Activity Report 2014

Project-Team ATHENA

Computational Imaging of the Central Nervous System

RESEARCH CENTER
Sophia Antipolis - Méditerranée

THEME
Computational Neuroscience and Medecine

Table of contents

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) use EEG, and translate in real-time the electrical activity of the brain in commands to control devices. While BCI is advocated as a means to communicate and help restore mobility or autonomy for very severe cases of disabled patients, it is also a new tool for interactively probing and training 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.

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 [64], Merboldt et al [68] and Taylor et al [80]. 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 [70], [71], Basser et al [45], [44] 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 $\mathbf{D}$ [45], [44]. 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 [65], [55]. 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 [67], [8] and [66]).

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 [76], [46]. Research groups currently agree that there is complex fiber architecture in most fiber regions of the brain [75]. 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 [47]. This has led to the development of various High Angular Resolution Diffusion Imaging (HARDI) techniques [82] such as Q-Ball Imaging (QBI) or Diffusion Spectrum Imaging (DSI) [83], [84], [86] 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 [63] or Diffusion Orientation Transform [88]. 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) [86], [83], [84]. 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 [54]. They are at the core of our probabilistic and deterministic tractography algorithms devised to best exploit the full distribution of the fiber ODF (see [52], [4] and [53],[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 [87], [89] or 4th order Tensor Model [43]. For more details, we refer the reader to our articles in [56], [79] where we review HOT models and to our articles 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. 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) [59].

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 [58], [79].

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 [69].

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 [69], [49], [50]. 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 [69], [49], [50].

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 [57]

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

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].
- 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], [9] and means to calibrate them [85] 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 [77], [81]. 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/FacultÃ© de mÃ©decine UniversitÃ© de MontrÃ©al (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 (BCI) aim to allow direct control of external devices using brain signals such as measured through EEG. In our project, BCI can be seen as an application of EEG processing techniques, but also as an object of fundamental and applied research as they open 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.

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

5. New Software and Platforms

5.1. OpenMEEG

Participants: Théodore Papadopoulo, Maureen Clerc, Kai Dang, 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 [60], [61]. 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 many more indirect downloads. Work is under progress to integrate it into the BESA commercial software, and discussions with other software companies are also ongoing.

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. High Performance Diffusion MRI

Participants: Aurobrata Ghosh, Théodore Papadopoulo, Rachid Deriche.

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. Contributions to the open source dMRI platform DIPY

Participants: Demian Wassermann, Rutger Fick.

DIPY (Diffusion Imaging in Python) is a fast growing open source platform for dMRI image processing. It aims to be a reference implementation platform for most dMRI processing technologies and it has several contributors around the world including Stanford Universtiy, USA; Berkeley University, USA; Sherbrooke University, Canada; and University of Cambridge, UK. This aims to provide a dMRI library easy to use in research-intensive cases where developments of new technologies are simpler than in high performance C++ libraries.

In 2014 D. Wassermann and R. Fick got involved in this open source platform. Their work spans from minor public extensions to private developments within this framework. They developed an improved implementation of the 3D-SHORE [72] basis, which is designed to reconstruct the three-dimensional diffusion propagator from three-dimensional q-space measurements. Moreover, they optimized the computation of the basis coefficients and introduced the analytical Laplacian regularization [19]. They also implemented the MAP-MRI basis [73], which is an extension of the 3D-SHORE basis to better deal with highly anisotropic data. Finally, they extended this work by again introducing the analytical Laplacian regularization. Also, we implemented a novel generalized basis that fits diffusion MRI data over both three-dimensional q-space and diffusion times (3D+t). The theoretical developments related to these two last contributions have been submitted to ISBI 2015 and IPMI 2015 respectively.

- License: Revised BSD license.
- Platform: Multiplatform
- Programming language: Python & C

5.4. 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.

5.5. 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

5.6. CoAdapt P300 Stimulator

Participants: Maureen Clerc, Théodore Papadopoulo, Loïc Mahé, Nathanaël Foy, Jérémie Mattout [Centre de Recherche en Neurosciences de Lyon, INSERM], Emmanuel Maby [Centre de Recherche en Neurosciences de Lyon, INSERM].

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. This software was developped in the context of the ANR project CoAdapt. It runs with OpenViBE as an external plugin.

- Version: 1.0
- Keywords: Brain Computer Interfaces
- Multiplatform: Windows - Linux - MacOSX
- Programming language: C++
- APP IDDN FR.001.020003.000.S.P.2015.000.31235

6. New Results

6.1. Highlights of the Year

Maureen Clerc was awarded the PIERRE FAURRE Prize by the French Academy of Sciences. This award recognizes her outstanding contributions to the modelling and interpretation of electrical signals in the brain. The ceremony took place at the Institut de France on October 14th, 2013.

Emmanuel Caruyer was awarded the AFRIF Best PhD thesis award 2013 for his work “Q-space diffusion MRI: Acquisition and Signal Processing” performed under the direction of Rachid Deriche. He received the award thesis AFRIF 2013 during RFIA Conference held from June 30 to July 4, 2014 in Rouen.

Rachid Deriche was awarded the title of Honorary Doctor (honoris causa) from the University of Sherbrooke, Canada. This award recognises his achievements and contributions to image processing, computer vision and computational brain imaging. The title was awarded at the academic conferment ceremony held on September 20th, 2014 at the University of Sherbrooke.

Théo Papadopoulo has been promoted to the position of Research Director Class 2, starting from October 1st, 2014.

6.2. Modeling in Diffusion MRI

6.2.1. Non-Negative Spherical Deconvolution (NNSD) for estimation of fiber Orientation Distribution Function in single-/multi-shell diffusion MRI

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

Spherical Deconvolution (SD) is commonly used for estimating fiber Orientation Distribution Functions (fODFs) from diffusion-weighted signals. Existing SD methods can be classified into two categories: 1) Continuous Representation based SD (CR-SD), where typically Spherical Harmonic (SH) representation is used for convenient analytical solutions, and 2) Discrete Representation based SD (DR-SD), where the signal profile is represented by a discrete set of basis functions uniformly oriented on the unit sphere. A feasible fODF should be non-negative and should integrate to unity throughout the unit sphere SS2. However, to our knowledge, most existing SH-based SD methods enforce non-negativity only on discretized points and not the whole continuum of SS2. Maximum Entropy SD (MESD) and Cartesian Tensor Fiber Orientation Distributions (CT-FOD) are the only SD methods that ensure non-negativity throughout the unit sphere. They are however computational intensive and are susceptible to errors caused by numerical spherical integration. Existing SD methods are also known to overestimate the number of fiber directions, especially in regions with low anisotropy. DR-SD introduces additional error in peak detection owing to the angular discretization of the unit sphere. This work proposes a SD framework, called Non-Negative SD (NNSD), to overcome all the limitations above. NNSD is significantly less susceptible to the false-positive peaks, uses SH representation for efficient analytical spherical deconvolution, and allows accurate peak detection throughout the whole unit sphere. We further show that NNSD and most existing SD methods can be extended to work on multi-shell data by introducing a three-dimensional fiber response function. We evaluated NNSD in comparison with Constrained SD (CSD), a quadratic programming variant of CSD, MESD, and an L1-norm regularized non-negative least-squares DR-SD. Experiments on synthetic and real single-/multi-shell data indicate that NNSD improves estimation performance in terms of mean difference of angles, peak detection consistency, and anisotropy contrast between isotropic and anisotropic regions.

