Acronyme	**SIMUDMRI**		
Titre du projet en français	Simulation du signal d'IRM diffusion dans tissu biologique		
Titre du projet en anglais	Simulation of diffusion MRI signals in biological tissue		
Axe(s) thématique(s)	**x**☐ 1 ☐ 2 ☐ 3		
Type de recherche	☒ Recherche Fondamentale ☐ Recherche Industrielle ☐ Développement Expérimental		
Types de projets spécifiques	☐ Plate-forme (cocher si ce projet est une mise en place/construction de plate-forme au sens de l'appel à projets)		
Aide totale demandée	400038 €	**Durée du projet**	36 mois

1. RÉSUMÉ

Water diffusion magnetic resonance imaging (DMRI) is a method which uses a combination of applied magnetic fields to measure, statistically, the diffusion of water molecules due to Brownian motion. Its spatial resolution is on the order of millimeters. An apparent diffusion coefficient (ADC) or diffusion tensor (DT) is computed for each voxel based on a model relating these quantities to signal attenuation. In the past three decades, DMRI has been successfully used to track brain white matter fibers and to detect acute brain ischemia. Diffusion functional MRI has also begun to gain momentum as an active area of research. The goal of this project is to go beyond the ADC or the DT to get more detailed information on tissue properties from the DMRI signal.

The cellular structure inside the human brain varies on the scale of micrometers, which is much smaller than the size of a voxel. There may be thousands of irregularly-shaped cells within a voxel, and they all contribute to the environment seen by water molecules whose displacement is measured by the MRI scanner. In the typical DMRI experiment, the time interval over which water diffusion is measured is in the range of 50-100 milliseconds. Using the diffusion coefficient of 'free' water at 37 degrees Celsius, $D = 3e-9$ m^2/s, we get an estimated diffusion distance of 15-25 micrometers. Clearly, in a DMRI experiment, water molecules encounter numerous times inhomogeneities in the cellular environment, such as cell membranes, fibers, and macromolecules.

We simulate the DMRI signal at the scale of a single voxel, while taking into account realistic cellular structure and the true shape and duration of the diffusion gradients. We will obtain the geometrical description of several samples of brain tissue from 3D electron microscopy. The membranes of the various cells making up each sample will then be extracted using dedicated segmentation tools. The finite duration and ramp time of the gradient coils will be accurately reflected in the simulation.

The numerical simulation will approached in two directions. One is based on the numerical solution of the Bloch-Torrey partial differential equation using Green's functions. The other is Monte Carlo simulation. The end result is a hybrid code incorporating both methods: the Green's function method will be used to speed up the Monte Carlo simulation in regimes where the results of the simulation satisfies the Bloch-Torrey equation and where the geometry can be modelled by simple objects such as smooth surfaces. The two methods will be coupled in a unified numerical code where the coupling will occur across spatial regions and also in time.

The end goal of this project is the simulation of DMRI signal taking into account realistic 3D cellular structure, gradient sequence, while producing results which are reliably accurate, scalable, all in reasonable simulation time. This simulation tool will be valuable in

understanding the tissue microstructure that gives rise to the DMRI signals and also aid in the design of new diffusion imaging protocols.

2. CONTEXTE ET POSITIONNEMENT DU PROJET

This project concerns fundamental research into the understanding of the origins of the signals of DMRI. In the past few decades, DMRI has become a fundamental research tool in mapping brain architecture and its many potential uses in clinical diagnosis are being actively pursued by many teams across the world. DMRI is a non-invasive method of imaging which measures the effect of the natural random movements of water molecules in tissue by way of applied of magnetic fields. In acute brain ischemia, it was demonstrated both in animal models and human patients with stroke that the measured water diffusion coefficient decreased significantly within several minutes [12, 13]. By contrast, T2-weighted images remained normal for several hours. More recently, in functional imaging, it has been shown that the diffusion of water slightly slows down in the activated brain cortical areas, several seconds in advance of hemodynamic response detected by BOLD fMRI [6].

The basic mechanism underlying the decrease in measured diffusion is still unknown. Since free diffusion of water in a homogeneous medium would give rise to a single decaying exponential and the signal from DMRI experiments in biological tissue is more accurately fit by the sum of two decaying exponentials, a frequent conjecture is the existence of (at least) two distinct diffusion compartments. Often one considers that biological tissue consists of intracellular space and extracellular space in which water molecules diffuse 'freely' except where they encounter the cell membrane (or possibly macro-molecules). It is assumed that the intracellular and extracellular compartments each possess a diffusion coefficient and the exchange of water between the compartments occurs through the cell membranes.

Different hypotheses to explain the decrease in measured diffusion include a decrease in either or both of the diffusion coefficients in the intra-cellular or the extra-cellular compartments, a shift of water from the fast diffusion compartment (supposed to be the extra-cellular) to the slow diffusion compartment (intra-cellular), a decreased permeability of the cell membranes, increased 'tortuosity' in the extracellular space due to cell swelling. In [6] the proposed mechanism is the increased volume of a slowly diffusing compartment near the cell membranes.
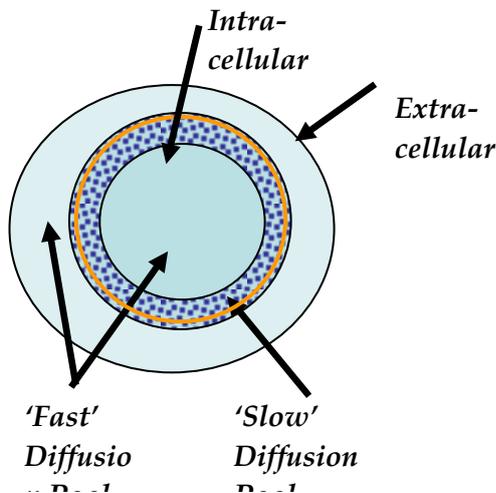
Figure: Hypothesis of fast and slow diffusion compartments

The purpose of this project is to simulate the signals from DMRI given a set of physical parameters, such as cellular geometry, diffusion coefficients, and membrane permeability, among others.

2.1. CONTEXTE ET ENJEUX ECONOMIQUES ET SOCIETAUX

A more insightful understanding of the biological mechanism which triggers the change in measured diffusion in DMRI experiments can potentially lead to new and more nuanced interpretations of DMRI data; demonstrate links with underlying physiological phenomena such as cell swelling, changes in permeability, etc. This can have important clinical applications, leading to more reliable ways of diagnosing diseases. Such simulation can also be used in the design of special pulse sequences to target the probing of cellular structure at scales much smaller than the conventionally used pulsed gradients. A numerical code which can aid sequence design can be patented and potentially commercialized.

In addition, such a simulation tool could greatly help the design of innovative MRI gradient coils of higher order than the standard linear gradient systems used in clinical and preclinical systems. As time/frequency RF simulators based on Maxwell equations play an important role to design emission or reception coil antennas, the simulator developed in the frame of this project may impact the design of gradient coils in the future to better encode the diffusion process. Static magnetic coil have long been of interest to improve the signal to noise ratio of the MR data, but gradient coils playing a key role in diffusion-weighted imaging have not been so much improved other than in terms of power. It is now clear that giving more degrees of freedom, for instance, in terms of spatial order would drastically open the field of new diffusion-weighted sequences designed to probe the microstructure.

2.2. POSITIONNEMENT DU PROJET

Many simulations of the diffusion process have been attempted in the past, but none of them allow large scale simulations in a large field of view or use realistic shapes corresponding to what can be found in the brain parenchyma. They are all focused either on simplistic geometries (spheres, planes, cylinders) lacking the plethora of tortuous and anisotropic shapes of the brain microstructure or make too many assumptions on the diffusion-weighted pulse sequence leading to practically unfeasible experiments on real imaging systems.

Early in 2008, we (Denis LeBihan, Cyril Poupon, Chun-Hung Yeh) started to develop a Monte-Carlo simulator in the frame of an ANR Programme Blanc France-Taiwan focused on functional diffusion imaging (project acronym="DFMRI") aimed at mimicking the reality of diffusion experiments in terms of brain structure and function as well as of real imaging system possibilities, in order to better understand the structural modifications occurring during brain activity, and to better correlate this information with the signal acquired on clinical or preclinical systems. We have now reached a point where, to go to the next step, we need to improve the scale of our code using a large computing facility in order to perform some large scale realistic simulations using real geometries and large sample sizes. We have increased the manpower working on the simulation with the addition of Jing-Rebecca Li and Antoine Lejay and Marina Spivak who will work on speeding up the Monte Carlo simulation by a Green's function method.

