets, obtained in rats and humans under physiological and epileptogenic conditions, which will be used to develop the biophysical models and to test their face validity and predictability.

Specifically, the following questions are dealt with:

- How can models be integrated in order to link data from different modalities (electro/magneto-encephalography, optical imaging, functional MRI)?
- What is the influence of hidden parameters on the observed signals (e.g. ratio of excitation/inhibition and synchronization degree across regions)?
- To what extent can biophysical modelling bring valuable insights on physiological and pathological brain activity ?

We operate at the level of population of cells, i.e. at a scale compatible with the resolution of neuroimaging tools (at the level of the mm). A novel model structure is being investigated, which includes astrocytes at this "mesoscopic" level and operates in networks of connected regions. Moreover, models in physiological and pathological conditions will be compared, which is a step towards a better understanding of mechanisms underlying epileptic condition.

8.1.1.6. ANR VIBRATIONS

Participants: Théodore Papadopoulo, Maureen Clerc, Rachid Deriche.

Duration: *Early 2014 to early 2018*

This Translational ANR project has just been been accepted.

Computational modeling, under the form of a "virtual brain" is a powerful tool to investigate the impact of different configurations of the sources on the measures, in a well-controlled environment.

The VIBRATIONS project proposes to simulate in a biologically realistic way MEG and EEG fields produced by different configurations of brain sources, which will differ in terms of spatial and dynamic characteristics. The research hypothesis is that computational and biophysical models can bring crucial information to clinically interpret the signals measured by MEG and EEG. In particular, they can help to efficiently address some complementary questions faced by epileptologists when analyzing electrophysiological data.

The project follows a three-fold strategy:

- construct virtual brain models with both dynamic aspects (reproducing both hyperexcitability and hypersynchronisation alterations observed in the epileptic brain) and a realistic geometry based on actual tractography measures performed in patients
- explore the parameter space though large-scale simulations of source configurations, using parallel computing implemented on a computer cluster.
- confront the results of these simulations to simultaneous recordings of EEG, MEG and intracerebral EEG (stereotactic EEG, SEEG). The models will be tuned on SEEG signals, and tested versus the surface signals in order to validate the ability of the models to represent real MEG and EEG signals.

The project constitutes a translational effort from theoretical neuroscience and mathematics towards clinical investigation. A first output of the project will be a database of simulations, which will permit in a given situation to assess the number of configurations that could have given rise to the observed signals in EEG, MEG and SEEG. A second – and major - output of the project will be to give the clinician access to a software platform which will allow for testing possible configurations of hyperexcitable regions in a user-friendly way. Moreover, representative examples will be made available to the community through a website, which will permit its use in future studies aimed at confronting the results of different signal processing methods on the same 'ground truth' data.

8.1.2. ADT

8.1.2.1. ADT MedInria-NT

Participants: Jaime Garcia Guevara, Loïc Cadour, Théodore Papadopoulo, Maureen Clerc, Rachid Deriche.

Duration: *December 2010 to December 2012, prolongated to December 2014*

The goal of this technical project, funded by Inria for 2 years, is to introduce some tools developed at ATHENA into the medInria platform. There are basically two such facilities:

- Integrate the tools developed for the statistical characterization of brain white matter fiber bundles.
- Develop an interface for M/EEG data within MedInria. This will focus on two main goals:
  - Create a facility to read and visualize M/EEG signals.
  - Integrate M/EEG forward problem tools.

8.1.2.2. ADT OpenViBe-NT

Participants: Théodore Papadopoulo, Maureen Clerc, Loïc Mahé.

Duration: *October 2012 to December 2014*

OpenViBE is an opensource software which development started in 2005 with the goal of offering an open research tool for BCI and for supporting disabled people. Since its release in 2009, this software has received a lot of success (+10.000 downloads). But since 2005, new use have appeared as well as some limitations. The current software thus lacks of some features that limit its use, deployment and perennity. The goal of this ADT is to solve these problems, to improve and to extend OpenViBe One main goal is to improve the usability and the attractivity of the software and to retain a large community of users so as to ensure its sustainability. This ADT will allow to support the research made in four Inria teams (ATHENA, HYBRID, NEUROSYS and POTIOC) on hot topics such as adaptive or hybrid BCIs.

8.2. International Initiatives

8.2.1. Inria Associate Teams

8.2.1.1. BRAINCONNECTIVITIES

Title: Fusing anatomical and functional connectivity information using diffusion MRI, MEG and EEG.