This work has been published in [11].

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

Participants: Alessandro Daducci [LTS5, Ecole Polytech. Fed. de Lausanne (EPFL)], Maxime Descoteaux [SCIL Lab., Sherbrooke University], Michael Paquette [SCIL Lab., Sherbrooke University], Sylvain Merlet, Emmanuel Caruyer, Rachid Deriche.

Validation is arguably the bottleneck in the diffusion magnetic resonance imaging (MRI) community. This work evaluates and compares 20 algorithms for recovering the local intra-voxel fiber structure from diffusion MRI data and is based on the results of the "HARDI reconstruction challenge" organized in the context of the "ISBI 2012" conference. Evaluated methods encompass a mixture of classical techniques well known in the literature such as diffusion tensor, Q-Ball and diffusion spectrum imaging, algorithms inspired by the recent theory of compressed sensing and also brand new approaches proposed for the first time at this contest. To quantitatively compare the methods under controlled conditions, two datasets with known ground-truth were synthetically generated and two main criteria were used to evaluate the quality of the reconstructions in

every voxel: correct assessment of the number of fiber populations and angular accuracy in their orientation. This comparative study investigates the behavior of every algorithm with varying experimental conditions and highlights strengths and weaknesses of each approach. This information can be useful not only for enhancing current algorithms and develop the next generation of reconstruction methods, but also to assist physicians in the choice of the most adequate technique for their studies.

This work has been published in [12]

6.2.3. Comparison of sampling strategies and sparsifying transforms to improve compressed sensing diffusion spectrum imaging

Participants: Michael Paquette [SCIL Lab., Sherbrooke University], Sylvain Merlet, Guillaume Gilbert [SCIL Lab., Sherbrooke University], Maxime Descoteaux [SCIL Lab., Sherbrooke University], Rachid Deriche.

Diffusion Spectrum Imaging enables to reconstruct the ensemble average propagator (EAP) at the expense of having to acquire a large number of measurements. Compressive sensing offers an efficient way to decrease the required number of measurements. The purpose of this work is to perform a thorough experimental comparison of three sampling strategies and six sparsifying transforms to show their impact when applied to accelerate compressive sensing-diffusion spectrum imaging. In this work, we propose a novel sampling scheme that assures uniform angular and random radial q-space samples. We also compare and implement six discrete sparse representations of the EAP and thoroughly evaluate them on synthetic and real data using metrics from the full EAP, kurtosis, and orientation distribution function. The discrete wavelet transform with Cohen–Daubechies–Feauveau 9/7 wavelets and uniform angular sampling in combination with random radial sampling showed to be better than other tested techniques to accurately reconstruct the EAP and its features. In conclusion, it is important to jointly optimize the sampling scheme and the sparsifying transform to obtain accelerated compressive sensing-diffusion spectrum imaging. Experiments on synthetic and real human brain data show that one can robustly recover both radial and angular EAP features while undersampling the acquisition to 64 measurements (undersampling factor of 4).

This work has been published in [16]

6.2.4. DSI 101: Better ODFs for Free

Participants: Michael Paquette [SCIL Lab., Sherbrooke University], Sylvain Merlet, Maxime Descoteaux [SCIL Lab., Sherbrooke University], Rachid Deriche.

Diffusion Spectrum Imaging (DSI) is a well established method to recover the Ensemble Average Propagator (EAP). The orientation distribution function (ODF) is computed from this discretized EAP and used for tractography. However, there are several important implementation considerations that are tossed aside in the literature and the publicly available softwares. We investigate all the real steps necessary to go from the DSI signal to the ODF and provide applicable recommendations that greatly improve the accuracy of the local orientation detected. These recommendations come ”free-of-charge” as they are applicable to all existing DSI data and do not require a significant increase in computation time.

This work has been published in [26]

6.2.5. Comparison between discrete and continuous propagator indices from Cartesian q-space DSI sampling

Participants: Mauro Zucchelli [Dpt of Computer Science, University of Verona], Eleftherios Garyfallidis [SCIL Lab., Sherbrooke University], Michael Paquette [SCIL Lab., Sherbrooke University], Maxime Descoteaux [SCIL Lab., Sherbrooke University], Gloria Menegaz [Dpt of Computer Science, University of Verona], Sylvain Merlet.

DSI is often considered the state-of-the-art technique to analyze q-space measurements sampled from a Cartesian grid. The 3D fast Fourier transform is used to directly obtain a discrete version of the EAP (Ensemble Average Propagator). DSI was one of the first techniques used to infer complex fiber configurations as it allows resolving crossings. In principle, DSI also captures some radial information which,in theory, can be used to extract diffusion features of the EAP. However, a discrete propagator representation suffers from a limited frequency band, which makes infinite integration impossible. Hence, EAP derived indices 2,3 are problematic and quantitatively questionable, as one needs to artificially normalize and approximate the infinite integrals. Combined with the recent popularity of DSI in the Human Connectome Project, it is important to investigate the different angular and EAP indices that can be computed from these DSI datasets. In this work, we investigate alternatives to the discrete model-free approach of DSI and investigate the Simple Harmonic Oscillator based Reconstruction and Estimation 3 (SHORE) models based on the evaluation of (i) the orientation distri bution function (ODF) ; (ii) the return to the origin probability (RTOP) and (iii) the mean square displacement (MSD).

This work has been published in [33]

6.2.6. Odf Maxima Computation Using Hill Climbing Algorithm

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

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 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 published in [24]

6.2.7. Greedy NNLS: Fiber Orientation Distribution from Non-Negatively Constrained Sparse Recovery

Participants: Aurobrata Ghosh, Rachid Deriche.

In this work, we validated experimentally the merits of the Non-Negative Least Squares (NNLS) for the constrained sparse recovery of the Fiber Orientation Distribution (FOD) and compared it with classical l1-minimization. The FOD is a robust model for mapping crossing white matter fibers. However, its angular resolution depends on the spherical harmonic basis order, which can imply a large number of acquisitions. Further, it is necessary to compute the maxima of the FOD to derive the fiber directions. It is possible to kill the two proverbial birds with a single stone by using a non-negatively constrained sparse recovery FOD estimation with NNLS.