This project is unique in that it combines the expertise of MRI physicists who have developed innovative imaging modalities in both anatomical and functional MRI, with the expertise of biologists who can give some advices about the cellular environment in order to establish an accurate model of the microstructure and of the biological parameters underlying the various functions of the brain that may modify the diffusion process inside tissues, with computer scientists who have experience with large scale code development, on parallel and cluster environments along with applied mathematicians experienced in the numerical simulation of diffusion phenomena in complex media.

The availability of advanced imaging facilities at Neurospin, a world class high field NMR facility, located on the site of the CEA, means that MRI experiments can be conducted to complement the effort at simulation. The ready access to high power computing at the CCRT will make the parallelization of the simulation code in the latter stage of the project convenient. The numerical algorithms experts of INRIA have experience formulating accurate and reliable algorithms in both stochastic and analytical modelling.

This project corresponds to 'Axe thématique 1: simulation et calcul intensif' of the call. Both the Green's function method code and the Monte-Carlo code are large scale simulations. The typical time step used in Monte Carlo is on the order of a microsecond; the time interval to be simulated is around 100 milliseconds, hence 100,000 time steps are to be used. At each time step, Monte-Carlo may involve moving 100,000 to 1 million particles. The Green's function simulation uses larger time steps and may require 50,000 to 200,000 degrees of freedom depending on the desired accuracy. Both approaches are highly parallelizable. The spatial scale of the problem is also challenging, the typical voxel is on the order millimeters

and the dimension of the cells can be on the order of micrometers. Hence in three dimensions, spatial domain to be simulated can be 1 million times the spatial resolution required. The dimension of the cell membranes can be on the order of nanometers; hence, if cell membranes are to be treated as a separate diffusion compartment the degrees of freedoms in space would be even vastly larger. In this case, it is essential to couple a code that computes the diffusion near the membrane with a much more coarsely discretized solver away from the membrane. An efficient and accurate coupling between the different scales is needed. Parallel implementation is essential.

This is also an element of visualization of the results, to be able to visualize the diffusion of water molecules in the complex cellular environment over a large interval of time.

3. DESCRIPTION SCIENTIFIQUE ET TECHNIQUE

3.1. ÉTAT DE L'ART

Bloch-Torrey equation and Karger's model:

In a MR experiment, a uniform magnetic field is applied in the z direction. After a 90 degree pulse the spins lie along the x − y plane and a linear gradient field g(t) = gf(t)u, in the direction u with time profile gf(t), is applied. The Bloch-Torrey equation describes the evolution of the complex transverse magnetization m(x,t,g,u) while taking into account diffusion:

$$\frac{\partial \mathbf{m}(\mathbf{x},t,g,\mathbf{u})}{\partial t} = -i\gamma(gf(t)\mathbf{u}\cdot\mathbf{x})\,\mathbf{m}(\mathbf{x},t,g,\mathbf{u}) + \nabla\cdot(D\nabla\mathbf{m}(\mathbf{x},t,g,\mathbf{u})).$$

λ= 42.58 × 2π MHz is the gyromagnetic ratio and D is the diffusion coefficient. The diffusion MRI signal is the measured (normalized) signal attenuation as a function of g and u over the volume of a voxel. There are a few groups [14, 4] working on finite difference or finite elements methods in the simulation by solving the Bloch-Torrey equation. There are also several researchers who worked on expressing the solution of the Bloch-Torrey equation under simplified conditions in analytical terms (see [2] for a review). An alternate approach to Bloch-Torrey is the Karger's model, where is a model based on physical considerations by using quantities called residence times in the different diffusion compartments [5]. The residence times derived analytically, but under simplified conditions.

We solve the Bloch-Torrey equation with a Green's function method that is more efficient and accurate than finite different or finite elements methods. This method has been explained for the diffusion equation [8, 9]. Its use in the Bloch-Torrey equation appears preliminarily in [10]. We use more reasonable and realistic boundary conditions between the diffusing compartments than either the groups working on analytical expressions or the Karger model.

Monte Carlo Brownian dynamics simulator:

In a parallel effort, we design and code a Monte Carlo Brownian dynamics simulator capable of simulating diffusion of spins in arbitrarily complex geometries with a DW signal integrator emulating various MR pulse sequences. The flexibility and power of Monte-Carlo modeling enable us to investigate detail dynamics and mechanisms of molecular diffusion in complex systems which cannot be handled through analytical models [11, 3]. Hence, the CEA NeuroSpin partner has developed software to reproduce various tissue configurations using dynamic meshes. Complicated geometries mimicking neural tissue components, such as neurons, astrocytes, axons, etc. can be emulated, as well as tissue features (e.g. cell size, density, membrane permeability) and basic diffusion mechanisms in different compartments (presence of attractors, local viscosity, membrane interactions, etc.). This framework allows to bridge the gap between elementary processes occurring at a micrometer scale and the resulting DW signal measured at millimeter scale, providing a better understanding of the features observed in DW MRI (variation of apparent diffusion coefficient (ADC) with cell size, diffusion anisotropy) and to optimize acquisition schemes for different applications (e.g. fiber-tracking algorithms).

The Monte-Carlo simulation software described in [15] and is general and flexible to mimic diffusion in biological tissues and to generate realistic synthetic data for diffusion MRI. Since the properties of the diffusing spins and tissue structure are all manageable, this software enables investigations on the underpinning mechanisms affecting the DW signal and the consequent diffusion measured parameters (e.g. ADC and fractional anisotropy (FA) [1]. Specifically, it can be utilized to investigate mechanistic hypotheses for various scenarios (acute ischemia or neuronal activation and cell swelling, cancer and cell proliferation, axonal fiber anisotropy in complex bundles or cortex, etc.).

One main objective of the project will be to merge both Green's function and Monte-Carlo approaches in an hybrid simulator developed by the two partners in order to go beyond the actual limitations of the multiple compartment model stemming from Karger's equations. This project is developed in the next session.

3.2. OBJECTIFS ET CARACTERE AMBITIEUX/NOVATEUR DU PROJET

The Green's function method which we propose has the advantage over competing methods in that it is reliably accurate. There is a reliable way of estimating the degrees of freedom needed to achieve a certain level of accuracy. The aim of this project is to provide a code that produces results within 1 percent relative accuracy in fairly complex geometry.

The Green's method is a competing method to finite difference or finite elements methods and offers the advantage of high accuracy and is not subject to stability restrictions on the time step of simulation, hence larger time steps can be taken in the simulation compared to finite difference/elements methods. This method has been implemented for the short pulse

approximation of pulsed field gradient. The extension for generally shaped time-varying gradients is underway. Only the Green's function changes from the short pulse approximation.

The Monte-Carlo part of the project will be highly optimized and the geometrical description very efficient and flexible. The large scale CCRT facility of the CEA proposes an adequate grid configuration of 1024 processors. The Monte-Carlo code is highly scalable as all the simulated water molecules move independently following a random walk. Only the geometrical scene needs to be shared among nodes of the computer grid, but with read-only access. Therefore, the parallelization of the code will be straightforward, and it is likely that the computational efficiency of the code will be almost linear with the number of processors, as no communication between processors will occur during the simulation.

One of the challenging aspects of this project will be to replace the usually synthetic planar, tubular, or spherical geometry by a more realistic numerical rendering of the tissue geometry. To this aim, we plan to obtain the geometrical description of several samples of brain tissue from 3D electron microscopy. The membranes of the various cells making up each sample will then be extracted using dedicated segmentation tools.

