NeuroImage 75 (2013) 204–212

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A computational model for diffusion weighted imaging of myelinated white matter

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ARTICLE INFO

Article history:
Accepted 25 February 2013
Available online 15 March 2013

Keywords:
Diffusion weighted imaging
Myelination
White matter
Monte Carlo simulation

ABSTRACT

The signal for diffusion weighted magnetic resonance imaging has previously been represented analytically and simulated numerically for a variety of model problems with idealized geometries. Numerical simulations hold the promise of computing the diffusion weighted MR signal for more complex realistic tissue architectures and physiological models. This paper investigates a white matter model consisting of a matrix of coated cylinders with distinct diffusion coefficients and spin concentrations for each of the cylinder core, the coating, and the surrounding bath and compares results with an the analytical solution developed by Sen and Basser for the long diffusion time limit.

Numerical simulations of diffusion weighted imaging experiments are performed for the three-medium model using a Monte Carlo diffusion simulation. Experiments are carried out for model parameters representing normal white matter. Pulse sequence parameters range from a low *b* value, long time limit, short pulse approximation to realistic clinical values.

For simulations in the short pulse width, long diffusion time limit, numerical simulations agree with the Sen–Basser analytical result. When tested with realistic pulse sequence parameters, numerical simulations show lower anisotropy than the analytical model predicts.

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Introduction

Diffusion-weighted MRI (DWI) provides a non-invasive imaging modality that offers the potential to probe tissue microstructure and physiology and thus provide important and unique information that informs a wide range of research and clinical applications. Its application to white matter is of particular interest because of its central role in neural connectivity and the devastating effects of the numerous degenerative white matter diseases. However, the signal attenuation caused by diffusion in the presence of magnetic field gradients provides information only about the aggregate diffusion within an imaging voxel. Unfortunately, the architectural and physiological complexity of intravoxel tissues precludes a simple relationship between the DWI signal and the underlying tissue structure and physiology. For example, diffusion anisotropy is typically used as a proxy for tissue integrity, but, in reality, inferring complex tissue characteristics from this quantity is severely ill-posed.

Analytical models for the signal attenuation have long been available for some simple geometries and idealized physiologies, such as impermeable boundaries, and these models have been useful analogs for biological structures, allowing some inferences about the structure and physiological state of the imaged tissue. But in order to obtain closed-form solutions, significant simplifications are typically employed. Analytical models generally leave out complicating details such as complex cellular structures and heterogeneous media, they frequently represent cell membranes as impermeable boundaries, and they often focus on simple pulse sequences. This disparity between simplified models and imaging situations and actual neural tissues in realistic DTI acquisitions makes inferences about tissue structure and integrity from real data problematic.

Numerical modeling offers an alternative, allowing more complex geometries, the inclusion of multiple tissue types and variable membrane permeability, and the specification of arbitrary pulse sequences in tractable ways. A versatile Monte Carlo based MR diffusion simulator (DiffSim) capable of modeling diffusion within arbitrary triangulated geometries and applying user-specified pulse sequence parameters has been demonstrated previously (Balls and Frank, 2009). Other packages are also available for diffusion-weighted MRI simulations. Hwang et al. (2003) developed a finite-difference method for simulating diffusion using histological images. They compared their results with known analytical solutions for impermeable cylinders. Camino (Cook et al., 2006; Hall and Alexander, 2009), like the approach in DiffSim, uses a Monte Carlo method to model diffusion. Differences between the DiffSim simulation environment and other options and the relative strengths of each approach have been discussed previously (Balls and Frank, 2009).

The critical importance of simulations becomes more evident as increasingly realistic representations of neural tissues are investigated. With the continuing development of more sensitive methods of DTI

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1053-8119/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.neuroimage.2013.02.076

data acquisitions and the broadening scope of their applicability to a wide range of basic science and important clinical applications, the ability to accurately infer quantitative information about tissue architecture, integrity, and connectivity from DTI should be enhanced. However, this goal is significantly hampered by the inability of simplistic analytical models to accurately parameterize complex neural tissues. One important application in which this issue arises is in the characterization of white matter changes—demyelination or other changes to white matter integrity—which play a central role in many degenerative disorders (Kraus et al., 2007; Kumra et al., 2004; Kutzelnigg et al., 2005; Madden et al., 2008; Phillips et al., 2001; Stricker et al., 2009). This is precisely the type of extension of an analytical model to a more realistic scenario where numerical simulations are essential.

In this paper, we are interested in extending the proposed analytical model of Sen and Basser (2005a,b), developed as an idealized, two-dimensional diffusion model in cylindrical coordinates, into a more realistic three-dimensional model of packed fibers within an actual DTI experiment. The Sen–Basser model describes diffusion in myelinated white matter consisting of an analytical solution for diffusion in an array of permeable, coated cylinders in the long-time limit. This model of multiple permeable media allows additional insight into the diffusion properties of white matter, and in particular the role of myelin, but its direct applicability to MR diffusion experiments with specific pulse sequence parameters remained an open question. Despite the potential importance of this model to the experimental investigation of white matter in both research and clinical applications, to our knowledge, there have been no experimental studies—physical or numerical—to determine how dependent their analytical model is on the assumption of a long diffusion time or how results might vary in research or clinical settings with realistic pulse sequences. One study did, however, examine some of the effects of geometry in this model (Davoodi-Bojd and Soltanian-Zadeh, 2011).