From our experiments, we confirmed results from literature to show that NNLS converges to highly sparse solutions which are correctly constrained, while l1-minimization is less sparse, contains negative solutions and is unstable with noisy data. Finally, we discussed the NLS algorithm and attributed the sparsity to its design, which mirrors the design of Orthogonal Matching Pursuit (OMP)

This work has been published in [22]

6.2.8. Crossing Fibers Detection with an Analytical High Order Tensor Decomposition

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

Diffusion magnetic resonance imaging (dMRI) is the only technique to probe in vivo and noninvasively the fiber structure of human brain white matter. Detecting the crossing of neuronal fibers remains an exciting challenge with an important impact in tractography. In this, we tackle this challenging problem and propose an original and efficient technique to extract all crossing fibers from diffusion signals. To this end, we start by estimating, from the dMRI signal, the so-called Cartesian tensor fiber orientation distribution (CT-FOD) function, whose maxima correspond exactly to the orientations of the fibers. The fourth order symmetric positive definite tensor that represents the CT-FOD is then analytically decomposed via the application of a new theoretical approach and this decomposition is used to accurately extract all the fibers orientations. Our proposed high order tensor decomposition based approach is minimal and allows recovering the whole crossing fibers without any a priori information on the total number of fibers. Various experiments performed on noisy synthetic data, on phantom diffusion, data and on human brain data validate our approach and clearly demonstrate that it is efficient, robust to noise and performs favorably in terms of angular resolution and accuracy when compared to some classical and state-of-the-art approaches.

This work has been published in [15] and [34].

6.2.9. Complete set of Invariants of a 4th order tensor: the 12 tasks of HARDI from Ternary Quartics

Participants: Théodore Papadopoulo, Auro Ghosh, Rachid Deriche.

In this work, we presented a simple and systematic method to compute a functionally complete set of invariants of a non-negative 3D 4th order tensor with respect to 3D rotations. Intuitively, this transforms the tensor's non-unique ternary quartic (TQ) decomposition (from Hilbert's theorem) to a unique canonical representation independent of orientation.

Invariants play a crucial role in diffusion MRI. In DTI (2nd order tensors), invariant scalars (FA, MD...)have been successfully used in clinical applications. But DTI has limiations and HARDI models (e.g. 4th order tensors) have been proposed instead. These, however, lack invariant features and computing them systematically is challenging.

The invariants we propose, can be computed from two simple reduction steps, which first reduce an orthogonal class and then a rotation transform class of equivalent representations from the TQ coefficients. The resulting invariants are, by construction, (1) functionally complete, (2) functionally irreducible (if desired), (3) computationally efficient and (4) reversible – or mappable to the TQ coefficients or shape. These were the novelties of our contribution in comparison to prior work.

This work has been published in [25]

6.2.10. Fiber Orientation Distribution from Non-Negative Sparse Recovery

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

In this work, we tested our non-negatively constrained sparse recovery algorithm for estimating the FOD on single shell phantom data provided by the ISBI'2014 challenge. We used the NNLS algorithm to estimate high order FODs (24th order) from just 20, 30 and 60 gradient directions and for various b-values of 1000, 2000, and 3000.

From the results, which are yet to be published, but can be viewed in their preliminary form online, it is clear that amongst the single shell algorithms, ours was good at fitting the signal and estimating the number of compartments. It performed well even with as low as 20 gradient acquisitions. Its major shortcoming was in underestimating the crossing angle and this needs to be improved upon.

This work has been published in [35]

6.2.11. How to get more out of a clinically feasable 64 gradient dMRI acquisition: Multi-Shell versus Single-Shell

Participants: Rutger H.j Fick, Mario Zuccheli [Dpt of Computer Science, University of Verona], Gabriel Girard [SCIL Lab., Sherbrooke University], Maxime Descoteaux [SCIL Lab., Sherbrooke University], Gloria Menegaz [Dpt of Computer Science, University of Verona], Rachid Deriche.

For clinical applications the number of diffusion MRI (dMRI) samples that can be obtained is often limited by scanner time and patient comfort. For this reason one often uses short scanning protocols that acquire just 32 or 64 gradient directions using a single b-value to obtain diffusion measures such as the fractional anisotropy from Diffusion Tensor Imaging (DTI) or to estimate the white matter orientation using Constrained Spherical Deconvolution (CSD). Using 3D-SHORE and MAP-MRI, we show that by spreading the same number of dMRI samples over different b-shells (sampling angularly and radially) we can estimate not only the directionality of the white matter using the ODF, but also the radially dependent higher order diffusion measures that SHORE and MAP-MRI provide. This approach lends itself well for situations where acquisition time is limited, and is therefore particularly well suited for clinical applications.

This work has been submitted to ISMRM'2015.

6.3. From dMRI to Fiber Pathways

6.3.1. Towards quantitative connectivity analysis: reducing tractography biases

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

Diffusion MRI tractography is often used to estimate structural connections between brain areas and there is a fast-growing interest in quantifying these connections based on their position, shape, size and length. However, a portion of the connections reconstructed with tractography is biased by their position, shape, size and length. Thus, connections reconstructed are not equally distributed in all white matter bundles. Quantitative measures of connectivity based on the streamline distribution in the brain such as streamline count (density), average length and spatial extent (volume) are biased by erroneous streamlines produced by tractography algorithms. In this work, solutions are proposed to reduce biases in the streamline distribution. First, we propose to optimize tractography parameters in terms of connectivity. Then, we propose to relax the tractography stopping criterion with a novel probabilistic stopping criterion and a particle filtering method, both based on tissue partial volume estimation maps calculated from a T1-weighted image. We show that optimizing tractography parameters, stopping and seeding strategies can reduce the biases in position, shape, size and length of the streamline distribution. These tractography biases are quantitatively reported using in-vivo and synthetic data. This is a critical step towards producing tractography results for quantitative structural connectivity analysis.

This work has been published in [13]

6.3.2. Choosing tractography parameters to improve connectivity mapping

Participants: Gabriel Girard [SCIL Lab., Sherbrooke University], Kevin Whittingstall [SCIL Lab., Sherbrooke University], Maxime Descoteaux [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 to 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 published in [20]

6.3.3. Connectivity directionally-encoded color map: a streamline-based color mapping

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

In this work, we provide a novel method to map streamlines in a color image, which can be generated from any set of streamlines. We show that this novel orientation color-coded map based on streamline tractography can improve connectivity analysis.

This work has been published in [23]

6.4. From dMRI to Microstructures Recovery

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

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

In this work, we are interested in retrieving information about the axon diameter distributions in white matter fiber bundles using NMR, which are commonly modelled as ensembles of parallel cylinders. We add regularization to the 1D-SHORE basis which results in more stable characterization of diameter distributions. To validate the method, we simulate NMR signals using the open source toolkit CAMINO. The results illustrate the enhanced estimation accuracy given by the regularization and provide an alternative validation of the SHORE based method.

This work has been published in [30]

6.4.2. 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 published in [29] and [28]

6.4.3. Magnitude and complex based diffusion signal reconstruction

Participants: Marco Pizzolato, Timothe Boutelier [Olea Medical, La Ciotat], Rachid Deriche.

In Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) the modeling of the magnitude signal is complicated by the Rician distribution of the noise. It is well known that when dealing instead with the complex valued signal, the real and imaginary parts are affected by Gaussian distributed noise and their modeling can thus benefit from any estimation technique suitable for this noise distribution. We present a quantitative analysis of the difference between the modeling of the magnitude diffusion signal and the modeling in the complex domain. The noisy complex and magnitude diffusion signals are obtained for a physically realistic scenario in a region close to a restricting boundary. These signals are then fitted with the Simple Harmonic Oscillator based Reconstruction and Estimation (SHORE) bases and the reconstruction performances are quantitatively compared. The noisy magnitude signal is also fitted by taking into account the

Rician distribution of the noise via the integration of a Maximum Likelihood Estimator (MLE) in the SHORE. We discuss the performance of the reconstructions as function of the Signal to Noise Ratio (SNR) and the sampling resolution of the diffusion signal. We show that fitting in the complex domain generally allows for quantitatively better signal reconstruction, also with a poor SNR, provided that the sampling resolution of the signal is adequate. This applies also when the reconstruction is compared to the one performed on the magnitude via the MLE.

This work has been published in [27]

6.4.4. Extracting a biomarker for the mean cross-sectional area from the ODF

Participants: Rutger H.j Fick, Gonzalo Sanguinetti, Rachid Deriche.

Finding new biomarkers related to the microstructure of white matter (WM) is an active area of research in the MRI community. As opposed to the usual MRI markers such as fractional anisotropy (FA), these biomarkers provide a closer insight on the tissue structure. We introduce a new microstructure based biomarker that is related to the axon diameter distribution (ADD) and can be obtained with a q-space imaging technique like DSI or MAP . This feature is related with the nature and purpose of WM paths in bothnormal and pathological conditions and is obtained from the Orientation Distribution Function (ODF) as twice its maximum value. We show that this value is related with the mean cross-sectional area (MCSA) of an ensemble of parallel axons. The same geometric feature was proposed as a scalar index of microstructure, but was not related to the ODF. In this work we give the formal relation between this microstructure feature and the ODF, and validate it using state-of-the-art numerical simulations.

This work has been published in [18].

6.4.5. An Analytical 3D Laplacian Regularized SHORE Basis and Its Impact on EAP reconstruction and Microstructure Recovery

Participants: Rutger H.j Fick, Demian Wassermann, Gonzalo Sanguinetti, Rachid Deriche.

In diffusion MRI, the reconstructed Ensemble Average Propagator (EAP) from the diffusion signal provides detailed insights on the diffusion process and the underlying tissue microstructure. Recently, the Simple Harmonic Oscillator based Reconstruction and Estimation (SHORE) basis was proposed as a promising method to reconstruct the EAP. However, the fitting of the basis is sensitive to noise. To solve this we propose to use the Laplacian of the SHORE basis as a natural regularization functional. We provide the derivation of the Laplacian functional and compare its effect on EAP reconstruction with that of separated regularization of the radial and angular parts of the SHORE basis. To find optimal regularization weighting we use generalized cross-validation and validate our method quantitatively on synthetic and qualitatively on human data from the Human Connectome Project. We show that Laplacian regularization provides more accurate estimation of the signal and EAP based microstructural measures.

This work has been published in [19]

6.4.6. Using 3D-SHORE and MAP-MRI to obtain both Tractography and Microstructural Contrasts from a Clinical DMRI Acquisition

Participants: Rutger H.j Fick, Mario Zuccheli [Dpt of Computer Science, University of Verona], Gabriel Girard [SCIL Lab., Sherbrooke University], Maxime Descoteaux [SCIL Lab., Sherbrooke University], Gloria Menegaz [Dpt of Computer Science, University of Verona], Rachid Deriche.

Diffusion MRI (dMRI) is used to characterize the directional- ity and microstructural properties of brain white matter (WM) by measuring the diffusivity of water molecules. In clinical practice the number of dMRI samples that can be obtained is limited, and one often uses short scanning protocols that ac- quire just 32 to 64 different gradient directions using a single gradient strength (b-value). Such 'single shell' scanning protocols restrict one to use methods that have assumptions on the radial decay of the dMRI signal over different b-values, which introduces estimation biases. In this work, we show, that by simply spreading the same number of samples over multiple b-values (i.e. multi-shell) we can accurately estimate both the WM directionality using 3D-SHORE

and characterize the radially dependent diffusion microstructure measures using MAP-MRI. We validate our approach by undersampling both noisy synthetic and human brain data of the Human Connectome Project, proving this approach is well-suited for clinical applications.

This work has been submitted to ISBI'2015.

6.4.7. Laplacian-Regularized MAP-MRI Improving Axonal Caliber Estimation

Participants: Rutger H.j Fick, Demian Wassermann, Gonzalo Sanguinetti, Rachid Deriche.

In diffusion MRI, the accurate description of the entire diffusion signal from sparse measurements is essential to enable the recovery of microstructural information of the white matter. The recent Mean Apparent Propagator (MAP)-MRI basis is especially well suited for this task, but the basis fitting becomes unreliable in the presence of noise. As a solution we propose a fast and robust analytic Laplacian regularization for MAP-MRI. Using both synthetic diffusion data and human data from the Human Connectome Project we show that (1) MAP-MRI has more accurate microstructure recovery com- pared to classical techniques, (2) regularized MAP-MRI has lower signal fitting errors compared to the unregularized approach and a positivity constraint on the EAP and (3) that our regularization improves axon radius recovery on human data.

This work has been submitted to ISBI'2015.

6.4.8. A Unifying Framework for Spatial and Temporal Diffusion in Diffusion MRI

Participants: Rutger H.j Fick, Demian Wassermann, Marco Pizzolato, Rachid Deriche.

We propose a novel framework to simultaneously represent the diffusion-weighted MRI (dMRI) signal over diffusion times, gradient strengths and gradient directions. Current frameworks such as the 3D Simple Harmonic Oscillator Reconstruction and Estimation basis (3D- SHORE) only represent the signal over the spatial domain, leaving the temporal dependency as a fixed parameter. However, microstructure- focused techniques such as Axcaliber and ActiveAx provide evidence of the importance of sampling the dMRI space over diffusion time. Up to now there exists no generalized framework that simultaneously models the dependence of the dMRI signal in space and time. We use a functional basis to fit the 3D+t spatio-temporal dMRI signal, similarly to the 3D-SHORE basis in three dimensional 'q-space'. The lowest order term in this expansion contains an isotropic diffusion tensor that characterizes the Gaussian displacement distribution, multiplied by a negative exponential. We regularize the signal fitting by minimizing the norm of the analytic Laplacian of the basis. The continuous 3D+t signal representation can provide new insights on the anomalous nature of the dMRI signal in human tissues, i.e., when mean-squared molecular displacements varies slower than linearly with the diffusion time. From the fitting one can also estimate the axon radius distribution parameters along any direction using approaches similar to AxCaliber. We validate our technique on synthetic data generated using the theoretical model proposed by Callaghan et al. We show that our method is robust to noise and can accurately describe the restricted spatio-temporal signal decay originating from tissue models such as cylindrical pores. Moreover, we apply our method on real data from an ActiveAx acquisition. Overall our approach allows to represent the complete 3D+t dMRI signal which should prove helpful in understanding normal and pathologic nervous tissue.

