



INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team ATHENA

*Computational Imaging of the Central
Nervous System*

Sophia Antipolis - Méditerranée

Theme : Computational Medicine and Neurosciences

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R *eport*

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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

1. ATHENA has been created as a team on January 1st, 2010 and as an INRIA Project-Team on July 1st, 2010. The members of ATHENA were part of the former ODYSSEE Project-Team, created in 2002 and stopped in December 2009. Note that the members of NEUROMATHCOMP were also part of the ODYSSEE Project-Team.

2. The project of installing an EEG Laboratory in our Center has been successfully completed. The agreement from the “Agence régionale de Santé” will be delivered by the end of 2010 and the first experiments have been set up successfully.
3. The EADS Foundation’s Best Thesis Prize rewards top doctoral research work. Alexandre Gramfort’s PhD thesis entitled *Mapping, timing and tracking cortical activations with MEG and EEG: Methods and application to human vision* and defended late 2009 has been awarded the Best Interdisciplinary EADS Thesis Prize for 2010. This thesis has been prepared under the joint supervision of Maureen Clerc and Olivier Faugeras.
4. On January 6th, during the 2010 ANR Workshop, Maxime Descoteaux has been awarded the ASTI 2009 (Association Française des Sciences et Technologies de l’Information et de la Communication) prize, category “Recherche appliquée innovante” for his PhD thesis entitled *High Angular Resolution Diffusion MRI: From Local Estimation to Segmentation and Tractography* prepared under the supervision of Rachid Deriche. Maxime Descoteaux is now Assistant Professor at Département d’informatique de la Faculté des sciences de l’Université de Sherbrooke, Quebec.

3. Scientific Foundations

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 [68], Merboldt et al [72] and Taylor et al [81]. 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.

Diffusion Tensor Imaging

Shortly after the first acquisitions of diffusion-weighted images (DWI) were made in vivo [74], [75], Basser et al [53], [52] 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} [53], [52]. 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 [69], [60]. 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 driven 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 [71], [8] and [70]).

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 $1\mu\text{m}$ and $30\mu\text{m}$ [78], [54]. Research groups currently agree that there is complex fiber architecture in most fiber regions of the brain [77]. 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 [55]. This has led to the development of various High Angular Resolution Diffusion Imaging (HARDI) techniques [83] such as Q-Ball Imaging (QBI) or Diffusion Spectrum Imaging (DSI) [84], [85], [87] 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 [66] or Diffusion Orientation Transform [89]. 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) [87], [84], [85]. The method requires very strong imaging gradients ($500 \leq b \leq 20000 \text{ s/mm}^2$) 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. They are at the core of our probabilistic and deterministic tractography algorithms devised to best exploit the full distribution of the fiber ODF (see [58], [4] and [59],[5]).

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 [88], [90] or 4th order Tensor Model [51]. For more details, we refer the reader to our recent article in [63] where we review HOT models and to our article in [7], 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.

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], these imaging modalities raise a large amount of mathematical and computational challenges at the core of the research we develop at ATHENA.

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 measures of the magnetic field generated by the electrophysiological activity of the brain have been done in 1968 at MIT by D. Cohen. Nowadays, EEG is relatively inexpensive and used routinely 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 ODYSÉE/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 hundreds of simultaneous 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). Contrarily to fMRI, which "only" measures an haemodynamic response linked to the metabolic demand, MEG and EEG also 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 hundreds of 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].

- 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 [6], [76] and means to calibrate them [86] 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 is currently being set up at Athena.

4. Application Domains

4.1. Introduction

Our research helps to answer a strong societal and economical need. Indeed, about one third of the burden of all diseases in Europe is due to brain diseases. It is projected that this burden will further increase in the coming decades due to the aging of the European society. The European Brain Council (EBC) recently investigated the socio-economic impact of brain diseases on European society. In the *Cost of Disorders of the Brain in Europe* study [50] the EBC concluded: *In 28 (European) countries with a population of 466 million, 127 million were affected by at least one brain disorder. The total annual cost was Euros 386 billion (386 000 000 000). Brain research funding, health care resource allocation and teaching at medical schools are proportionately much smaller. The huge cost and burden of brain disorders calls for increased efforts in research, health care and teaching.* This very strong societal and economic need for improving diagnosis and therapy of brain diseases should eventually result in a reduction of the people suffering from brain diseases, as it may lead to improved therapies or disease modifying interventions in a very early or even asymptomatic stage of disease, thus improving quality of life and independent living.

4.2. 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 brainstem, 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 [79], [82]. 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).

4.3. Applications of M/EEG

Applications of EEG and MEG cover:

- **Clinical domain:** diagnosis of neurological disorders such as
 - 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.
- **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.

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 collaboration with the La Timone hospital in Marseille. M/EEG are also used in **cognitive research**, and we collaborate with the *Laboratory for Neurobiology of Cognition* in order to develop methods that suit their needs for sophisticated data analysis.

5. Software

5.1. OpenMEEG

Participants: Théodore Papadopoulo, Maureen Clerc, Emmanuel Olivi, Alexandre Gramfort [Parietal project-team].

