NeuroImage 70 (2013) 1–9

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

Detecting microstructural properties of white matter based on compartmentalization of magnetic susceptibility

Way Cherng Chen [a,b,*], Sean Foxley [a], Karla L. Miller [a]

[a] Centre for Functional MRI of the Brain, University of Oxford, Oxford, UK
[b] Singapore Bioimaging Consortium, A*STAR, Singapore

ARTICLE INFO

Article history:
Accepted 18 December 2012
Available online 23 December 2012

Keywords:
GRE phase images
R_2*
Magnetic susceptibility

ABSTRACT

The microscopic structure of neuronal tissue is crucial to brain function, with axon diameter, axonal density and myelination directly influencing signal conduction in the white matter. There is increasing evidence that these microstructural properties alter signal in magnetic resonance imaging (MRI) driven by magnetic susceptibility of different compartments (e.g., myelin sheaths and iron-laden cells). To explain these observations, we have developed a multi-compartmental geometric model of whitematter microstructure. Using a single set of literature parameters, this forward model predicts experimentally observed orientation dependence and temporal evolution of the MRI signal. Where previous models have aimed to explain only the orientation dependence of signal phase, the proposed approach encapsulates the full repertoire of signal behavior. The frequency distribution underlying signal behavior is predicted to be a rich source of microstructural information with relevance to neuronal pathology.

Introduction

White matter (WM) in the brain is composed of a highly complex cellular microstructure, consisting primarily of myelinated axons, glia, vasculature and interstitial space. This microarchitecture is fundamental to brain function, varies across different brain regions and is compromised in a range of neurodegenerative disorders. In general, the microstructural compartments have unique magnetic susceptibilities driven by their chemical compositions and molecular arrangements. In the presence of an external magnetic field, differences in magnetic susceptibilities between adjacent compartments generate local magnetic field perturbations, and hence a range of magnetic resonance frequencies. The precise field perturbation depends on the geometry of the compartments, their spatial arrangement and direction of the main magnetic field, B_0. This raises the intriguing possibility that this microenvironment might be reflected in MR signal changes driven by the magnetic field distribution within an imaging voxel. There is a long-standing literature on signal changes due to partially-oxygenated blood vessels, but brain parenchymal microstructure has received less attention.

Gradient echo (GRE) MR techniques that are sensitive to magnetic susceptibility effects, such as R_2* mapping and phase imaging, have been proposed to probe various aspects of WM microstructure (Duyn et al., 2007; Fukunaga et al., 2010; He and Yablonskiy, 2009; Lee et al., 2010a), with recent interest due to the high contrast afforded by ultra-high field strength scanners (≥7 Tesla). Correlation of R_2* and GRE phase images with non-heme iron (primarily the iron storage protein, ferritin) have been reported in the gray matter (Fukunaga et al., 2010; Gelman et al., 1999; Haacke et al., 2005; Ogg et al., 1999; Schipper, 2012; Yao et al., 2009); however, the relationship between WM regions is less studied. The degree of myelination has been shown to significantly affect both R_2* and phase in WM (Lee et al., 2012; Liu et al., 2011; Lodygensky et al., 2012). Recent studies have reported modulation of R_2* and phase with orientation of the WM fiber to B_0 (Bender and Klose, 2010; Cherubini et al., 2009; Denk et al., 2011; He and Yablonskiy, 2009; Lee et al., 2010a, 2011; Liu, 2010; Marques et al., 2009; Sati et al., 2012), which strongly implicates magnetic susceptibility as the origin of this effect.

Several mechanisms have been proposed to explain the observed signal properties, including magnetic susceptibility anisotropy (Lee et al., 2010a; Liu, 2010) and the presence of cylindrical susceptibility-shifted inclusions (He and Yablonskiy, 2009). These previous works have proposed models to explain orientation dependence of the signal phase and R_2* decay, which are driven by the first and second moments (mean and variance) of the frequency distribution, respectively. These models have attributed effects such as orientation dependence to the microenvironment, but without explicitly modeling the microstructure. For example, signal phase has been modeled as a mixture of susceptibilities with either intrinsic (Lee et al., 2010a) or apparent (He and Yablonskiy, 2009) orientation dependence. While providing a closed-form expression for the orientation dependence of signal phase, these models are designed to explain a limited range of signal behaviors.