This work has been submitted to IPMI'2015.

6.4.9. Fast and Robust EAP reconstruction using a Laplacian Regularized SHORE basis and its Impact on Microstructure Recovery

Participants: Rutger H.j Fick, Demian Wassermann, Emmanuel Caruyer [SBIA, University of Pennsylvania Medical School], Rachid Deriche.

In diffusion MRI, the reconstructed Ensemble Average Propagator (EAP) from the diffusion signal provides detailed insights on the diffusion process and the underlying tissue microstructure. Recently, the 3D Simple Harmonic Oscillator based Reconstruction and Estimation (3D-SHORE) basis was proposed as a promising method to reconstruct the EAP. However, the fitting of the basis is sensitive to noise. To solve this we propose to use the Laplacian of the SHORE basis as a natural regularization functional. We provide the derivation of the Laplacian functional and compare its effect on EAP reconstruction with that of separated regularization of

the radial and angular parts of the SHORE basis and imposing positive-definiteness in the estimation of the EAP. We validate our method on phantom data with known ground truth and on human data from the Human Connectome Project. We show that Laplacian regularization of the 3D-SHORE basis provides faster and more accurate estimation of the signal and EAP.

This work has been submitted to NeuroImage.

6.5. Functional and structural models analysis

6.5.1. Analyzing Brain Plasticity in Math Learning Using Automated Dissection and Analysis of White Matter Tracts Through dMRI

Participants: Dietsje Jolles [Stanford Medical School], Demian Wassermann, Ritika Chokhani [Stanford Medical School], Jennifer Richardson [Stanford Medical School], Caitlin Tenison [Stanford Medical School], Roland Bammer [Stanford Medical School], Lynn Fuchs [Vanderbit University], Kaustubh Supekar [Stanford Medical School], Vinod Menon [Stanford Medical School].

In a collaboration with Stanford Medical School, we explored longitudinal changes in white matter connectivity triggered by intensive math learning. Plasticity of white matter tracts is thought to be essential for cognitive development and academic skill acquisition in children. However, a dearth of high-quality diffusion tensor imaging (DTI) data measuring longitudinal changes with learning, as well as methodological difficulties in multi-time point tract identification have limited our ability to investigate plasticity of specific white matter tracts. With this contribution, we examined learning-related changes of white matter tracts innervating inferior parietal, prefrontal and temporal regions following an intense two-month math tutoring program. DTI data were acquired from 18 third grade children, both before and after tutoring. A novel fiber tracking algorithm based on a White Matter Query Language (WMQL) was used to identify three sections of the superior longitudinal fasciculus (SLF) linking frontal and parietal (SLF-FP), parietal and temporal (SLF-PT) and frontal and temporal (SLF-FT) cortices, from which we created child-specific probabilistic maps. The SLF-FP, SLF-FT, and SLF-PT tracts identified with the WMQL method were highly reliable across the two time points and showed close correspondence to tracts previously described in adults. Notably, individual differences in behavioral gains after two months of tutoring were specifically correlated with plasticity in the left SLF-FT tract. Our results extend previous findings of individual differences in white matter integrity, and provide important new insights into white matter plasticity related to math learning in childhood. More generally, our quantitative approach will be useful for future studies examining longitudinal changes in white matter integrity associated with cognitive skill development.

This work has been published in [14].

6.5.2. Quantifying Uncertainty in Diffeomorphic Medical Landmark Registration

Participants: Demian Wassermann, Matt Toew [Harvard Medical School - Brigham and Women's Hospital], Marc Niethammer [University of North Carolina at Chapel Hill], William Wells Iii [Harvard Medical School - Brigham and Women's Hospital, MIT].

In a collaboration with Harvard Medical School, the Brigham and Women's Hospital, MIT and the University of North Carolina at Chapel Hill, we proposed a novel mathematical framework to represent uncertainty in diffeomorphic registration techniques. Particularly, we introduced a novel mathematical framework for representing uncertainty in large deformation diffeomorphic image registration. The Bayesian posterior distribution over the deformations aligning a moving and a fixed image is approximated via a variational formulation. A stochastic differential equation (SDE) modeling the deformations as the evolution of a time-varying velocity field leads to a prior density over deformations in the form of a Gaussian process. This permits estimating the full posterior distribution in order to represent uncertainty, in contrast to methods in which the posterior is approximated via Monte Carlo sampling or maximized in maximum a-posteriori (MAP) estimation. The framework was demonstrated in the case of landmark-based image registration, including simulated data and annotated pre and intra-operative 3D images. This type of registration can be extended to several anatomical objects such as white matter tracts represented as streamlines.

This work has been published in [32].

6.5.3. Group Comparisons on White Matter Tracts in Native Space

Participants: Eleftherios Garyfallidis [University of Sherbrooke], Demian Wassermann, Maxime Descoteaux [University of Sherbrooke].

Let us suppose that we want to study specific fiber bundles in different subjects. The common approach would be to use a voxel-wise analyses which will warp scalar volumes in a common space, e.g. MNI space, and show how every subject differentiates from an average template. However, we know that with averaging and warping much of the specific information about the individual subjects' differences is lost. In this work, we provide a solution to this problem by using local streamline registration of specific bundles from different subjects. We show that with this new method we can keep track of the differences from every subject to every other subject in our group study.

This study was performed in collaboration with the SCIL lab of Sherbrook University within the framework of the Brain Connectivities Associate Team and published in [21].

6.5.4. Perfusion Deconvolution via SHORE and Laplacian Regularization

Participants: Marco Pizzolato, Auro Ghosh, Timothé Boutelier [Olea Medical, La Ciotat], Rachid Deriche.

Perfusion imaging comprehensively refers to the recovery of parameters of interest which are related to the passage of blood in the parenchyma (i.e. the functional part) of a tissue. The amount of perfusion is related to both the functionality of the parenchyma and its level of activity. By means of imaging techniques such as Dynamic Susceptibility Contrast MRI it is possible, in each voxel, to measure the tissue concentration $Ct(t)$ of a tracer injected before the scanning in the vascular system. According to the indicator dilution theory1 this is related to the concentration measured in an arterial region $Ca(t)$ described by a convolution with $R(t)$ that is the unknown residue function expressing the remaining time-dependent tracer quantity in the voxel. Historically $R(t)$ is obtained exploiting the convolution theorem $R(t) = FT - 1FT[Ct(t)]/FT[Ca(t)]$. However deconvolution is an ill-posed problem making this method very sensitive to noise. Many regularization techniques have been proposed but among all the most adopted technique is truncated Singular Value Decomposition, tSVD. However tSVD is known to underestimate an important perfusion parameter that is the blood flow BF, which can be computed as the maximum peak of the recovered $R(t)$. In this work we propose to use the Simple Harmonic Reconstruction and Estimation framework (SHORE) to estimate $R(t)$ in order to obtain a better parameter estimation. We regularize SHORE using Laplacian regularization. We compare the results with tSVD.