Up to now, no diffusion simulator rely on such realistic geometry, thus limiting the interpretation of the interaction between the NMR phase encoding of the diffusion process using pulsed gradients and the underlying geometry of the brain parenchyma. We hope such acquisitions could help providing more accurate answers to this question.
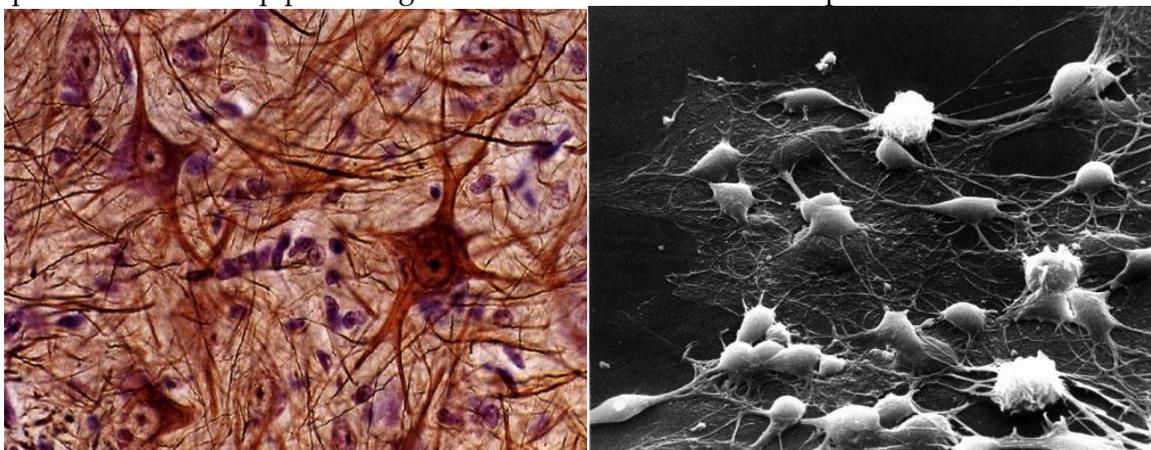
Figure: A realistic cellular geometry to be simulated by hybrid Monte-Carlo Green's function code using electron microscopy.

In the frame of this project, we propose to combine the two codes so as to be able to get the best of both worlds. The Green's function code will be used to speed up the Monte-Carlo code in parts where the geometry is simple and the coupling will be done to ensure accuracy and stability. This is unique. However it may be quite challenging in terms of parallel computation as the scalability of the code will be more difficult: a Green's function aims at replacing a pool of molecules, so we won't be able to consider the particles independent

anymore, but we'll have to determine the good code granularity that yield the optimum efficiency of the computer grid.

Last, it is obvious that NeuroSpin is the most adequate place for such a project, as its platform already makes available a range of MRI system covering all our needs (3T and 7T human clinical systems, 7T and 17T preclinical systems that will be used to perform imaging of the previous samples of brain parenchyma). MR physicists will also participate to the tuning of the high resolution imaging protocols that will be used to validate the simulator using either synthetic phantoms or post-mortem brain tissue samples. The NeuroSpin centre has also got a strong expertise in computational modelling and image processing through its LNAO laboratory (Laboratoire de Neuroimagerie Assistée par Ordinateur, headed by Dr Jean-François Mangin) and its INRIA Saclay and Rocquencourt onsite teams (Parietal team, headed by Dr Bertrand Thirion; Dr Jing Rebecca Li).

The final results will be a high optimized parallel code for the simulation in three dimensions of the DMRI signal for complicated cellular geometries obtained from electron micrographs and allow arbitrary diffusion gradients.

4. PROGRAMME SCIENTIFIQUE ET TECHNIQUE, ORGANISATION DU PROJET

4.1. PROGRAMME SCIENTIFIQUE ET STRUCTURATION DU PROJET

The work program consists of the following tasks.
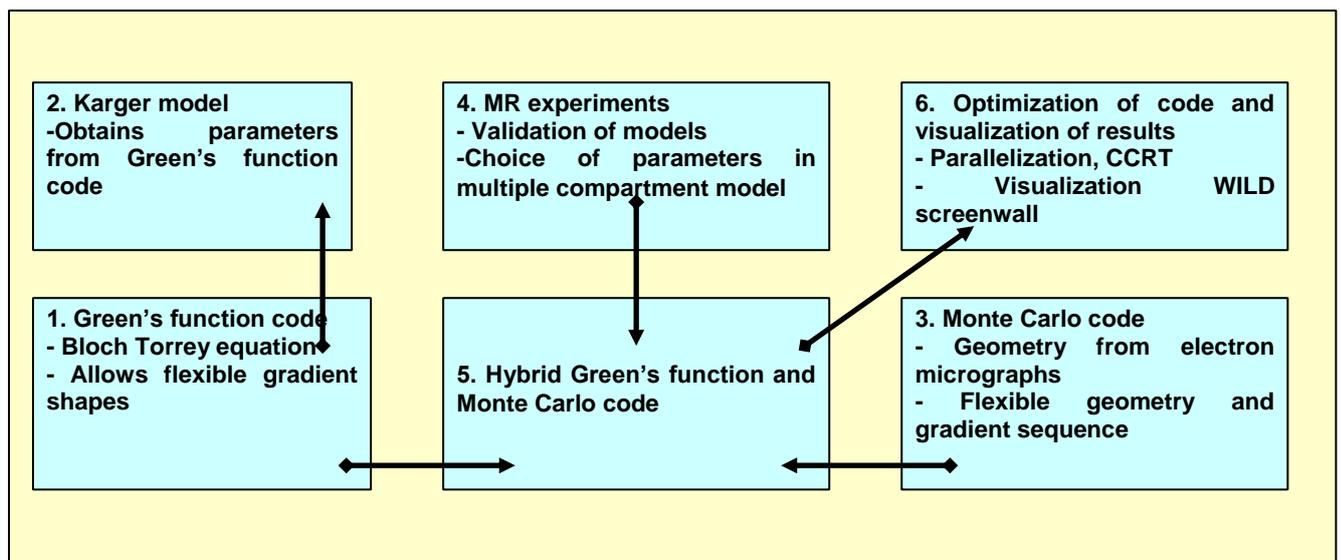
Bloch-Torrey PDE using Green's functions method
Leader: Jing-Rebecca Li (INRIA)
Team: Denis Le Bihan (Neurospin), Marina Spivak (post-doc candidate)

The numerical solution of the Bloch-Torrey partial differential equation using a Green's functions method. This task will be conducted by Jing-Rebecca Li (INRIA) and a post-doctoral researcher to be funded by the project. A candidate for this post-doctorial position has been found. She is Marina Spivak, who expects to obtain a Ph.D. in Computer Science from New York University in June 2010. Denis Le Bihan will work on the input of biologically reasonable parameters into the simulation. The code for simulation in 3 dimensions will be written in C++. We will pay particular attention to ensure its compatibility with existing simulation code at Neurospin.

Solution from the Green's functions method provides parameters for the Karger model
Leader: Jing-Rebecca Li (INRIA)
Team: Denis Le Bihan (Neurospin) and Irina Kezele (CNRS)
The Green's functions method will provide an accurate solution to multiple compartment diffusion. In particular, it will provide computed average residence times for the different compartments, given cellular geometry and membrane permeability. The compartment residence times are the input parameters to a popular 'approximate analytical model' called the Karger model for diffusion in composite systems. The Karger model is used by MRI scientists because it captures certain important properties of diffusion MRI signals and the model is simple to use in that it is 'a mixture of Gaussians'. By comparing the Karger model using these computed parameters with the simulation from the Green's function method, we will know for which regimes the Karger model is or is not valid.

Monte Carlo simulation in realistic cellular environment
Leader: Cyril Poupon (Neurospin)
Team: Chun-Hung Yeh (Neurospin), PhD student to be hired (Neurospin)
The Monte Carlo simulation of the water diffusion process in a heterogeneous cellular environment will ensure speed, flexibility, portability, and scalability. We combine a Monte Carlo Brownian dynamics simulator capable of simulating diffusion of spins in arbitrarily complex geometries with a DW signal integrator emulating various MR pulse sequences. The code for simulation in 3 dimensions will be written in C++. We will pay particular attention to ensure its compatibility with existing simulation code at NeuroSpin and to be fully compliant with the requirements of the large scale computation facility that will be used to accelerate the simulation.
It also includes the automatic segmentation of cellular geometry from electron micrographs.