A critical step in investigating the efficacy of a model in providing useful information in DWI experiments is to quantitate the interplay of pulse sequence parameters and model parameters as they are ultimately manifest in the DWI signal. However, the Sen–Basser model depends only on properties of the material and not on pulse sequence parameters, and thus the study presented here required redeveloping the theory within the context of a DWI experiment, revealing the assumptions implicit in the original formulation, and then extending these results to realistic imaging scenarios.

This paper develops a numerical model of white matter DWI based upon the physical model described by Sen and Basser, consisting of a matrix of coated cylinders with distinct diffusion coefficients and spin concentrations for each of the cylinder core, the coating, and the surrounding bath. The primary significance of this work is our ability to quantitatively assess how numerous physical variables contribute to anisotropy in the DW signal, including packing density of the fibers and the thickness, diffusion coefficient, and water concentration of the myelin sheathing. In particular, two models of myelin changes are considered in more detail: thinner myelin sheathing and higher water concentration within the myelin.

Numerical simulation results are found to match the analytical solution given by Sen and Basser in the low b-value, short pulse width, long diffusion time limit. Using our extended theoretical analysis, the numerical simulations are then extended over more realistic imaging parameters, showing variation in the measured apparent diffusion as a function of changes to pulse sequence parameters. We find that of the two models we consider, changes to myelin water concentration have a greater effect on signal anisotropy than thinning myelin. We have thus developed a simulation environment capable of investigating the complex interplay of the DWI signal and myelination changes in a model white matter system capable of capturing some of the essential features of real white matter systems. This allows us to test how myelination changes associated with white matter diseases may manifest in DWI protocols.

Theory

A spin, j, diffusing in a time (t) dependent magnetic field gradient $\mathbf{G}(t)$ accrues a phase, θ_j generated by the spin's displacement in the direction of the magnetic field gradient

$$\theta_j(t) = \int_{t_0}^{t} \mathbf{G}(\tau)\cdot\mathbf{x}_j(\tau)d\tau. \tag{1}$$

where "·" represents the dot product. If time is discretized into N_t time steps of length dt, such that the gradient and the displacement are given at each time t_i, the integral can be approximated by a discrete sum:

$$\theta_j(t) = \sum_{i=0}^{N_t} \mathbf{G}(t_i)\cdot\mathbf{x}_j(t_i)dt. \tag{2}$$

For a collection of N_p diffusing spins, the complex signal attenuation is given by

$$E = \frac{1}{N_p}\sum_{j=1}^{N_p} e^{i\gamma\theta_j}. \tag{3}$$

where γ is the gyromagnetic ratio of water. The signal from a realistically sized voxel represented by Eq. (3) involves the sum over a tremendous number N_p of spins, the phases of which must all be tracked. The MCell Monte Carlo diffusion simulator (Stiles and Bartol, 2001) is a good match for this formulation of diffusion-weighted MR (Balls and Frank, 2009). MCell tracks each diffusing molecule, or spin, independently, making the sum in Eq. (3) straightforward. More importantly, MCell does not use a fixed diffusion step, but instead a random diffusion step chosen from a distribution matching the probability distribution for unbounded particles. As a result, an MR simulation based on MCell can respond accurately to diffusion-weighting gradient changes within a single time step, whereas fixed step length methods would require multiple time steps to produce accurate results. Thus short pulses can be more easily modeled, and longer pulses can potentially be modeled with many fewer time steps.

Diffusion fundamentals

Both the numerical simulation and the analytical model discussed here describe restricted diffusion, for which careful consideration of boundary conditions is critical. The problem formulation involves multiple diffusion coefficients and boundaries, but some details of the more basic problem—diffusion within a single medium with constant diffusion coefficient—need to be highlighted first because they are critical to the details of the numerical implementation. Fick's first law,

$$J(\mathbf{x},t) = -D\nabla C(\mathbf{x},t), \tag{4}$$

states that the flux of particles, J, is given as a function of the diffusion coefficient, D, and the gradient of the particle concentration, C. Adding a continuity equation,

$$\frac{\partial C(\mathbf{x},t)}{\partial t} + \nabla\cdot J(\mathbf{x},t) = 0, \tag{5}$$

which states that the change in concentration at a point is balanced by the gradient of the flux (and mass is conserved), we derive Fick's second law:

$$\frac{\partial C(\mathbf{x},t)}{\partial t} = -\nabla\cdot J(\mathbf{x},t) = \nabla\cdot D\nabla C(\mathbf{x},t). \tag{6}$$