This work has been submitted to ISMRM 2015.

6.5.5. Perfusion MRI Deconvolution with Delay Estimation and Non-negativity Constraints

Participants: Marco Pizzolato, Auro Ghosh, Timothé Boutelier [Olea Medical, La Ciotat], Rachid Deriche.

Perfusion MRI deconvolution aims to recover the time-dependent residual amount of indicator (residue function) from the measured arterial and tissue concentration time-curves. The deconvolution is complicated by the presence of a time lag between the measured concentrations. Moreover the residue function must be non-negative and its shape may become non-monotonic due to dispersion phenomena. We introduce Modified Exponential Bases (MEB) to perform deconvolution. The MEB generalizes the previously proposed exponential approximation (EA) by taking into account the time lag and introducing non-negativity constraints for the recovered residue function also in the case of non-monotonic dispersed shapes, thus overcoming the limitation due to the non-increasing assumtion of the EA. The deconvolution problem is solved linearly. Quantitative comparisons with the widespread block-circulant Singular Value Decomposition show favorable results in recovering the residue function.

This work has been submitted to ISBI 2015.

6.6. Forward and Inverse Problems in MEEG

6.6.1. FindSource3D - Source Localization Using Rational Approximation on Plane Sections

Participants: Todor Jordanov [BESA GmbH, Germany], Jean-Paul Marmorat [École des Mines ParisTech, Sophia Antipolis], Maureen Clerc, Juliette Leblond, Andre Waelkens [BESA GmbH, Germany], Théodore Papadopoulo.

A new method for EEG source localization based on rational approximation techniques in the complex plane was suggested. The method is used in the context of a nested sphere head model, in combination with a cortical mapping procedure [51]. This method was shown to perform perfectly for numerical simulations without noise but its performance with respect to different signal-to-noise ratios (SNRs), to different number of sources and to real EEG data was not investigated until now. The method, formally called FindSource3D (FS3D), is evaluated with data simulations and a real EEG data set.

This work has been published in [40].

6.6.2. Diffusion Magnetic Resonance information as a regularization term for MEG/EEG inverse problem

Participants: Brahim Belaoucha, Anne-Charlotte Philippe, Maureen Clerc, Théodore Papadopoulo.

Several regularization terms are used to constrain the Magnetoencephalography (MEG) and the Electroencephalography (EEG) inverse problem. It has been shown that the brain can be divided into several regions with functional homogeneity inside each one of them. To locate these regions, we use the structural information coming from the diffusion Magnetic Resonance (dMRI) and more specifically, the anatomical connectivity of the distributed sources computed from dMRI. To investigate the importance of the dMRI in the source reconstruction, this work compares the solutions based on dMRI-based parcellation to random parcellation.

This work has been published in [37].

6.6.3. Dictionary learning for multitrial datasets

Participants: Maureen Clerc, Sebastian Hitziger, Théodore Papadopoulo.

Following the path opened with the Consensus matching Pursuit method (CMP) [48], 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. 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 [62]. 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 6.7).

This work has been published in [39].

6.7. Coupling functional and structural models

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

Participants: Anne-Charlotte Philippe, Théodore Papadopoulo, Christian Bénar [Hospital "La Timone", Marseille], Jean-Michel Badier [Hospital "La Timone", Marseille], Maureen Clerc, 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 [41].

6.7.2. Using diffusion MRI information in the Maximum Entropy on Mean framework to solve MEG/EEG inverse problem

Participants: Brahim Belaoucha, Jean-Marc Lina [Centre de Recherches Mathématique, Montréal], Maureen Clerc, Anne-Charlotte Philippe, Christophe Grova [McGill University], Théodore Papadopoulo.

Magnetoencephalography (MEG) and Electroencephalography (EEG) inverse problem is well-known to require regularization in order to avoid ill-posedness. Usually, regularization is based on mathematical criteria (minimum norm, ...). Physiologically, the brain is organized in functional parcels and imposing a certain homogeneity of the activity within these parcels was proven to be an efficient way to analyze the MEG/EEG data. The parcels information can be computed from diffusion Magnetic Resonances Imaging (dMRI) by grouping together source positions shared the same connectivity profile (computed as tractograms from diffusion images). In this work, three parcel-based inverse problem approaches have been tested. The first two approaches are based on minimum norm with added regularization terms to account for the parcel information. They differ by the use of a hard/soft constraint in the way they impose that the activity is constant within each parcel [74]. The third approach is based on the Maximum Entropy on Mean (MEM) framework [42]. It models source activity with a random variable and parcels are also used as a regularization. Several tests have been conducted with synthetic and real data that encompass the MEG/EEG and the diffusion magnetic resonance signals to compare these three approaches in terms of active region-detection accuracy.

This work has been published in [36].

6.8. Brain Computer Interfaces

6.8.1. CoAdapt P300 speller: optimized flashing sequences and online learning

Participants: Maureen Clerc, Théodore Papadopoulo, Loïc Mahé.

Our work in Brain Computer Interfaces was centered around the visual P300 speller system: a virtual keyboard allowing to type words by detecting the P300 wave, an automatic deflection of the central component of the electric potential, occurring approximately 300 ms after the apparition of an intermittent and rare event, on which the user's attention is focussing. The idea behind the P300 speller is very simple: the system displays series of stimuli (flashes), over the keyboard elements, and detects whether or not the EEG recorded after each flash contains a P300. Its implementation is not so simple, because of the low amplitude of the P300 compared to the background EEG, and of the inter-subject variability of this signal.

The advantage of this system is not to require any training on the part of the user. However the BCI system has to be trained to detect the P300 component from the background EEG: this is done through a calibration phase.

We developped a new method to reduce the calibration phase, with a transfer learning method called "mixture of experts" (MOE). The MOE classifier makes its predictions by averaging the decisions from a pre-recorded database of classifiers coming from other recording sessions (with other subjects) [31]. The decisions were made by using an evidence accumulation scheme, which updated the prediction at every flash of the keyboard [17].

Part of this work has been implemented in the software: CoAdapt P300 Stimulator.

6.8.2. P300 speller: clinical feasibility study with Amyotrophic Lateral Sclerosis

Participants: Maureen Clerc, Théodore Papadopoulo, Loïc Mahé, Asya Metelkina, Violaine Guy [Nice University Hospital], Claude Desnuelle [Nice University Hospital].

From September 2013 to July 2014, we were very involved in running an experiment with the Centre de Référence Maladies Neuromusculaires et SLA (CRMN/SLA) of Nice University Hospital. This study, partly funded by "Assocation pour la Recherche sur la Sclérose Latérale Amyotrophique", was conducted on 20 patients, who routinely come to be examined at the hospital. Each patient came for 3 sessions where he/she was allowed to use the P300 speller, after being equipped with an electro-encephalography cap, and watching a video explaining the modus operandi of the P300 and on their role in the study.