Validation of model by MR experiments
Leader: Denis Le Bihan (Neurospin)
Team: Jing-Rebecca Li (INRIA)
Denis Le Bihan is in charge of the modeling of diffusion at the cellular level, including the validation of model parameters, such as intra-cellular, extra-cellular, and membrane diffusion coefficients, membrane permeability, cell swelling. He will be assisted by Jing-Rebecca Li. This task includes conducting DMRI experiments on constructed phantoms on the 7 Tesla small animal available system and the future 17T small animal system at

NeuroSpin. The results of the simulation for both the Green's function code and the Monte-Carlo code will be checked against the results of the DMRI experiments.

<u>Hybrid Green's function and Monte Carlo simulation code</u>
Leader: Cyril Poupon (Neurospin)
Team: Jing-Rebecca Li (INRIA), Chun-Hung Yeh (Neurospin), Antoine Lejay (INRIA), and the future PhD student to be hired (Neurospin).
We formulate a hybrid method which switches between the Green's function code and the Monte Carlo code while ensuring accuracy and stability of the overall method. In smooth regions where the magnetization of the water molecules satisfies the Bloch-Torrey equation, the Green's function code will be used; the results are then exported to as inputs to the Monte-Carlo simulator to treat the regime with high heterogeneity where the Green's function method would be too slow.

<u>Code optimization and parallelization and visualization of simulation</u>
Leader: Cyril Poupon (Neurospin)
Team: Chun-Hung Yeh (Neurospin), and the future PhD student to be hired (Neurospin).
This task include the implementation and fine tuning of the hybrid code to run on the parallel and distributed architecture of the CCRT (Centre de Calcul Recherche et Technologie, CEA) and the visualization of the results of the large scale simulation: to be able to see the evolving diffusion of spins on water molecules in the cellular environment on a voxel scale.

4.2. MANAGEMENT DU PROJET

There are two partners in this project, one is INRIA and the other is Neurospin, CEA.

Participants from INRIA consist of Jing-Rebecca Li (INRIA-Rocquencourt, chercheur permanent) and Antoine Lejay (INRIA-Nancy, chercheur permanent) and a post-doctorial candidate Marina Spivak, who will arrive in France in September 2010. Jing-Rebecca Li and Marina Spivak will have an office at Neurospin and will be present at least 3-4 days per week at Neurospin.

The participants from Neurospin consist of Cyril Poupon (chercheur permanent), Denis LeBihan (permanent, directeur de Neurospin) and Chun-Hung Yeh (PhD student).

Other collaborators of this project include Irina Kezele (post-doc CNRS, based at Neurospin) and the IN-SITU team, Laboratoire de Recherche en Informatique (LRI), Université Paris Sud XI, co-headed by Dr Michel Beaudouin-Lafon.

All participants except Antoine Lejay (INRIA-Nancy) are in the Paris region. And all except Antoine Lejay and Michel Beaudouin-Lafon will have a regular presence at Neurospin.

Jing-Rebecca Li is the coordinator of the project. She is also charge of the Green's function code. She and Marina Spivak, the post-doctoral candidate, will complete and optimize this

code. Denis LeBihan and Jing-Rebecca Li will validate model parameters, such as intra-cellular, extra-cellular, and membrane diffusion coefficients, membrane permeability, cell swelling by conducting DMRI experiments on the 17 Tesla MRI scanner available at Neurospin. Jing-Rebecca Li and Irina Kezele will use this code to obtain residence times to enter as parameters in the Karger model. A weekly meeting will occur between Jing-Rebecca Li, Marina Spivak, Denis LeBihan (and during the Karger model phase Irina Kezele).

Cyril Poupon is the coordinator of the Monte-Carlo code. He and Chun-Hung Yeh will complete, optimize, and parallelize it for running on the CCRT. They will also be in charge of the visualization of the simulation results. A weekly meeting will occur between Cyril Poupon and Chun-Hung Yeh with the presence of Jing-Rebecca Li after the Green's function code has been completed.

After the completion of the two codes, Jing-Rebecca Li, Cyril Poupon and Antoine Lejay will implement a hybrid method combining the two codes. This will involve monthly meetings between the three people either at Neurospin or in Nancy. When we enter the visualization phase of the project, a meeting will be held with Michel Beaudouin-Lafon.

4.3. DESCRIPTION DES TRAVAUX PAR TACHE

4.3.1 TÂCHE 1

Bloch-Torrey PDE using Green's functions method
Leader: Jing-Rebecca Li (INRIA)
Team: Denis Le Bihan (Neurospin), Marina Spivak (post-doc candidate)

This task consists of producing a code that outputs the solution of the Bloch-Torrey partial differential equation using a Green's functions method. This task will be conducted by Jing-Rebecca Li (INRIA) and a post-doctoral researcher to be funded by the project. A candidate for this post-doctorial position has been found. She is Marina Spivak, who expects to obtain a Ph.D. in Computer Science from New York University in June 2010. Denis LeBihan will work on the input of biologically reasonable parameters into the simulation. The code for simulation in 3 dimensions will be written in C++. We will pay particular attention to ensure its compatibility with existing simulation code at Neurospin.

We solve the Bloch-Torrey equation with a Green's function method that is more efficient and accurate than finite different or finite elements methods. This method has been explained for the diffusion equation [8, 9, 7]. Its use in the Bloch-Torrey equation appears preliminarily in [10]. We use more reasonable and realistic boundary conditions between the diffusing compartments than either the groups working on analytical expressions or the Karger model.

Within the voxel, the diffusion environment is in fact heterogeneous. In a simple model, we will suppose that the diffusion coefficient is constant within the intra-cellular, the extra-cellular, and the membrane compartments. The volume V is the union of a very large number of these three kinds of compartments. The ensemble of all intra-cellular regions will be denoted by V^{in}, all the extra-cellular regions will be denoted by V^{ex}, and the membranes by V^{mem}. The volume will be the union of these three regions, with diffusion coefficients D^{in}, D^{ex}, and D^{mem}, respectively. In each V^j, the following equation is satisfied,

$$\frac{\partial \mathbf{m}^j(\mathbf{x}, t, g, \mathbf{u})}{\partial t} = -i\gamma(gf(t)\mathbf{u} \cdot \mathbf{x})\,\mathbf{m}^j(\mathbf{x}, t, g, \mathbf{u}) + \nabla \cdot (D^j \nabla \mathbf{m}^j(\mathbf{x}, t, g, \mathbf{u})), \quad \mathbf{x} \in V^j.$$

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and it is complemented by the following boundaries conditions, on B^{jk}, the boundary separating V^j and V^k:

$$\left.\begin{array}{l} \mathbf{m}^j(\mathbf{x}, t, g, \mathbf{u}) = \mathbf{m}^k(\mathbf{x}, t, g, \mathbf{u}), \\ D^j \dfrac{\partial \mathbf{m}^j(\mathbf{x}, t, g, \mathbf{u})}{\partial \mathbf{n}} = D^k \dfrac{\partial \mathbf{m}^k(\mathbf{x}, t, g, \mathbf{u})}{\partial \mathbf{n}} \end{array}\right\}, \quad \mathbf{z} \in B^{jk},$$

This is solved using a Green's functions method with the Green's function being

$$\hat{G}(\mathbf{k}, t, D^j) = e^{-D^j\left(\int_0^t dt' \left\| \mathbf{k} + \int_{t'}^t \gamma g f(s) \mathbf{u}\, ds \right\|^2\right)}.$$

The solution $m^j(x,t,g,u)$ will be written as a sum of an initial potential, a single layer potential, and a double layer potential. The layer potentials are convolutions of the above Green's function with unknown densities on the interfaces of the cells. The unknown densities are solved by matching the continuity boundary conditions above.

The advantages of this approach are that large time steps can be taken, up to 10 to 100 times larger than in Monte-Carlo simulation, and the high accuracy of the results. The implementation we use takes advantage of the Fourier transform of the Green's function, given above, and avoids the algorithmic complexity of the typical Green's function method. Instead of $O(M^2)$ work, where M is the number of time steps taken, we can return an accurate answer in $O(M)$ work. More details of the method can be found in [9].

The challenges of our approach are that integrals with singular integrands must be computed (numerically) accurately and the geometry must be simple enough to allow efficient and accurate computation of these singular or nearly singular integrals.