Inria principal investigator: Théodore PAPADOPOULO

International Partners (Institution - Laboratory - Researcher):

University of Québec, School of Higher Technology (Canada) - PhysNum Group, Centre de recherches mathématiques, Montréal - Théodore PAPADOPOULO

University of Sherbrooke (Canada) - Departement d'Informatique - Théodore PAPADOPOULO

Duration: 2012 - 2014

See also: http://brainconnectivities.inria.fr/wordpress/

Currently brain connectivity is studied through two different lenses: 1) Anatomical connectivity aims at recovering the "wires" that connect the various brain cortical "units", 2) Functional connectivity studies when and how cortical regions are connected. Providing tools to fuse these two complementary views is the central goal of this project. Our effort will focus on three imaging modalities: diffusion MRI (dMRI) , Electroencephalography (EEG) and Magnetoencephalography (MEG). dMRI (jointly with traditional MRI) provides a detailed anatomical view of the brain. It allows the recovery of the fiber structure of the white matter: these are the electrical connexions between distant cortical areas. But dMRI does not provide any clue on: 1) on the actual use of connexions during brain activity, 2) on the way information propagates along time for a given task. On the opposite, EEG and MEG (jointly named MEEG) provide (after source reconstruction) time courses of the activity of the cortical areas. It is possible to recover some connectivity information from these time courses, but these are purely signal based and do not take account of the anatomy so there are multiple solutions that are sometimes difficult to discriminate. Furthermore source reconstructions are regularized with purely mathematical a priori taking only partially account of the actual brain structures.The main goals of this project are to provide tools: 1) To acquire diffusion data more efficiently, 2) To use the information of dMRI to define better models and regularization schemes for spatio-temporal MEEG source reconstruction, 3) To use MEEG data to better understand the task-dependent spatio-temporal structure of connectivity patterns.

8.2.2. Inria International Partners

8.2.2.1. Informal International Partners

- CMRR, University of Minnesota, USA (Christophe Lenglet)
- Department of CISE, the University of Florida, Gainesville, USA (Baba C. Vemuri)
- Centre for Medical Image Computing (CMIC), Dept. Computer Science, UCL, UK (D. Alexander)

- SBIA, University of Pennsylvania Medical School, USA (R. Verma).
- University Houari Boumedienne (USTHB, Algiers) (L. Boumghar) and University of Boumerdes, (D. Cherifi), Algeria.
- BESA company of EEG/MEG source localisation.

8.3. International Research Visitors

8.3.1. Visits of International Scientists

- Maxime Descoteaux (USherbrooke) visited ATHENA (September 10-15 2013) and (December 13-20, 2013).
- Gabriel Girard (USherbrooke) has joined ATHENA for one year for a joint PhD (Samuel de Champlain grant) from October 10th, 2013 to September 30th, 2014. He is co-supervized by M. Descoteaux and R. Deriche.
- Jean-Marc Lina (CRM) visited ATHENA from December 17th to December 21th.

8.3.1.1. Internships

- Susana Merino-Caviedes (Valladolid University) visited ATHENA from Sep 2013 until Nov 2013.
- Mouloud Kachouane (USTHB, Algiers) visited ATHENA from October 20 until December 20, 2013).
- Thinhinane Megherbi (USTHB, Algiers) and Mouloud Kachouane (USTHB, Algiers) visited ATHENA (June 2013).

9. Dissemination

9.1. Scientific Animation

- R. Deriche is Adj. Director at the Doctoral School EDSTIC (http://edstic.i3s.unice.fr/index.html)
- R. Deriche is member of 4 Scientific Councils: University of Nice Sophia Antipolis, ITMO ITS (Institut des Technologies pour la Santé), OLEA MEDICAL Company (http://www.olea-medical.com/ and the GIS UNS-ENSL-CNRS-Inria.
- R. Deriche is member of the Administration Concil of AFRIF (Association Française pour la Reconnaissance et l'Interprétation des Formes) and of GRETSI (Groupe d'Etudes du Traitement du Signal et des Images).
- R. Deriche is member of the Editorial Board of the Journal of Neural Engineering, Associate Editor of SIAM Journal on Imaging Sciences (SIIMS) and editorial board member at Springer for the book series entitled Computational Imaging and Vision.
- R. Deriche has served for many years as area-chair and/or as program committee member for International Conferences as ICCV, MICCAI, ECCV, CVPR, ISBI and national conferences as AFRIF-AFIA RFIA and serves several international journals and conferences (NeuroImage, IEEE Transactions on Medical Imaging, Magnetic Resonance in Medicine, JMIV, Medical Image Analysis Journal, ISBI, ISMRM, HBM..).
- R. Deriche has co-organised MICCAI 2013 Workshop on Mathematical Methods for Brain Connectivity.
- R. Deriche has organised the "Computational diffusion MR imaging" session of the BASP: international biomedical and astronomical signal processing (BASP) Frontiers held in Villars-sur-Ollon (Jan. 27, Feb.1, 2013).
- M. Clerc is on the Editorial Board of Biomedical Engineering Online, and of the ISTE-Wiley book series (Neural Engineering committee).