The P300 speller system has been organized in a way to make it relatively easy to deploy in a clinical setting: it involves only one laptop, and requires limited intervention from the caregiver. The most intricate operation is to position the EEG headset and ensure a correct impedance (below 5 kΩ) for all electrodes.

Each session consisted of three blocks, after the initial calibration phase: a copy spelling task of two ten-letter words, a free spelling task of approximately twenty characters, and an optional block of free use of the system for writing. Finally, the patient was asked to answer a questionnaire. This study intends to investigate the feasibility of setting up and using the P300 speller, from an operational point of view at the hospital. Translational studies of this type are extremely important for the adaptation the BCI systems to the target patient populations, and a large-scale usability study for the P300 speller has never been done before in France.

6.8.3. BCI Challenge: A spell on you if you cannot detect errors!

Participants: Maureen Clerc, Théodore Papadopoulo, Jérémie Mattout [Centre de Recherche en Neurosciences de Lyon, INSERM], Emmanuel Maby [Centre de Recherche en Neurosciences de Lyon, INSERM].

We have proposed an international BCI Challenge on decoding Error Potential signals. The winners will be announced at the 7th International IEEE/EMBS Conference on Neural Engineering, Montpellier, in April 2015. The Challenge was open on the Kaggle platform on Nov 14, 2014 and will close on Feb 24, 2015, see: website. At this date the competition is still open, and it has so far attracted 212 participants forming 181 teams.

In the P300 speller paradigm (see above) and in other BCI where a discrete feedback can be presented to the user, the EEG evoked response to the feedback can be recorded and processed online in order to evaluate whether the item selection was correct or not. This decision, if reliable, could then be used to improve the BCI performance by implementing some error correction strategy. In this competition, participants are asked to submit an Error Potential detection algorithm, capable of detecting the erroneous feedbacks online and to generalize across subjects (transfer learning).

The data used in this competition was acquired in the scope of the CoAdapt ANR project.

7. Bilateral Contracts and Grants with Industry

7.1. 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 Kai Dang's 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.

7.2. PACA PhD contract with Olea Medical

Participants: Marco Pizzolato, Rachid Deriche.

Title: Diffusion & Perfusion MRI : From bench to bedside
The objectives of Marco Pizzolato's 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.

7.3. 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 2013 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 most recent milestones added on the road-map includes higher order models such as ODFs, FODs, EAPs, etc. This is currently followed up by tractography algorithms – both deterministic and probabilistic.

7.4. BESA GmbH

Participants: Maureen Clerc, Théodore Papadopoulo, Juliette Leblond [APICS], Christos Papageorgakis.

We are collaborating with the BESA company (Brain Electromagnetic Source Analysis) on modeling head tissue conductivity, and on forward and inverse problems of source localization. The PhD thesis of C. Papageorgakis, 50% funded by BESA, started in October 2014.

8. Partnerships and Cooperations

8.1. Regional Initiatives

8.1.1. Projets Blancs 2014: Axe Interdisciplinaire de Recherche à l'échelle du pôle Nice - Sophia Antipolis

8.1.1.1. Real time detection of morpho-phonological computation in the brain

Participants: Maureen Clerc, Rachid Deriche, Théodore Papadopoulo, Demian Wassermann, Fabien Mathy [Université de Nice-Sophia Antipolis], Tobias Sheer [Université de Nice-Sophia Antipolis], Lucas Drevillon.

Duration: *June 2014 to November 2014*

The overall idea of this project is that current work [78] shows that it is possible to discriminate between morphological (i.e. concatenative) and phonological activity that is produced by the brain upon linguistic stimuli. That is, the experimental setup provides an on-line diagnostic for the presence or absence of phonological computation in the production of words.

On the neuroimaging side, the long-term challenge is to reproduce Sahin et al.'s [78] experiment with non-invasive methods (see the following section). If successful, the study will show that a processing sequence predicted on linguistic grounds is implemented in the brain in fine-grained spatiotemporally patterned activity. From the neuroimaging point of view, the development of such non-invasive methods that can accurately identify events in known regions will have an important impact on both computer science and neuroscience. Replacing deep electrode probes (implanted in the patient's brain) with algorithms to map cognitive processes onto brain activation will help developing new applications of functional neuroimaging. Note that results could also turn out to foster clinical tools in the diagnosis of patients affected by white matter abnormalities and altered structure-function relationships in the connectional anatomy of language.

This project aimed to perform a feasibility study for this research area. More precisely to investigate whether current neuroimaging technologies are able to provide the tools for the proposed linguistic analysis.

8.1.2. ARSLA-funded clinical study with Nice University Hospital

Participants: Maureen Clerc, Théodore Papadopoulo, Loïc Mahé, Asya Metelkina, Violaine Guy [Nice University Hospital], Claude Desnuelle [Nice University Hospital].

We are partners of Nice University Hospital in a project funded by "Association pour la Recherche sur la Sclérose Latérale Amyotrophique" (ARSLA), thanks to which we are conducting a clinical feasibility study on a Brain Computer Interface system called the P300 speller (see section New Results on Brain Computer Interfaces).

8.2. National Initiatives

8.2.1. ANR

8.2.1.1. ANR CO-ADAPT

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

Duration: *December 2009 to April 2014*

The partners of this project were the INSERM U1028 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 was to study the co-adaptation between a user and a BCI system in the course of training and operation. The quality of the interface was judged according to several criteria (reliability, learning curve, error correction, bit rate). BCI were 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.

The aim of CO-ADAPT was 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).

This project has led to many concrete realizations, e.g. an international BCI Challenge on detecting Error Potentials, and software (CoAdapt P300 stimulator).

8.2.1.2. 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.

8.2.1.3. 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 were :

- 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 were 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 operated 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 was investigated, which includes astrocytes at this "mesoscopic" level and operates in networks of connected regions. Moreover, models in physiological and pathological conditions were compared, which is a step towards a better understanding of mechanisms underlying epileptic condition.

8.2.1.4. ANR VIBRATIONS

Participants: Théodore Papadopoulo, Maureen Clerc, Rachid Deriche, Demian Wassermann.

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.

8.2.2. ADT

8.2.2.1. ADT BOLIS

Participants: Théodore Papadopoulo, Juliette Leblond [APICS], Jean-Paul Marmorat [APICS].

Duration:*December 2014 to December 2016* ADT BOLIS aims to build a sofware platform dedicated to inverse source localisation, building upon the elements of software found in FindSources3D. The platform will be modular, ergonomic, accessible and interactive. It will offer a detailed visualisation of the processing steps and the results.

8.2.2.2. ADT OpenViBE-X

Participants: Théodore Papadopoulo, Maureen Clerc, Nathanaël Foy.

Duration: *October 2014 to October 2016*

The OpenViBE-X ADT addresses the OpenViBE Brain Computer Interfaces (BCI) platform, in order to:

1. make BCI easier to apprehend by end-users
2. enrich the interaction with multimodal biosignals (eye gaze, heart-rate)
3. implement methods for auto-calibration and online adaptation of the classification
4. provide support, maintenance and dissemination for this software.