OpenMEEG provides state-of-the art tools for low-frequency bio-electromagnetism, notably solving forward problems related to EEG and MEG. It implements the symmetric BEM, thus providing excellent accuracy. OpenMEEG is a free open software written in C++. It can be accessed either through a command line interface or through Python / Matlab interfaces.

OpenMEEG is multiplatform (Linux, MacOS, Windows) and it is distributed under the French opensource license CeCILL-B. See also the web page <http://www-sop.inria.fr/athena/software/OpenMEEG/>.

5.2. Diffusion MRI

Participants: Aurobrata Ghosh, Rachid Deriche.

The algorithms previously developed within the ODYSSEÉ Project team and related to the Diffusion Tensor and Q-Ball imaging are available upon request from the INRIA source forge (<https://gforge.inria.fr>). One can use all the estimation and visualization tools developed, ranging from estimation, regularization, segmentation to Q-ball estimation, fiber ODF estimation and tractography algorithms. New visualization tools for Q-Ball images represented by spherical harmonic decomposition have also been developed.

The software library comprises geometric and variational methods devised to estimate, regularize, segment and perform tractography in DT (Diffusion Tensor) and HARDI (High Angular Resolution) MRI images. The library is multi-platform (Linux, Windows and OS X) and is embedded into two open-source high level languages, TCL and Python.

Thanks to the *ADT MedInria-NT*, this library is in the process to be partly integrated within the interactive medical imaging platform **MedINRIA**.

6. New Results

6.1. Computational Diffusion MRI

This sub-theme is dedicated to describe our various contributions performed within the framework of Computational Diffusion MRI. In 6.1.1, we start by presenting our contributions to optimize dMRI acquisition schemes, then, we present our contributions related to the problem of reconstructing and characterizing important Diffusion MRI features such as the Orientation Distribution Function (ODF) in 6.1.2 and the Ensemble Average Propagator (EAP) in 6.1.3. Finally, we end up with some additional contributions related to the characterization of the relation structure-function from functional and diffusion MRI in 6.1.4 and to more general applications such as the reconstruction and the clustering of fibers and an application related to the straightening of the spinal cord, in 6.1.5.

6.1.1. Improving dMRI Acquisitions

6.1.1.1. Compressed Sensing for Accelerated EAP Recovery in Diffusion MRI

Participants: Rachid Deriche, Sylvain Merlet.

Compressed Sensing (CS) or Compressive Sampling is a recent technique to accurately reconstruct sparse signals from under sampled measurements acquired below the Shannon-Nyquist rate. In this work, we presented a CS based method for accelerating the reconstruction of the Ensemble Average Propagator (EAP), also known as the Propagator in Diffusion MRI, by significantly reducing the number of measurements. Contrarily to the time consuming acquisition technique known as the Diffusion Spectrum Imaging (DSI), our method is developed and implemented to efficiently reconstruct the EAP from reduced and non uniformly under sampled Diffusion Weighted (DW) MRI images combined to an efficient and accurate l_1 norm based reconstruction algorithm. In [48], we have illustrated in detail the artifacts occurring in a classical EAP reconstruction à la DSI, and qualitatively and quantitatively demonstrated good and better results in recovering the EAP and some of its important features such as the Orientation Distribution Function (ODF) from non-regularly undersampled and l_1 norm based reconstructed data. This opens an original and very interesting road to shorten the dMRI acquisition time and opens new opportunities to render High Angular Resolution Diffusion Imaging (HARDI) feasible in a clinical setting.

This work has been published in [48].

6.1.2. Modelling, Reconstructing and Characterizing the Orientation Diffusion Function

6.1.2.1. Online orientation distribution function reconstruction in constant solid angle and its application to motion detection in high angular resolution diffusion imaging

Participants: Rachid Deriche, Emmanuel Caruyer, Iman Aganj [Department of Electrical and Computer Engineering, University of Minnesota], Ryan Muetzel [Center for Magnetic Resonance Research, University of Minnesota], Christophe Lenglet [Department of Electrical and Computer Engineering, University of Minnesota], Guillermo Sapiro [Department of Electrical and Computer Engineering, University of Minnesota].

This work was partly supported by the CD-MRI Associated Team.

The diffusion orientation distribution function (ODF) can be reconstructed from q-ball imaging (QBI) to map the complex intravoxel structure of water diffusion. As acquisition time is particularly large for high angular resolution diffusion imaging (HARDI), fast estimation algorithms have recently been proposed, as an on-line feedback on the reconstruction accuracy. Thus the acquisition could be stopped or continued on demand. In this work, we adapted our real-time algorithm [3] to the ODF in constant solid angle (CSA), and developed a motion detection algorithm upon this reconstruction. Results of improved fiber crossing detection by CSA ODF have been obtained, and motion detection was implemented and tested in vivo.

This work has been published in [25].

6.1.2.2. *Model-Free, Regularized, Fast, and Robust Analytical Orientation Distribution Function Estimation.*

Participants: Rachid Deriche, Jian Cheng [ATHENA and LIAMA, China], Aurobrata Ghosh, Jiang Tianzi [LIAMA, China].