- T. Papadopoulo served as a referee for the international conferences MICCAI 2013, ICVS 2013, NER 2013 and ISBI 2013 and 2014. He was area chair for the national conference GRETSI 2013. In 2013, he has been reviewer for the journals Image and Vision Computing and Signal, Image and Video Processing.
- T. Papadopoulo has reviewed a BPI proposal and a Futur & Rupture de l'Institut Mines-Télécom proposal.
- T. Papadopoulo (since september 2011) is the coordinator of the Master of Science in Computational Biology and Biomedicine from University of Nice Sophia Antipolis (Website: http://cbb.unice.fr). The scientific goal of this program is to focus on the human being from different perspectives (understanding and modeling functional aspects or interpreting biomedical signals from various devices) and at different scales (from molecules to organs and the whole organism).
- T. Papadopoulo is a member of the local (Sophia Antipolis) committees for software development (CDT) and for Sustainable development. He is also member of the piloting committee for the platform dtk.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Master: R. Deriche, *Variational approaches and Geometrical Flows for Brain Imaging*, 36 ETD, M2 "Computational Biology and Biomedicine", University of Nice Sophia Antipolis, France.

Master: M. Clerc and T. Papadopoulo, *Inverse Problems in Brain Functional Imaging*, 36 ETD, M2 "Computational Biology and Biomedicine", University of Nice Sophia Antipolis, France.

Master: T. Papadopoulo, *3D Computer Vision*, 36 ETD, M2, SSTIM/VIM/MAM5 option at Polytechnic Engineering School, University of Nice Sophia Antipolis, France.

Master: T. Papadopoulo, *Inverse problems for brain functional imaging*, 24 ETD, M2, Mathématiques, Vision et Apprentissage, ENS Cachan, France.

Doctorat: M. Clerc *Inverse Problems in Brain Imaging*, 6 ETD, OIPE Doctoral Course, Ghent University, Belgium.

9.2.2. Supervision

PhD: Sylvain Merlet, "Compressive Sensing in dMRI", Université Nice Sophia Antipolis, Sept. 11, 2013. Supervisor : Rachid Deriche

PhD: Anne-Charlotte Philippe, "MEG inverse problem regularization via Diffusion MRI", Université Nice Sophia Antipolis, Dec. 19th, 2013. Supervisors: Rachid Deriche and Maureen Clerc.

PhD in progress: Brahim Belaoucha, "Using diffusion MR information to reconstruct networks of brain activations from MEG and EEG measurements", Université Nice Sophia Antipolis, started October 2013, Supervisor: Theo Papadopoulo.

PhD in progress: Kai Dang, "Conductivity models for optimizing cochlear implant stimulation", started December 2013, Supervisor: Maureen Clerc.

PhD in progress: Rutger H.J. Fick, "Microstructure Recovery via dMRI", started Oct. 2013, Université Nice Sophia Antipolis. Supervisor: Rachid Deriche.

PhD in progress: Gabriel Girard, "fMRI & dMRI", started Sept. 2012, Supervisors: Rachid Deriche & Maxime Descoteaux (University of Sherbrooke, CA).

PhD in progress: Sebastian Hitziger, "MEEG signal processing", started Nov. 2011, Supervisors: Théodore Papadopoulo & Maureen Clerc.

PhD in progress: Mouloud Kachouane, "Invariants and biomarqueurs in dMRI", started Oct. 2012, Supervisors: Rachid Deriche & L. Boumghar (USTHB, Algiers).

PhD in progress: Thinhinane Megherbi, “HARDI & High Order Tensors”, started Sept. 2011, Supervisors: Rachid Deriche & L. Boumghar (USTHB, Algiers).

PhD in progress: Marco Pizzolato, “Diffusion & Perfusion MRI : From bench to bedside” started Dec. 2013, Université Nice Sophia Antipolis. Supervisor: Rachid Deriche.

PhD in progress: Romain Trachel, “A Brain Machine Interface for enhancing human performance”, started Oct. 2010. Supervisors: Maureen Clerc & Thomas Brochier.

9.2.3. Juries

- M. Clerc participated in the PhD juries of Maxime Rio (Université de Lorraine), Janis Hofmanis (Université de Lorraine) and Anne-Charlotte Philippe (UNS, Nice).
- M. Clerc participated in a jury for CR2 recruitement at Inria Nancy Grand Est.
- R. Deriche participated in the PhD juries of Alexandre Chapoulie (UNS, Nice), Lihui Wang (INSA, Lyon), Gonzalo Vegas Sanchez Ferrero (Valladolid University, Spain), Yacine Morsli (EMP, Algiers), Nicolas Bourdis (Télécom ParisTech, Paris), Sylvain Merlet (UNS, Nice), Stamm Aymeric (Université de Rennes 1) and Anne-Charlotte Philippe (UNS, Nice).
- R. Deriche participated in the HDR juries of Iasonas Kokkinos (Université Paris Est) and Olivier Coulon (Université d’Aix-Marseille).
- T. Papadopoulo participated in the PhD juries of Carolina Saavedra à Inria Nancy (Université de Lorraine).

10. Bibliography

Major publications by the team in recent years

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