The OpenViBE platform is a central element to BCI research at Inria, and in the international community.

8.2.2.3. 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 was 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 also supported the research made in four Inria teams (ATHENA, HYBRID, NEUROSYS and POTIOC) on hot topics such as adaptive or hybrid BCIs. In September 2014, the partners of this ADT organized a workshop on OpenViBE at the 6th international conference on Brain Computer Interfaces in Graz.

8.2.2.4. 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.

8.3. European Initiatives

8.3.1. ChildBrain ETN

Duration: *March 2015 to March 2019*

ATHENA is an Associated Partner in this European Training Network: the team will participate in training workshops and receive PhD students in secondments.

Program: European Training Network
Project acronym: ChildBrain
Project title: Advancing brain research in children's developmental neurocognitive disorders
Duration: mois année début - mois année fin
Coordinator: Prof. Paavo Leppänen, University of Jyväskylä, Finland
Other partners: University of Leuven (Belgium), University of Münster (Germany), Rabboud University (The Netherlands), Aston University (United Kingdom), IcoMetrix (Belgium), Elekta (Finland), BESA (Germany)
Abstract: The purpose of the ChildBrain ETN is to train young scientists, i.e. Early Stage Researchers (ESRs), to utilise evidence-based neuroscientific knowledge for helping children, especially those at high risk for dropout due to neurocognitive disorders, to meet future educational and societal demands.

8.4. International Initiatives

8.4.1. Inria Associate Teams

8.4.1.1. BRAINCONNECTIVITIES

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

International Partner (Institution - Laboratory - Researcher):

Ecole de Technologie Supérieure, Université du Québec, (CANADA)

Duration: Jan. 2012 - Dec. 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.

8.4.2. Inria International Partners

8.4.2.1. 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 on EEG/MEG source localisation.

8.4.3. Participation In other International Programs

- Programme Samuel de Champlain - Université de Sherbrooke, Canada.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

- Thinhinane Megherbi (USTHB, Algiers) visited ATHENA from May 30 until June 30, 2014.
- Kevin Whittingstall (Université de Sherbrooke) visited ATHENA from June 2 until June 5, 2014.
- Cristina Campi (Genoa University) visited ATHENA on March 28, 2014.

8.5.1.1. Internships

- Hughes Thomas (Queens's University, Ontario) visited ATHENA from May 5h until July 31
- Russel Taylor (Queens's University, Ontario) visited ATHENA from May 5th until July 31

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. General chair, Scientific chair

- R. Deriche is Adj. Director at the Doctoral School EDSTIC (http://edstic.i3s.unice.fr/index.html)
- M. Clerc is "Vice-Présidente du Comité des Projets" (Deputy Head of Science) of Inria Sophia Antipolis Méditerranée Research Center.
- 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).

9.1.1.2. Member of the organizing committee

- 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 Council of AFRIF (Association Française pour la Reconnaissance et l'Interprétation des Formes) .

9.1.2. Scientific events selection

9.1.2.1. Member of the conference program committee

- M. Clerc is member of the conference programme committee of International Conference on Basic and Clinical Multimodal Imaging (BACI2015), and of the award committee of the IEEE EMBC conference on Neural Engineering (NER2015).
- T. Papadopoulo is member of the conference programme committee for the national conference GRETSI 2015.

9.1.2.2. Reviewer

- R. Deriche serves several international conferences (Isbi, MICCAI, ISMRM...).
- T. Papadopoulo served the international conferences: ISBI 2014, ISBI 2015, NER 2015, VISAPP 2015.
- M. Clerc served as reviewer for the international conferences: EMBC 2014, ICASSP 2014.

9.1.3. Journal

9.1.3.1. Member of the editorial board

- 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.
- M. Clerc is member of the Editorial Board of Biomedical Engineering OnLine, and the ISTE-Wiley book series.

9.1.3.2. Reviewer

- R. Deriche serves several international journals (NeuroImage, IEEE Transactions on Medical Imaging, Magnetic Resonance in Medicine, JMIV, Medical Image Analysis Journal,...).
- In 2014, T. Papadopoulo served as a reviewer for the journals TBME, PMB, Frontiers In Neuroscience.
- In 2014, M. Clerc served as a reviewer for the Proceedings of the IEEE, Physiological Measurement

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: R. Deriche, Advanced Image Processing Techniques, 12 ETD, M1 International CBB & Ubinet, 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*, 12 ETD, M1 International Ubinet, 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.
- PhD: M. Clerc gave a course in a workshop dedicated to the OpenViBE software at the 6th International Brain Computer Interface Conference in Graz, September 2015.

9.2.2. Supervision

- PhD in progress: Kai Dang, “Modeling and characterizing electrical conductivity for cochlear implantation”, started Dec. 2013, Université Nice Sophia Antipolis. 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: 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: Sebastian Hitziger, “MEEG signal processing”, started Nov. 2011, Supervisors: Théodore Papadopoulo & 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.
- Master: Lucas Drevillon, ISEN Brest, Élève Ingénieur Master 2 - Majeur: Technologies Biomédicales. Supervised by D. Wassermann.
- Master: Atousa Setoodegan, Université Nice Sophia Antipolis, Memoire Master 2. Supervised by D. Wassermann.
- Master: Aymeric Reshef, ENS Cachan, Memoire Master 2, Mathématiques / Vision / Apprentissage. Supervised by D. Wassermann & William Wells III (Harvard Medical School / MIT).

- Master: Asya Metelkina, Université Nice Sophia Antipolis, Memoire Master 2, Supervised by M. Clerc.
- Master: Christos Papageorgakis, Université Nice Sophia Antipolis, Memoire Master 2, Supervised by T. Papadopoulo.
- Master: Alicia Malé, Télécom Physique Strasbourg, Memoire Master 2, Supervised by T. Papadopoulo.

9.2.3. Juries

- Rachid Deriche participated in the PhD juries of H.T. Nguyen (Neurospin, Saclay), C. Herold (Telecom ParisTech), Lars Lau Rakêt (CS Dept. University of Copenhaguen), C.Y. Sun (Insa, Lyon), S. Razakarivony (Caen Basse Normandie Univ.)
- Rachid Deriche participated in the HDR juries of J.P Da Costa (Université de Bordeaux).
- Demian Wassermann participated in the PhD Jury of V. Siless (Parietal EPI - Inria Saclay / Neurospin CEA, Orsay).
- Maureen Clerc participated in the PhD jury of Alexandre Fouchard (mi-parcours, CEA-LETI, Grenoble).

10. Bibliography

Major publications by the team in recent years

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[2] E. CARUYER, I. AGANJ, C. LENGLET, G. SAPIRO, R. DERICHE. *Motion detection in diffusion MRI via online ODF estimation*, in "International Journal of Biomedical Imaging", January 2013, vol. 2013, http://dx.doi.org/10.1155/2013/849363

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