High Angular Resolution Diffusion Imaging (HARDI) can better explore the complex micro-structure of white matter compared to Diffusion Tensor Imaging (DTI). Orientation Distribution Function (ODF) in HARDI is used to describe the probability of the fiber direction. There are two type definitions of the ODF, which were respectively proposed in Q-Ball Imaging (QBI) and Diffusion Spectrum Imaging (DSI). Some analytical reconstructions methods have been proposed to estimate these two type of ODFs from single shell HARDI data. However they all have some assumptions and intrinsic modeling errors. In this work, we proposed, almost without any assumption, a uniform analytical method to estimate these two ODFs from DWI signals in q space, which is based on Spherical Polar Fourier Expression (SPFE) of signals. The solution is analytical and is a linear transformation from the q-space signal to the ODF represented by Spherical Harmonics (SH). It can naturally combines the DWI signals in different Q-shells. Moreover, it can avoid the intrinsic Funk-Radon Transform (FRT) blurring error in QBI and it does not need any assumption of the signals, such as the multiple tensor model and mono/multi-exponential decay. We validated our method using synthetic data, phantom data and real data. Our method works well in all experiments, especially for the data with low SNR, low anisotropy and non-exponential decay.

This work has been published in [26].

6.1.2.3. *Riemannian Median and Its Applications for Orientation Distribution Function Computing.*

Participants: Rachid Deriche, Jian Cheng [ATHENA and LIAMA, China], Aurobrata Ghosh, Jiang Tianzi [LIAMA, China].

The geometric median is a classic robust estimator of centrality for data in Euclidean spaces, and it has been generalized in analytical manifold. Recently, an intrinsic Riemannian framework for Orientation Distribution Function (ODF) was proposed for the calculation in ODF field [2]. In this work, we proved the unique existence of the Riemannian median in ODF space. Then we explored its two potential applications, median filtering and atlas estimation.

This work has been published in [30]

6.1.3. *Modelling, Reconstructing and Characterizing the Ensemble Average Propagator*

6.1.3.1. *Multiple q-Shell Diffusion Propagator Imaging.*

Participants: Rachid Deriche, Maxime Descoteaux [Sherbrooke University, Quebec], Denis Le-Bihan [NeuroSpin, IFR 49 CEA Saclay], Jean-François Mangin [NeuroSpin, IFR 49 CEA Saclay], Cyril Poupon [NeuroSpin, IFR 49 CEA Saclay].

This work was partly supported by the EADS Grant Number 2118 and the Association France Parkinson for the NucleiPark project.

Many recent high angular resolution diffusion imaging (HARDI) reconstruction techniques have been introduced to infer an orientation distribution function (ODF) of the underlying tissue structure. These methods are more often based on a single-shell (one b-value) acquisition and can only recover angular structure information contained in the ensemble average propagator (EAP) describing the three-dimensional (3D) average diffusion process of water molecules. The EAP can thus provide richer information about complex tissue microstructure properties than the ODF by also considering the radial part of the diffusion signal. In this work, we presented a novel technique for analytical EAP reconstruction from multiple q-shell acquisitions. The solution is based on a Laplace equation by part estimation between the diffusion signal for each shell acquisition. This simplifies greatly the Fourier integral relating diffusion signal and EAP, which leads to an analytical, linear and compact EAP reconstruction. An important part of this work is dedicated to validate the diffusion signal estimation and EAP reconstruction on real datasets from ex vivo phantoms. We also illustrated multiple q-shell diffusion propagator imaging (mq-DPI) on a real in vivo human brain and performed a qualitative comparison against state-of-the-art diffusion spectrum imaging (DSI) on the same subject. mq-DPI is shown to reconstruct robust EAP from only several different b-value shells and less diffusion measurements than DSI. This opens interesting perspectives for new q-space sampling schemes and tissue microstructure investigation.

This work has been published in [14].

6.1.3.2. Model-Free and Analytical EAP Reconstruction via Spherical Polar Fourier Diffusion MRI.

Participants: Rachid Deriche, Jian Cheng [ATHENA and LIAMA, China], Aurobrata Ghosh, Jiang Tianzi [LIAMA, China].

How to estimate the diffusion Ensemble Average Propagator (EAP) from the DWI signals in q-space is an open problem in diffusion MRI field. Compared with ODF, EAP has the full information about the diffusion process which reflects the complex tissue micro-structure. Diffusion Orientation Transform (DOT) and Diffusion Spectrum Imaging (DSI) are two important methods to estimate the EAP from the signal. However, DOT is based on mono-exponential assumption and DSI needs a lot of samplings and very large b values. In this work, we have proposed Spherical Polar Fourier Imaging (SPFI), a novel model-free fast robust analytical EAP reconstruction method, which almost does not need any assumption of data and does not need too many samplings. SPFI naturally combines the DWI signals with different b-values. It is an analytical linear transformation from the q-space signal to the EAP profile represented by Spherical Harmonics (SH). We validated the proposed methods in synthetic data, phantom data and real data. It works well in all experiments, especially for the data with low SNR, low anisotropy, and non-exponential decay.