We show the results of simulation in 2 dimensions for an infinite array of circular cells placed L=12 μm apart in x and y directions using the short pulse approximation. Each intra-cellular compartment is a disk with a radius of 4 μm and D =10^{-3} μm²/μs, each 'membrane' compartment is an annulus with an inner radius of 4 μm and an outer radius 5 μm, with D = 10^{-4} μm²/μs, the exact-cellular compartment is the volume that remains and has D=10^{-3} μm²/μs. We simulate up to Δ =10 ms. As a demonstration, we place a **single point source** in the interior of each intra-cellular compartment, at [-0.95,-1.29] μm from the center, and obtain the probability density distribution and the attenuation for four values of g**,** using the orientation [1,1] and strengths 0, 0.1, 0.2, and 0.3 μm^{-1}. The computed probability density distribution at Δ=5ms and Δ=10ms is plotted in Figure 1a and 1b, for one period of the lattice.

We see that there is high probability of finding the particle in the interior compartment and the membrane compartment by the end of simulation time, but very little probability that it has entered the exterior compartment by that time. The attenuation is plotted in Figure 1c and 1d at Δ= 0.5ms, and10ms. The bottom line is a plot of $e^{-ig*gD\Delta}$, D =10^{-3} $\mu m^2/\mu s$, the free diffusion attenuation with the larger D, the top line the free diffusion attenuation due to D = 10^{-4} $\mu m^2/\mu s$. The black line (diamond) is the volume weighted sum of the two free diffusion exponentials (no exchange case). The black line (circle) is free diffusion with a single weighted-averaged D = 8.23x10^{-4} $\mu m^2/\mu s$. The red line (x) is the computed attenuation, exhibiting a behaviour that changes from fast free diffusion at the short times (the particle not having seen the membrane) and exhibits slow diffusion for long times as the particle seems trapped by the slow diffusion compartment near the membrane. The time step we used in the present simulation was 100 μs, hence only 100 time steps were needed to compute the results discussed here.

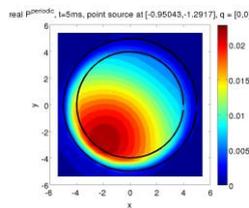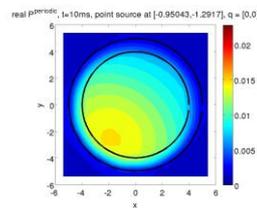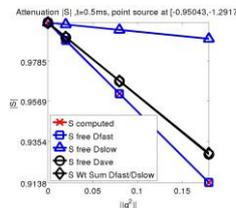Figure 1a. t=5ms   Figure 1b. t=10ms   Figure 1c. t=0.5ms   Figure 1d. t=10ms
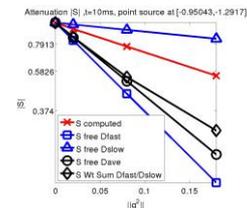
4.3.2 TÂCHE 2

<u>Solution from the Green's functions method provides parameters for the Karger model</u>
Leader: Jing-Rebecca Li (INRIA)
Team: Denis Le Bihan (Neurospin) and Irina Kezele (CNRS)
The Green's functions method will provide an accurate solution to multiple compartment diffusion. In particular, it will provide computed average residence times for the different compartments, given cellular geometry and membrane permeability. The compartment residence times are the input parameters to a popular 'approximate analytical model' called the Karger model for diffusion in composite systems. The Karger model is used by MRI scientists because it captures certain important properties of diffusion MRI signals and the model is simple to use in that it is 'a mixture of Gaussians'. By comparing the Karger model using these computed parameters with the simulation from the Green's function method, we will know for which regimes the Karger model is or is not valid.

This task simply involves running the Green's function code for diffusion (Bloch Torrey is not needed, the simple diffusion equation can be used) and compute the average residence times in each compartment and put these times into the Karger model. By comparing the sum of mixed Gaussians given by the Karger model thus obtained with the actual simulation results of the Bloch Torrey equation (which we trust is accurate using our code), we can definitely judge the validity of the Karger model in different regimes (how long or short diffusion times must be compared to average compartment sizes, among other possibilities).

The end results may be some rules of thumb on when the Karger model should be used when modeling multiple compartment diffusion.

4.3.3 TÂCHE 3

Monte Carlo simulation in realistic cellular environment
Leader: Cyril Poupon (Neurospin)
Team: Chun-Hung Yeh (Neurospin), PhD student to be hired (Neurospin)

Monte Carlo (MC) simulations have been shown to be a powerful and flexible tool to explore a wider class of systems and address several questions in DW MRI (Balls 2009, Farrell 2009, Fieremans 2009a, Fieremans 2009b, Fonteijn 2009, Ford 1997, Grinberg 2009, Hall 2009, Harkins 2009, Landman 2009, Liu 2004, Nilsson 2009). Particularly, MC framework allows tracking the dynamic events over space and time. Therefore, diffusion MR synthetic data based on MC approach provides the ability to examine the influence of specific biological properties on the diffusion process. Since the shape and the organization of biological structures are extremely complicated at the cellular level (e.g. the gray matter (GM)), the issue turns into how to represent the geometry of neural tissue in the MC simulation framework. Several studies have been presented to simulate water diffusion in various geometric models. Hall and Alexander optimize the parameters for the diffusion MC simulations in packed and swelling cylindrical tissue model (Hall 2009, Cook 2006). Meanwhile, Landman et al. and Farrell et al. simulate diffusion in mesh-based geometries to study the effect of axonal injury and beading (Landman 2009, Farrell 2009). The MC simulations described above mainly focused on the geometry of neuronal fibre bundles (i.e. WM), while it is interesting to investigate the behavior of water diffusion in cerebral cortex and deep nuclei areas (i.e. GM) as well. Lipinski carried out the first MC simulation in a simplified 2D environment with tissue geometries created using digital images captured from the histological preparations of GM (Lipinski 1990). Extension from a 2D MC simulation to a 3D space is closer to the realistic situation, whereas it is also a great computational challenge. Balls developed the famous MCell physiological simulation framework and mainly focused on large-scale MC simulations of high angular resolution DW imaging (HARDI) experiments (Balls 2004, Balls 2009). The large-scale MC method allows simulations to efficiently process a large amount of random walkers at high temporal resolution, and hence has great potential in mimicking water diffusion in a complicated neural medium.

In this task we present a novel large-scale MC simulation tool dedicated to DW MR experiments. We combine a Monte Carlo Brownian dynamics simulator capable of simulating diffusing spins in arbitrarily complex geometries with a DW signal integrator feasible to simulate various MR pulse sequences. Furthermore, we develop methods to form various tissue configurations using dynamic meshes in our software, which is applicable to create complicated geometries analogous to neural structures, such as neurons, axons, myelin, astrocytes, oligodendrocytes, macromolecules, etc.., with different tissue features

(e.g. cell size, density, membrane permeability). In addition, we have developed different types of spin-barrier interaction models (presence of attractors, local viscosity, membrane interactions, etc).

This software allows investigating the mechanism driving the DW signal and the features observed in DW MRI. The simulation code is fully 3D and is implemented in C++. Main features are described as following: 'Cell membranes' are generated using meshes to model different cell types with heterogeneous shapes and sizes. This module allows users to specify cell properties including the thickness, permeability, and diffusion coefficient (D). In addition, we incorporates the mesh with dynamic morphological evolution, thus it can be utilized to simulate sequential changes of tissue shapes including expansion, shrinkage, and deformation. 'Diffusing particle' ('spin') is modeled as a random walker and the average free displacement for an elementary time step of length is scaled to its associated compartmental D. For each simulation step, the spatial positions of particles are updated subject to a series of potential interactions: (i) In accordance with the permeability, the particle may penetrate through the related cell membrane or be elastically reflected. (ii) The diffusivity of the particle may be modified into that of the interacting membrane layers. 'The MR pulse sequence' module is flexible to model a variety of pulse sequences with different combinations of radio frequency and gradient pulses. 'DW signal' of each synthetic MR voxel is computed numerically by performing integration on the accumulated phase of each particle belonging to the voxel. Users can add imaging (Rician) noise to the synthetic MR signal.