This work has been published in [29], [28]

6.1.3.3. Fast and Closed-Form Ensemble-Average-Propagator Approximation from the 4th-Order Diffusion Tensor

Participants: Rachid Deriche, Aurobrata Ghosh.

Generalized Diffusion Tensor Imaging (GDTI) was developed to model complex Apparent Diffusivity Coefficient (ADC) using Higher Order Tensors (HOT) and to overcome the inherent single-peak shortcoming of DTI. However, the geometry of a complex ADC profile doesn't correspond to the underlying structure of fibers. This tissue geometry can be inferred from the shape of the Ensemble Average Propagator (EAP). Though interesting methods for estimating a positive ADC using 4th order diffusion tensors were developed, GDTI in general was overtaken by other approaches, e.g. the Orientation Distribution Function (ODF), since it is considerably difficult to recuperate the EAP from a HOT model of the ADC in GDTI. In this work, we presented a novel closed-form approximation of the EAP using Hermite Polynomials from a modified HOT model of the original GDTI-ADC. Since the solution is analytical, it is fast, differentiable, and the approximation converges well to the true EAP.

This work has been published in [33]

6.1.3.4. Analytical Q-Ball Imaging with Optimal Regularization

Participants: Rachid Deriche, Maxime Descoteaux [Sherbrooke University, Quebec], Cheng Guan Koay [NIH, NICHD/STBB, Bethesda].

This work was partially supported by the CD-MRI Associated team.

Several approaches such as diffusion tensor imaging, q-ball imaging (QBI), spherical deconvolution and many others high angular resolution diffusion imaging (HARDI) have been proposed to describe the angular distribution of the white matter fibers within a voxel. The analytical QBI technique [4] uses a predetermined regularization parameter ($\lambda=0.006$), which has been well adopted in many clinical studies. Although there are well-known strategies, e.g., the generalized cross-validation (GCV) or the L-curve, for selecting the optimal regularization parameter λ , the predetermined regularization parameter was adopted for reasons related to practical and computational efficiency based on L-curve simulations. In this work, we incorporated the GCV technique into the analytical qball formalism. We compared and contrasted the fixed λ -regularization parameter (“Fixed λ ”) and the automatic GCV-selected optimal λ -regularization (“GCV-based λ ”), for estimating diffusion MRI data. We also discussed the potential consequences of our work on quantitative HARDI anisotropy measures and tractography studies.

6.1.3.5. *Challenges in Reconstructing the Propagator via a Cumulant Expansion of the One-Dimensional q-Space MR Signal*

Participants: Rachid Deriche, Aurobrata Ghosh, Evren Ozarslan [NIH, NICHD/STBB, Bethesda].

This work was partially supported by the CD-MRI Associated team.

Generalized Diffusion Tensor Imaging (GDTI) is one of the few methods that estimate the ensemble average diffusion propagator from the diffusion weighted signal. It has a statistical approach and views the signal, which under the q-space formalism is the Fourier transform of the propagator, as the characteristic function of the propagator. Instead of taking the inverse Fourier transform of the signal, GDTI estimates the cumulants of the propagator from the signal (characteristic function) and then approximates the propagator using the Gram-Charlier Type-A series, which is a series approximation of a probability density function based on its cumulants. However, it is well known that the Gram-Charlier series has a poor convergence, especially since only a truncated series is considered (order-4 usually). The Edgeworth series, which is a reordering of the terms from the Gram-Charlier series, is known to perform better since it is a true asymptotic expansion. GDTI has never been validated numerically. We proposed, in this work, to compare the Gram-Charlier and the Edgeworth series in 1D on known diffusion propagators, where the propagator, the signal and the cumulants have analytical forms. We also compared with cumulants estimated from the signal. Our experiments strongly suggest that for analytical cumulants the Edgeworth series improves on the Gram-Charlier series, and estimating the cumulants from the signal is numerically a sensitive and important problem.

This work has been published in [34]

6.1.4. *Relation Structure-Function via fMRI and dMRI*

6.1.4.1. *Characterization of the relation structure-function from Functional and Diffusion MRI*

Participants: Rachid Deriche, Arnaud Messé, Habib Benali [Laboratoire d’imagerie fonctionnelle INSERM : U678 – IFR14 – IFR49 – Université Pierre et Marie Curie - Paris VI].

This work has been performed at INSERM : U678 – Université Pierre et Marie Curie - Paris V within the framework of Arnaud Messé’s PhD thesis under the joint supervision of H. Benali and R. Deriche. Various concepts and aspects on how to link function to structure using both fMRI and dMRI have been investigated among which a study that shows that small-world attributes characterize the relationship between functional and structural connectivity using fMRI and DTI [73], a spatial autoregressive model to link structure to function through a combined fMRI and DTI approach [40], a connectivity-based delineation of basal ganglia using hierarchical classification [39], a comparison of functional and anatomical segregation in the basal ganglia using fMRI and fiber tracking [36], an enhanced voxel-based morphometry method to investigate structural changes with its application to Alzheimer’s disease [19] and a study on diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment [38]. Other related contributions can also be found in [35], [37], [43]

6.1.5. *Applications*

6.1.5.1. *Unsupervised white matter fiber clustering and tract probability map generation: Applications of a Gaussian process framework for white matter fibers*

Participant: Rachid Deriche.

With the increasing importance of fiber tracking in diffusion tensor images for clinical needs, there has been a growing demand for an objective mathematical framework to perform quantitative analysis of white matter fiber bundles incorporating their underlying physical significance.

This work presents such a novel mathematical framework that facilitates mathematical operations between tracts using an inner product between fibers. Such inner product operation, based on Gaussian processes, spans a metric space. This metric facilitates combination of fiber tracts, rendering operations like tract membership to a bundle or bundle similarity simple. Based on this framework, we have designed an automated unsupervised atlas-based clustering method that does not require manual initialization nor an a priori knowledge of the number of clusters. Quantitative analysis can now be performed on the clustered tract volumes across subjects, thereby avoiding the need for point parameterization of these fibers, or the use of medial or envelope representations as in previous work. Experiments on synthetic data demonstrate the mathematical operations. Subsequently, the applicability of the unsupervised clustering framework has been demonstrated on a 21-subject dataset.

This work has been published in [21], [11]

6.1.5.2. Straightening the spinal cord using fiber tractography

Participants: Rachid Deriche, Demian Wassermann, Julien Cohen-Adad [Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital / Harvard Medical School, Charlestown, MA, USA], Stéphane Lehericy [Center for NeuroImaging Research - CENIR, Department of Neuroradiology CHUPS, Paris], Habib Benali [Laboratoire d'imagerie fonctionnelle INSERM : U678 – IFR14 – IFR49 – Université Pierre et Marie Curie - Paris VI], Serge Rossignol [CRSN/Faculté de médecine Université de Montréal].

Spinal Cord MRI (SC-MRI) is a challenging research field with numerous important clinical and basic research applications. Some of the SC-MRI applications strongly need to deal with a well straightened spinal cord either for appropriate methodological developments, for better visualization or diagnostic purposes. In this work, we developed an efficient and automatic method to straighten the spinal cord image and fibres. Diffusion Tensor MRI is first used to recover by tractography the bundles of fibres contained in the spinal cord white matter. An efficient Gaussian process framework is then used to automatically recover in a robust way the most representative fibre which is used to interpolate and straighten the spinal cord image and fibres. Our method is successfully tested on real images of one cat with partial spinal cord injury and two healthy volunteers. This capability to reliably reconstruct straightened animal and human spinal cord opens new opportunities for SC-MRI research.

This work has been published in [46], [45], [11]

6.2. Brain functional imaging using MEG/EEG

The work depicted in this sub-theme concerns various aspects related to the problem of estimating the sources in the brain corresponding to some given activity. Besides the forward and inverse EEG/MEG problems (see sections 6.2.1 and 6.2.2) which are directly connected to this problem, there are a number of additional problems such as finding the events of interest in the recorded signal (section 6.2.3), or jointly modeling multimodal signals by studying generative models (section 6.2.4). Some of the tools described in this sub-theme are distributed in the opensource library OpenMEEG (see section 5.1).

6.2.1. Inverse problems of MEG and EEG

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

Investigating on brain activity with EEG or MEG measurements requires the solution of ill-posed inverse problems, whose solution implies regularization. Source models for EEG and MEG can be either distributed dipoles or isolated dipoles. In distributed models, the relationship between sources and measurements is linear, but the problem is underconstrained because thousands of putative positions for the cortical activity must be handled at the same time. In isolated dipole models, on the contrary, there are less unknowns than measurements, but the relationship between sources and measurements is more complex.

We are pursuing our collaboration with the APICS project-team, on rational approximation for source localization, when the sources are modeled as isolated dipoles. The force of the method is to provide a good and stable estimation of the number of sources and of their positions and moments. It requires the knowledge of the potential on the inner skull surface, provided by a Cortical Mapping method [2]. Cortical Mapping and rational approximation techniques are now being combined, leading to a dipolar source localization directly from scalp electrode measurements [56].

We are involved in an ANR grant on Multimodal Neuroimaging of Rapid Brain Processes in the Human Visual System (ViMAGINE). An initial step in the exploration of the Human Visual System has been to perform retinotopy, i.e. determine the subject-dependent mapping linking positions in the visual field to the positions of the associated activity in the low-level visual cortex [57]. Since brain activity is not static, but varies in time, the regularization of the inverse problem should take time into account. A new approach has been proposed to track cortical activity with spatio-temporal constraints, and its implementation uses graph-cuts for computational efficiency [18]. This spatio-temporal regularization is a post-processing which is applied to a minimum-norm inverse problem.

6.2.2. *Forward models for MEG and EEG*

Participants: Maureen Clerc, Alexandre Gramfort [Parietal project-team], Emmanuel Olivi, Théodore Papadopoulo, Sylvain Vallaghé [Laboratoire Jean Kuntzmann].

Most methods for the inverse source problem in electroencephalography (EEG) and magnetoencephalography (MEG) use a lead field as an input. The lead field is the function which relates any source in the brain to its measurements at the sensors. Its computation requires solving a forward problem.