Figure 1 shows the diffusing particles (colored in blue) and the cell membranes (colored in pink) generated using meshes to represent different neural structures. The dynamic surface evolution function was applied to the cells pointed by the green arrows to simulate cell swelling, which has been identified as an important factor in the changes of the apparent diffusion coefficient (ADC) observed in acute ischemia or during neural activation.
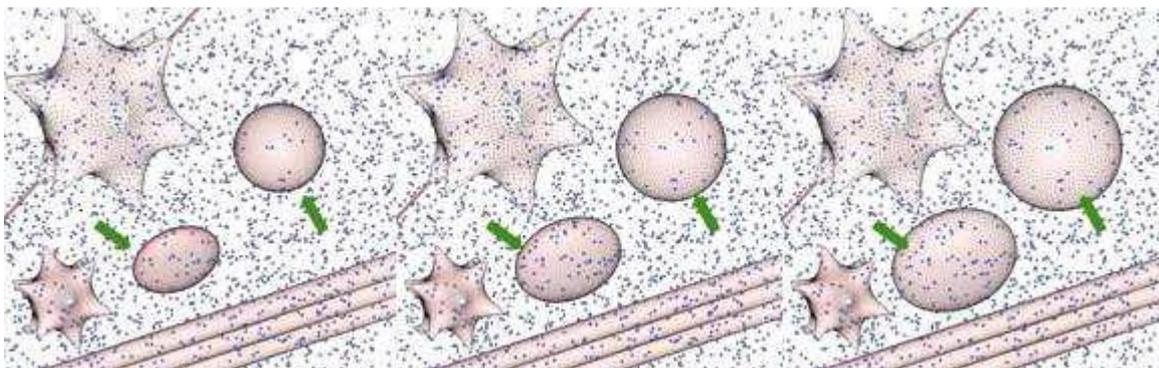
Figure 1: OpenGL rendering of a complex geometry mimicking a tissue sample; the geometry is represented by membranes that can evolve dynamically and the water molecules by small spheres following a random walk; the green arrows depict the cell swelling feature that can be used to represent local brain activity

We performed two simple experiments to illustrate the potential of this software: (i) we simulated water diffusion in a neural medium containing various types of neural cells; (ii) we generated two fiber bundles in a 0.6x0.6x0.6 mm space filled with a million diffusing

particles. A high angular resolution diffusion imaging (HARDI) experiment was simulated using b=3,000s/mm2 and 80 diffusion-weighted gradient orientations. Fiber orientations were estimated using the diffusion tensor (DT) and analytical q-ball imaging (QBI) method. Figure 2 shows the simulated crossing fibers and the results of orientation distribution function (ODF) reconstructed from the synthetic high angular resolution diffusion imaging simulated data (Top: mesh-based crossing fibers and a zoomed area showing some of the diffusing spins (blue spheres) and their motion trajectories (yellow curves); bottom: ODF reconstructed using DT and analytical Q-ball approaches respectively). The SNR measured on the null DW image (b = 0) was 18.4. ODFs were scaled to corresponding generalized fractional anisotropy (GFA) displayed as background images
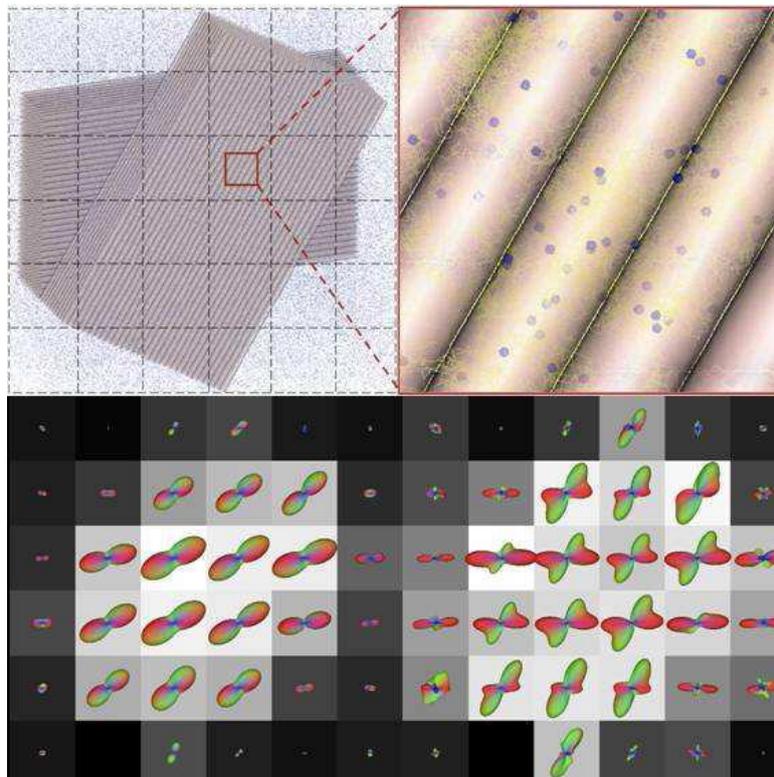
Figure 2: simulated crossing fibers and the results of orientation distribution function (ODF) reconstructed from the synthetic high angular resolution diffusion imaging simulated data

4.3.4 TÂCHE 4

Validation of model by MR experiments
Leader: Denis Le Bihan (Neurospin)
Team: Jing-Rebecca Li (INRIA)
Denis Le Bihan is in charge of the modeling of diffusion at the cellular level, including the validation of model parameters, such as intra-cellular, extra-cellular, and membrane diffusion coefficients, membrane permeability, cell swelling. He will be assisted by Jing-Rebecca Li. This task includes conducting DMRI experiments on the 17 Tesla small animal scanner available at Neurospin. The results of the simulation for both the Green's function code and the Monte-Carlo code will be checked against the results of the DMRI experiments.

4.3.5 TÂCHE 5

Hybrid Green's function and Monte Carlo simulation code
Leader: Cyril Poupon (Neurospin)
Team: Jing-Rebecca Li (INRIA), Chun-Hung Yeh (Neurospin), Antoine Lejay (INRIA), and the future PhD student to be hired (Neurospin).
We formulate a hybrid method which switches between the Green's function code and the Monte Carlo code while ensuring accuracy and stability of the overall method. In smooth regions where the magnetization of the water molecules satisfies the Bloch-Torrey equation, the Green's function code will be used; the results are then exported to as inputs to the Monte-Carlo simulator to treat the regime with high heterogeneity where the Green's function method would be too slow.

In terms of software development, the hybrid method will rely on the design and architecture of the existing Monte-Carlo code and will be modified accordingly. A specific API will be developed in order to manage a pool of molecules. This API will allow dealing with this pool according to the Green's function code or according to the Monte Carlo code. It will facilitate the distribution and parallelism of the code that will occur during the next optimization task.

4.3.6 TÂCHE 6

Code optimization and parallelization and visualization of simulation
Leader: Cyril Poupon (Neurospin)
Team: Chun-Hung Yeh (Neurospin), and the future PhD student to be hired (Neurospin).
This task include the implementation and fine tuning of the hybrid code to run on parallel and distributed architecture of the CCRT (Centre de Calcul Recherche et Technologie, CEA) and the visualization of the results of the large scale simulation: to be able to see the evolving diffusion of spins on water molecules in the cellular environment on a voxel scale.

Three actions have to be conducted during this task:
- optimization of the code on a single processor basis
- multiple threading of the code
- distribution of the code on a grid of processors of the CCRT.

This work must be done for the two simulators, the Monte Carlo simulator and the Hybrid simulator. A preliminary work was performed on the existing Monte Carlo prototype. The code was designed in such a way that it is already optimum: quad-trees have been implement to accelerate the localization of the closest membrane for a given particle, access to the triangles interacting with a specific particle was also accelerated using look-up tables, and profiling of the code was performed in order to systematically optimize each C++ function starting with the most time consuming methods to the less time consuming methods. For a simple scene containing a set of 1000000 particles interacting with a single

sphere located at the centre of the field of view, the code was speeded-up by a factor of around 100.

Two levels of distribution have to be considered:

- Inside a single node of the grid, POSIX based multiple threading was used to split the simulation over the 16 processors, and another gain of 15 was observed, as almost no communication occurs between moving particles during the full simulation. This gain was reached because the distribution of the Monte Carlo simulation is straightforward, which might not be necessarily the case when the Hybrid simulator will be implemented. However, we believe that the concept of pool of particles may efficiently drive the implementation of the Hybrid simulator to a strongly scalable code, thus taking full advantage of the use of the CCRT facility. The choice of POSIX threading may be modified in the future to possibly use the MPI library if the resulting implementation results in a faster code.