The inverse source localization problem of EEG and MEG strongly depends on the quality of the forward solution. The information required to specify the forward problem are the geometrical and physiological description of the head, in terms of its electrical conductivity.

Appropriate computational methods are compulsory for solving the M/EEG forward problem: either by surface-based Boundary Element Methods (BEM) or volume-based Finite Element or Finite Difference Methods. Until recently, the state of the art in BEM consisted in using a double-layer formulation [62], with an accuracy improvement provided by the isolated Skull Approach [64]. We have proposed a new, symmetric BEM [67] which improves over the state of the art in terms of accuracy. This has been implemented within **OpenMEEG** which we continue to push through the community [18], [22].

Finite Element Methods (FEM) are also being studied for M/EEG because of their ability to account for anisotropic media. The cumbersome meshing procedure associated to the FEM should be alleviated with our recent development of the Implicit Mesh FEM [10],[44]. It is quite tempting to combine the Boundary Element Method and FEM in an hybrid model that would exploit each model for its strengths (Symmetric BEM for its accuracy for tissues having an isotropic homogeneous conductivity, FEM for its ability to deal with anisotropy) to provide even better forward problems [41], [42].

For complex geometries, there is no analytical formula of the lead field. The common approach is to numerically compute the value of the lead field for a finite number of point sources (dipoles). There are several drawbacks: the model of the source space is fixed (a set of dipoles) and the computation can be expensive for as much as 10000 dipoles. The common idea to bypass these problems is to compute the lead field from a sensor point of view. We use the adjoint method to derive general EEG and MEG sensor-based lead field equations [9]. Within a simple framework, we provide a complete review of the explicit lead field equations, and we are able to extend these equations to non-pointlike sensors [23].

6.2.3. *Single trial analysis and Brain Computer Interfaces*

Participants: Maureen Clerc, Théodore Papadopoulo, Joan Fruitet, Alexandre Gramfort [Laboratoire Jean Kuntzmann], Antoine Saillenfest, Renaud Keriven [ENPC], Christian Bénar [INSERM U751, La Timone], Bruno Torrèsani [LATP, CMI, Université de Provence].

Extracting information from multi-trial MEG or EEG recordings is challenging because of the very low signal-to-noise ratio (SNR), and because of the inherent variability of brain responses. The problem of low SNR is commonly tackled by averaging multiple repetitions of the recordings, also called trials, but the variability of response across trials leads to biased results and limits interpretability.

We have explored a data-driven way of decoding the variability of neural responses, which makes use of graph representations. First, a manifold learning algorithm based on a graph Laplacian offers an efficient way of ordering trials with respect to the response variability, under the condition that this variability itself depends on a single parameter. Second, the estimation of the variability is formulated as a combinatorial optimization that can be solved very efficiently using graph cuts. We have applied this method to the problem of latency estimation, on P300 oddball experiments [16].

For Brain Computer Interfaces (BCI), a challenge is to extract from ongoing EEG information that is specific, and to use it to control an interface. In the ANR project Co-Adapt, we are studying an error potential that is generated by a central region of the brain, when a BCI user perceives that the system is producing an error. Detecting this error potential online could help improve the BCI, by bringing more information into the system. Antoine Saillenfest's Master's thesis was devoted to developing an experimental setup controlling the error potentials produced by the experimental subjects and to analyzing the measurements in order to detect trials in which there is an error. We have pursued our work on source localization for BCI, by comparing several inverse source reconstruction methods for their efficiency in preprocessing the signal before classification [32].

6.2.4. Unified generative source models

Participants: Maureen Clerc, Théodore Papadopoulo, Nicole Voges, Habib Benali [Laboratoire d'Imagerie Fonctionnelle, INSERM U678, Faculté de Médecine, Univ Paris 6 / Hôpital Pitié-Salpêtrière], Solenna Blanchard [INSERM U642, Rennes], Christian Bénar [INSERM U751, Faculté de Médecine, La Timone, Marseille], Olivier David [INSERM U594, Grenoble], Fabrice Wendling [INSERM U642, Rennes].

The models of source activities usually differ with various image modalities such as M/EEG, fMRI or optical imaging (OI). This is mostly due to the fact that these modalities deal with differing views of the functioning brain (different physical phenomena, different spatial or temporal scales). Various models cope with either the metabolic [61], [80] or the electrophysiologic [65] aspects of brain function. It is quite tempting to couple these two kinds of models into a unified neural-mass computational model that can explain a broad variety of measurements obtained with different image modalities. To be efficient, such a model should have a limited number of parameters while keeping its expressiveness, and be computationally tractable. The paper [12] is a first exploration of such models. This model has been used to investigate the linearity of the metabolic response using epileptic spikes [49], [47].

7. Other Grants and Activities

7.1. National Actions

7.1.1. CD-MRI Associated Team

Participants: Rachid Deriche, Emmanuel Caruyer, Demian Wassermann, Aurobrata Ghosh.

Duration: January 2009 to December 2012

Our research group together with the group of Peter Basser (Laboratory of Integrative & Medical Biophysics, NICHD, NIH, Bethesda NIH) and the groups of Guillermo Sapiro (Department of Electrical and Computer Engineering, University of Minnesota) and Kamil Ugurbil (CMRR, Center for Magnetic Resonance Research, University of Minnesota) have been developing increasingly strong ties over the past several years. This associated team, started since January 2009, helps us combining our great expertise, as well our strong scientific synergy and our respective computing and experimental facilities, to help resolve some of the most difficult problems and mathematical challenges in Diffusion MRI.

Through an extensive exchange program involving junior as well senior scientists from all the partners, our Associate Team is pursuing and intensifying our past collaborative work on this subject. We started to develop new mathematical models and computational tools to unleash the full power and multivariate information content of diffusion MRI and advance the state-of-the-art in Computational Diffusion MRI. One of our objective is to write joint publications in international conferences and journals dedicated to promoting advances in computational methods for Diffusion MRI analysis [25], [34], [31] and use of diffusion MRI in clinical and neuroscience (web site <http://www-sop.inria.fr/teams/odyssee/ext/AssociateTeamOdyNIHMin>).

7.2. National Initiatives

7.2.1. ANR ViMAGINE

Participants: Maureen Clerc, Rachid Deriche, Alexandre Gramfort [Parietal project-team], Emmanuel Olivi, Théodore Papadopoulo, Anne-Charlotte Philippe.

Duration: July 2008 to July 2012

The partners of this project are Athena, the LENA (CHU Pitié-Salpêtrière), 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.

7.2.2. ANR CO-ADAPT

Participants: Maureen Clerc, Joan Fruitet, Emmanuel Olivi, Théodore Papadopoulo, Antoine Sallinenfest, Nicolas Servant.

Duration: September 2009 to December 2013

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>).

7.2.3. ANR NucleiPark

Participants: Rachid Deriche, Emmanuel Caruyer, Aurobrata Ghosh, Anne-Charlotte Philippe, Demian Wassermann.

Duration: *September 2009 to December 2012*

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*

7.2.4. ANR MULTIMODEL

Participants: Théodore Papadopoulo, Maureen Clerc.

Duration: *December 2010 to March 2014*

The general objectives of the MULTIMODEL project are twofold:

- Develop computational models at the level of neuronal systems that will help interpreting neuroimaging data in terms of excitation-, inhibition- and synchronization-related processes.
- 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, during this 3-year project, the following questions will be 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 will operate at the level of population of cell, i.e. at a scale compatible with the resolution of neuroimaging tools (at the level of the mm). A novel model structure will be investigated. It will include astrocytes at this “mesoscopic” level and will operate in networks of connected regions. Moreover, models in physiological and pathological conditions will be compared, which will be a step towards a better understanding of mechanisms underlying epileptic condition.

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).

7.2.5. ADT Immersive BCI

Participants: Théodore Papadopoulo, Maureen Clerc, Nicolas Servant, Joan Fruitet.

Duration: *December 2009 to December 2011*

The goal of this technical project, funded by INRIA for 2 years, is to facilitate the use of EEG within a new immersive environment at INRIA Sophia Antipolis Méditerranée, in order to make it possible to perform BCI or cognitive experiments within this environment. Using a BCI within an immersive environment will open up new possibilities for scientific research, both in BCI and in Virtual Reality. All development linked to this project will take place within an integrative software platform. This development will include electrode localization and real-time EEG processing with feedback to the user.

7.2.6. ADT MedInria-NT

Participants: Théodore Papadopoulo, Maureen Clerc, Rachid Deriche.

Duration: *December 2010 to December 2012*

The goal of this technical project, funded by INRIA for 2 years, is to introduce some tools developed at ODYSSEÉ/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.

7.3. European Initiatives

7.3.1. FACETS: Fast Analog Computing with Emergent Transient States

Participant: Théodore Papadopoulo.

Duration: *September 2005 to July 2010*

FACETS is an integrated project within the biologically inspired information systems branch of IST-FET. The FACETS project aims at addressing, with a concerted action of neuroscientists, computer scientists, engineers and physicists, the unsolved question of how the brain computes. It combines a substantial fraction of the European groups working in the field into a consortium of 13 groups from Austria, France, Germany, Hungary, Sweden, Switzerland and the UK. About 80 scientists have joined their efforts over a period of 4 years, starting in September 2005. A project of this dimension has rarely been carried out in the context of brain-science related work in Europe, in particular with such a strong interdisciplinary component (web site: <http://facets.kip.uni-heidelberg.de/>).

7.4. International Initiatives

We have initiated a collaboration entitled *Computational Brain Imaging Through Diffusion MRI* with the Computer Vision and Pattern Analysis Laboratory led by Pr. Gozde Unal at the Faculty of Engineering and Natural Sciences, Sabanci University, Istanbul (Turkey). Our main objectif in this *PHC Bosphore 2010* project is focused on automating the tractography process for white matter fibers. Building on the expertise of the two teams at INRIA and Sabanci University (SU), we will develop novel computational techniques for processing Diffusion Tensor-MRI (DTI), and study specific pathways for their analysis and visualization using new mathematical models. This project started in January 2010 and is granted for 2 years.