- The distribution of the simulation will be performed using the MPI library. This choice was guided by the recommendations of the CCRT facility that mainly offers the MPI infrastructure to users. The MPI API is adequate to create a server that will distribute the motion of the particles in the case of pure Monte Carlo simulation or the motion of the pools of particles in the case of Hybrid simulation on clients, each client corresponding to a single thread on a single processor.

It is likely that the Hybrid code will speed-up the simulation since each pool represent putatively a large set of particles, but the design will be challenging because the continuity between pools may be preserved using boundary conditions.

In order to prepare a first prototype of this MPI implementation of both the Monte Carlo and Hybrid simulators, we will use a small cluster of 3 high performance Dell R900 nodes. Each node is equipped with 16 processors and 64 GB of memory, and the 3 nodes will be connected through a 1Gbit network. This small architecture is mandatory, as making test directly at the CCRT facility won't be possible without a specific booking procedure. The CEA CCRT facility generally ask for developing the code on a third-part cluster before allocating large bay time on its computer grids or clusters.

Last, large scale simulations using the complex geometry stemming from electron microscopy will be launched at the CCRT facility. We will use the new Titane architecture. The Titane supercomputer is a hybrid cluster. 1068 processing nodes are provided, each equipped with 2 Intel Nehalem quad-core processors at 2.93GHz and 24GB of memory. 24 further nodes are dedicated to administration and I/O tasks. This cluster also provides 48 graphical NVidia Tesla S1070 servers, each equiped with 4 processors and 4 GB of memory. Each server is attached to two processing nodes through a PCI-express connection. Processing nodes are connected with a Voltaire network based n the InfiniBand technology. The storage infrastructure offers a 500TB disk space. The operating system is based on Linux (NovaScale Master) and on the Bull HPC software platform, providing a C++ compiler, and the OpenMPI library.

The visualization of the huge amount of particles will be addressed using the WILD screenwall (IN-SITU team, Laboratoire de Recherche en Informatique (LRI), Université Paris Sud XI, co-headed by Dr Michel Beaudouin-Lafon). This task will be conducted within a scientific collaboration already started between the Laboratory of Computer Assisted Neuroimaging of NeuroSpin and the LRI, under the joint management of Dr Jean-François Mangin and Dr Michel Beaudouin-Lafon. The WILD project proposes a unique wall made up of 32 screens equipped with a specific OpenGL software platform and with specific tools to interactively manipulate, visualize and analyze the dynamic geometrical scene.

4.4. CALENDRIER DES TACHES, LIVRABLES ET JALONS

The project was divided into 6 tasks corresponding to different fields:
- applied mathematics (Tasks 1 & 2)
- software development (Tasks 3, 5, 6)
- MR physics and validation (Task 4)

Each task yields a specific deliverable:
- Task 1: Bloch Torrey PDE using Green's function
- Task 2: Parameters required for the Karger's equation stemming from solution of Task 1
- Task 3: a Monte-Carlo diffusion simulator software
- Task 4: a set of acquisitions performed at high field to validate the model of task 1
- Task 5: an Hybrid Green's function + Monte-Carlo simulator software
- Task 6: a fully optimized and distributed hybrid simulator running at the CEA CCRT facility

Tâche/Tasks	Partenaires/Partners		Année 1 Year 1		Année 2 Year 2		Année 3 Year 3	
	1	2	6	12	18	24	30	36
1. Tâche 1 Bloch-Torrey PDE using Green's functions method Leader: Jing-Rebecca Li	█		█	█				
2. Tâche 2 Solution from the Green's functions method provides parameters for the Karger Leader: Jing-Rebecca Li	█		█	█				
3. Tâche 3 Monte Carlo simulation in realistic cellular environment Leader: Cyril Poupon		█						
4. Tâche 4 Validation of model by MR experiments Leader: Denis Le Bihan	█	█		█	█	█	█	█
5. Tâche 5 Hybrid Green's function and Monte Carlo simulation code Leader: Cyril Poupon	█				█	█		
6. Tâche 6 Code optimization and parallelization and visualization of simulation Leader: Cyril Poupon	█					█	█	

Rapports d'avancement semestriel Progress report/expenses						☺	☺	☺	☺	☺
Accord de consortium / rapport final Consortium agreement/final report						✪				☆

5. STRATEGIE DE VALORISATION DES RESULTATS ET MODE DE PROTECTION ET D'EXPLOITATION DES RESULTATS

The results will be published in scientific journals (NeuroImage, Medical Image Analysis, Magnetic Resonance in Medicine, Journal of Magnetic Resonance Imaging) and conferences (ISMRM, MICCAI).

A more insightful understanding of the biological mechanism which triggers the change in measured diffusion in DMRI experiments can potentially lead to a new and more nuanced interpretation of DMRI data, demonstrating links with underlying physiological phenomena as cell swelling, changes in permeability, etc. This can have important clinical applications, leading to more reliable ways of diagnosing diseases. Such simulation can also be used in the design of special pulse sequences to target the probing of cellular structure at scales much smaller than the conventionally used pulsed gradients. A numerical code which can aid sequence design can be patented and potentially commercialized.

In French:
"Les conditions de dévolution des droits de la propriété intellectuelle et d'exploitation des résultats seront indiquées dans l'accord de consortium qui sera établi après le démarrage du projet, sur la base des principes suivants :
1.1.1   Propriété intellectuelle et exploitation des résultats
Propriété intellectuelle antérieure
Chaque partenaire conserve la propriété (information, données techniques brevetées ou non...) de la connaissance produite avant le projet ou indépendamment des travaux du projet (savoir-faire ou connaissance pré existant) et des améliorations de ces connaissances. Le savoir-faire ou les connaissances antérieures utiles pour le projet seront listées dans l'annexe de l'accord de consortium.
Propriété des résultats ex-nihilo
Les résultats produits et réalisés par un seul partenaire dans le cadre du projet seront la propriété de ce partenaire (résultats propres).
Les résultats produits et réalisés conjointement par plusieurs partenaires dans le cadre du projet (résultats communs) seront la copropriété desdits partenaires. Les parts de copropriété (ou parts indivises) seront déterminées au prorata des apports intellectuels des inventeurs (ou auteurs) des partenaires. En revanche, en cas de valorisation commercial d'un actif, les partenaires ayant fait un apport financier ou matériel substantiel pour la création de l'actif auront droit à un juste retour.
Gestion et exploitation

Les résultats communs feront l'objet d'un accord indiquant le mécanisme de distribution de la propriété et les droits d'exploitation de ces résultats communs, toute exploitation par un des copropriétaires devant donner lieu à la rémunération des autres copropriétaires.

Un mandataire unique pour la valorisation d'un actif ou d'un groupe d'actifs pourra être désigné.

1.1.2 Confidentialité

Des engagements de confidentialité seront également écrits dans l'accord de consortium. Dès que cet accord sera signé, chaque partenaire ayant accès à des informations, données ou plans confidentiels, en particulier les modèles scientifiques de n'importe quelle nature, appartenant aux autres partenaires desquels il pourrait avoir été informé au moment du montage ou de l'exécution du projet, ne pourra pas les divulguer.

1.1.3 Publications

Tout résultat du projet soumis à publication dans une conférence, un journal ou une revue, devra comporter la mention du financement de l'ANR.

Les partenaires seront libres de publier sur leurs résultats propres mais devront obtenir l'accord préalable des partenaires intéressés en cas de résultats communs.

"

6. ORGANISATION DU PARTENARIAT

6.1. DESCRIPTION, ADEQUATION ET COMPLEMENTARITE DES PARTENAIRES

This project will be driven by the two scientific partners:

INRIA (Partner 1), National institute of computer science and applied mathematics with multiple sites in France.

NeuroSpin (Partner 2), a ultra high-field MRI facility dedicated to neurosciences within the Institute of BioMedical Imaging (I2BM) of the Life Science Division (DSV) of the Commissariat à l'Energie Atomique (CEA), Saclay, France

The two partners have long been collaborating mainly about image processing and neuroimaging for approximately two decades. They share the same scientific projects, i.e. delivering an anatomo-functional mapping of the human brain. The strong relationship between the two institutions was recognized by the creation of a first INRIA Saclay team, Parietal, directly located inside the NeuroSpin building, and in the future of a second INRIA team more focused on the topic of this project, ie at the interface between applied mathematics and physics, under the direction of Dr Jing-Rebecca Li.