We have also a collaboration within the framework ECOS-Sud on a project based on Diffusion MRI and Autism with Prof. Mariano Sigman (Buenos-Aires University) and INCM UMR 6193 CNRS (B. Wicker et C. Deruelle) and le LSIS/ESIL UMR 6168 (O.Coulon). This project started in Sept. 2009 and is granted for 2 years.

8. Dissemination

8.1. Animation of the scientific community

Maureen Clerc is a member of two local (Sophia Antipolis) committees: the Bureau du Comité des Projets and Commission d'Animation Scientifique. She has served since 2008 as a member of the Program Committee of RFIA 2010, and of the EADS Foundation PhD Award Committee. She is on the organizing board of the 2012 International Conference on Biomagnetism, to be held in Paris. She has given invited talks at the International Conference on Biomagnetism (Dubrovnik), at a CNRS workshop on Biomedical Signal Analysis (Marseille) and at the POEMS Seminar (INRIA Rocquencourt). She serves as reviewer for several journals (Journal of Neuroscience Methods, Inverse Problems, IEEE Transactions on Biomedical Engineering, IEEE Transactions on Pattern Analysis and Machine Intelligence, Biomedical Engineering Online, Physics in Medicine and Biology, NeuroImage). She is the coordinator of the ANR DEFIS grant "CoAdapt".

Rachid Deriche has been Project committee vice-chairman at INRIA Sophia Antipolis - Méditerranée and member of the Direction of the Sophia Antipolis Research Center (DGSA) from Sept. 2007 to June 2010. Rachid Deriche is Adj. Director at the Doctoral School EDSTIC (<http://edstic.i3s.unice.fr/index.html>) and member of the Scientific Council of the ITMO ITS (Institut des Technologies pour la Santé).

Rachid Deriche is Associate Editor of SIAM Journal on Imaging Sciences (SIIMS), editorial board member at Springer for the book series entitled Computational Imaging and Vision, editorial board member of International Journal of Computer Vision (IJCV). He served as Area-Chair for RFIA 2010 and currently serves as Co-Chair for Track VI: Bioinformatics and Biomedical Applications for the 20th International Conference on Pattern Recognition 2010. R. Deriche has also 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 also served as president, reviewer and examiner in the jury committee of a number of PhD thesis.

Rachid Deriche gave plenary talks at the Medical Imaging Symposium in IIT Delhi (Dec. 2010) and during the MICCAI 2010 CD-MRI Workshop held at Beijing in Sept. 2010.

Théo Papadopoulos served as a referee for the international workshop MCV (MICCAI 2010 satellite), for the international conferences MICCAI 2010 and CVPR 2011. He is also area chair for the national conference GRETSI 2011. In 2010, he has been reviewer for the journals NeuroComputing, Annals of Biomedical Engineering, Physics in Medicine and Biology, SIAM Journal on Imaging Sciences and Transactions on Image Processing. From July 2007 to August 2010, he was the task leader of the WP8 work package of the European project FACETS 7.3.1. He is the coordinator of the ADT "Immersive BCI" and the Athena contact for the ADT MedINRIA-NT and the ANR MULTIMODEL. Théo Papadopoulos was also in the PhD committee of A.

J. Salgado de la Nuez (University of Las Palmas). He has given invited talks at the International Conference on Biomagnetism (Dubrovnik), at the "Journée GDR-STIC santé", BCI and at the "Journées du laboratoire WHIST". He has participated in two INRIA working groups ("New Forge" and "New Visual Identity") and was involved in an IT expertise mission in Shanghai.

8.2. Teaching

- Maureen Clerc and Théo Papadopoulo teach "Inverse problems for brain functional imaging" at ENS Cachan (21h) and at the Master in Computational Biology at University of Nice Sophia Antipolis (24h)
- Maureen Clerc teaches a "Mathematics for Engineers" class at the Polytechnic Engineering School of the University of Nice-Sophia Antipolis (24H).
- Théo Papadopoulo teaches "Computer Vision" at the Polytechnic Engineering School of the University of Nice-Sophia Antipolis (24H).
- Rachid Deriche teaches "Variational approaches and Geometrical Flows for Brain Anatomical Imaging" (24H) at the Master in Computational Biology at University of Nice Sophia Antipolis.
- Rachid Deriche is in charge of the module "PDE's and Geometric Flows in Computer Vision and Image Processing" in the Master MPRI *Master Parisien de Recherche en Informatique* - University of Paris 7, ENS and Ecole Polytechnique and teaches - (15H).
- Rachid Deriche teaches "Advanced Image Processing and Computer Vision" at Telecom & Management Sud Paris School (ex INT - Evry) - (12H).
- Emmanuel Olivi is teaching assistant for the course "Mathematics for Engineers" class at the Polytechnic Engineering School of the University of Nice-Sophia Antipolis (28H).
- Arnaud Messé teaches biophysics in PCEM1 (first medical year) at Université Pierre et Marie Curie - (30H).

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