The two partners started to collaborate on the simulation of the diffusion process of water molecules in the brain parenchyma early in 2009. In the past year, there were two common publications involving the members of the Neurospin team and the INRIA team [15, 10].

The two teams have complementary skills: applied mathematics and computational biology for the INRIA team, MR physics, neurobiology, image processing using large scale computing facilities for the NeuroSpin team. The two teams have developed substantial

skills that have been regularly acknowledged by publications in the major journals (NeuroImage, IEEE Transaction in Medical Imaging, Magnetic Resonance in Medicine, …) of the field and by communications in the recognized conferences of the domain (ISMRM, ISBI, IPMI, MICCAI).

INRIA team:

INRIA has several sites across France grouping computer scientists and applied mathematicians. The researchers work in research teams (equipe-projet) around a unifying topic. The two participating teams of INRIA are

- Action exploratoire DMRI: Jing-Rebecca Li, who is currently a member of the team POEMS (modelization of waves), is starting an entity called an 'action exploratoire' at the Saclay site of INRIA. This is a step before the creation of a new research team on this topic. She is a specialist in the simulation of diffusion phenomena in physical applications.
- Equipe-project TOSCA: Antoine Lejay. The research theme of TOSCA is the simulation and calibration of stochastic models. Antoine Lejay is a specialist in the simulation of stochastic models and the analysis of Monte Carlo methods in heterogeneous media.

NeuroSpin team:

NeuroSpin is a ultra-high field MRI facility which opened in 2007. Its is dedicated to molecular imaging and translational research in neurosciences to man with a strong emphasis on clinical and cognitive neurosciences. The aim of NeuroSpin is to push as far as possible the current limits of Magnetic Resonance Imaging to study the central nervous system, from mouse to man. NeuroSpin is equipped with 2 human MRI systems operating at 3T and 7T, a small animal horizontal MRI system operating at 17.7T (first in the world) and will house the first whole-body 11.7T MRI system in 2013. NeuroSpin staff includes basic scientists in many disciplines from physics to cognitive neurobiololgy and clinicians. It is organized into 5 laboratories:

- a Nuclear Magnetic Resonance lab (LRMN)
- a Computer Assisted Neuroimaging lab (LNAO)
- a Cognitive Neurosciences lab (LCOGN)
- a Clinical (Human) Investigation Center (LBIOM)
- a Preclinical (Animals) Integrated Biology lab (LBIOP)

The members of the NeuroSpin centre (partner 2) involved in this project are:

- Dr. Cyril Poupon, permanent researcher
- Dr. Denis Le Bihan, director of Neurospin
- Chun-Hung Yeh, PhD student

6.2. QUALIFICATION DU COORDINATEUR DU PROJET

Jing-Rebecca Li obtained her PhD in applied mathematics from MIT in the United States in 2000, was a post-doc at the Courant Institute, NYU from 2000-2003 and was hired at INRIA as a permanent researcher in 2003. She is preparing her 'habilitation a diriger des recherches' to be defended in 2010.

Jing-Rebecca Li holds a permanent research position at INRIA (chargee de recherche (CR1)) and is in the process of transfering to INRIA-Saclay and will start a new research axis (action exploratoire) on DMRI simulation. She has directed internships (stage de DEA) while at INRIA and was on the organizing committee of the conference WAVES 2007. She is an associate editor of SIAM Journal on Scientific Computing and was an editor of a special issue of Journal of Computational and Applied Mathematics for Waves 2007.

7. JUSTIFICATION SCIENTIFIQUE DES MOYENS DEMANDES

7.1. PARTENAIRE 1 : INRIA

- *Équipement*

n/a

- *Personnel*

We request the funding of 24 months of a post-doc who will participate in the completion and optimization of the Green's function code and the hybrid Green's function Monte Carlo code. This position requires a Ph.D. in computer science or applied mathematics or related fields, experience working in the formulation and implementation of numerical algorithms for PDEs and knowledge of basic biology. We have a candidate who is interesting in obtaining this position and a meeting has taken place between her and the main participants of this project. The candidate is Marina Spivak, who expects to obtain a Ph.D. in Computer Science from New York University in June 2010.

- *Prestation de service externe*

We request 2 individual Matlab licenses and 2 Mathematica licences, a high performance desk top computer for the post-doc and a high performance laptop for Jing-Rebecca Li. Total: 10 000 euros.

We request 150 hours of scanner time on the 7 Tesla small animal system and the future 17T small animal system at NeuroSpin. Total: 80 000 euros.

- *Missions*

We request funding for the travel of Antoine Lejay from Nancy to the Paris regions and the travel of Jing-Rebecca Li from Paris to Nancy. There will be 3 trips for each person. We also request travel and conference fees for the post-doc candidate and Irena Kezele to MICCAI (Medical Image Computing and Computer Assisted Intervention) and ISMRM (conference of the International Society for Magnetic Resonance in Medicine) and Jing-Rebecca Li to ISMRM. Total: 10000 euros.

- *Dépenses justifiées sur une procédure de facturation interne*

n/a

- *Autres dépenses de fonctionnement*

n/a

7.2. PARTENAIRE 2 : CEA I²BM NEUROSPIN

- *Équipement*

The following equipment is required to achieve this project:

2 Server Dell R900 (16 processors, 64GB of memory) = 13.2k€

2 NetApp controlers to manage large disk storage space V3140A-IB-BASE-R5 + software + maintenance : 34000€

The two servers will be associated to an already existing server in order to create a small parallel architecture of 48 processors that will be used to study different strategies of parallelization and distribution of the simulation code. This preliminary step will help defining the optimum strategy of distribution on the target CCRT facility and corresponds to the preparation of the code that will then be launched on the Titanium supercomputer of the CEA CCRT facility.

The network active cards will be used to extend the NeuroSpin network file system, as it is actually too small to manage the really huge amount of data that will be collected in the frame of this project.

- *Personnel*

A PhD student (Chun-Hung Yeh) is already participating to the development of the prototype of the diffusion Monte-Carlo simulator, and has published the first results using this prototype at ISMRM conference. Chun-Hung Yeh will defend his PhD thesis in spring 2011, and the project needs to maintain his task-force to perform the developments required to achieve the goals of this project.

We propose to hire a second PhD student funded by the ANR that will work at the beginning in close collaboration with Chun-Hung Yeh and will then replace him after he leaves the NeuroSpin centre.

This new PhD student must have a Master 2 and/or engineering diploma in image processing and computer science. Knowledge in MR physics or medical imaging is also recommended, even if it is less mandatory.

He will be involved in the software development of the hybrid simulation code as well as its distribution and optimization on the cluster provided by the CEA CCRT facility. He will also take in charge the development of realistic geometries from electron micrographs of tissue samples, and launch large scale simulations based on them. Last, he will investigate the role of the geometry of the membranes (permeability, tortuosity, cell swelling, viscosity) on the diffusion-weighted signal stemming from MRI experiments.

- *Prestation de service externe*

The NeuroSpin centre will pay a electron microscopy facility to get 3D high resolution images of several post-mortem brain samples. Many such facilities belong to academic laboratories and provides this external service (Laboratoire de Physique des Solides, Université Paris Sud XI; Institut Curie, Paris; Laboratoire de Microscopie Electronique Analytique INSERM ERM 0203. Université de Reims Champagne Ardenne). The cost is around 500€ per acquisition and sample.

We planned to acquire 20 different samples covering various typical regions of the brain, yielding a cost equal to 20x500=10000€

- *Missions*

A participation to the international conference of the Society for Magnetic Resonance in Medicine will be paid per year, yielding a travel and accomodation budget of 3x2000€=6000€.

- *Dépenses justifiées sur une procédure de facturation interne*

N/A

- *Autres dépenses de fonctionnement*

A 10k€ budget is asked to cover the purchase of Linux workstations, the manufacturing of synthetic harware phantoms used to validate the simulations , software licenses and lab materials used during the MRI experiments.

8. ANNEXES

8.1. RÉFÉRENCES BIBLIOGRAPHIQUES

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