* Corresponding author at: Centre for Functional MRI of the Brain, University of Oxford, Oxford, UK.
E-mail address: wcchen@fmrib.ox.ac.uk (W.C. Chen).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2012.12.032

In the present work, we introduce an explicit multi-compartmental geometric model of the WM that encapsulates magnetic properties to investigate the contribution of the tissue microarchitecture in generating signal properties. The power of this approach is that it predicts the entire frequency distribution contained within a voxel, not just the low-order moments, capturing the full richness of information in this distribution. This work is closely related to susceptibility models of the vasculature, but with a crucial difference: low blood volume results in distributions that are well-characterized by the field patterns surrounding an isolated blood vessel (Yablonskiy and Haacke, 1994), whereas the field perturbations surrounding densely-packed WM axons interact such that the field distribution depends on the packing geometry. Modeling this geometry explicitly provides a simple but powerful approach that is able to describe both low- and high-order moments (Miller et al., 2010; van Gelderen et al., 2012). Specifically, we demonstrate that this model predicts the experimentally-observed dependence of signal phase and R_2^* (low-order moments) on the orientation of WM fiber to B_0. High-order moments are expected to encapsulate interesting aspects of compartmentalization to which lower-order moments are less sensitive. We demonstrate that the model agrees with measurements of the deviation of signal behavior from low-order moment approximations, as indicated by non-linear phase and non-mono-exponential magnitude time courses (van Gelderen et al., 2012). We then use the model to predict changes due to two sources of susceptibility contrast in WM: demyelination and iron concentration. These properties are physiologically relevant to WM function, plasticity and disease, making GRE signal measures potential biomarkers for myelin and iron.

Materials and methods

Geometric model

The geometric model (Fig. 1a) consists of a circular bundle of WM fibers surrounded by a reference medium. The WM fiber bundle is divided into 3 types of micro-compartments corresponding to axon, myelin and extra-axonal space. For ease of computation, the model is calculated in 2D as a single plane transecting the WM fiber bundle. Each axon is modeled as an infinite cylinder with myelin represented as an annular ring surrounding the axon with a pre-defined g-ratio (the ratio of inner to outer diameter of the myelin sheath Rushton, 1951) of 0.65 ± 0.1 (Albert et al., 2007; Jacobs and Love, 1985) unless otherwise stated. Axons are densely-packed at random location using a circle-packing algorithm (Collins and Stephenson, 2003). The volume fraction of WM fibers used was approximately 0.7 (assuming 0.2 extracellular space Nicholson and Syková, 1998; Syková, 2005 and 0.1 glia volume fraction Lehre and Rusakov, 2002). The WM fibers have a mean diameter of approximately 1 μm and the fiber diameter follows a gamma distribution (Aboitiz et al., 1992). The WM fibers are approximately parallel with slightly randomized orientation (angular variance of 5°). The magnetic susceptibility of the myelin compartment is -0.08 ± 0.01 ppm (Lee et al., 2012; Liu et al., 2011) and the axonal and extra-axonal compartments and reference space are set at 0 ppm (unless otherwise specified). T_2 values for the myelin and extra-axonal compartments were set to 25 ms and 75 ms, respectively (Laule et al., 2004). The axonal bundle is simulated for a range of orientations (θ) with respect to B_0 (by rotating B_0 relative to the simulated 2D plane). For realism, the magnetic susceptibility, g-ratio and WM fiber orientations are randomly varied from one axon to the next. The magnetic field perturbation (see Fig. 1b) was calculated using analytical solutions (Haacke et al., 1999). Magnetization evolution at each grid point is calculated using Bloch equations with short time steps, and the signal is calculated as the complex sum over the WM fiber bundle (excluding the reference medium, Fig. 1d). The proton density in the myelin compartment was assumed to be half that of the other compartments. The 2D model was

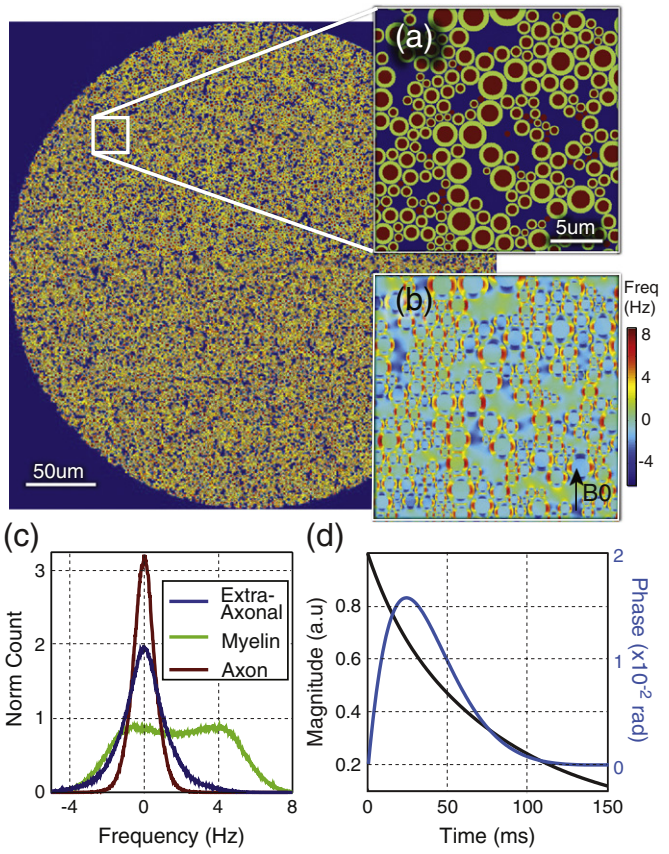

Fig. 1. 2D geometric model of white matter (WM). (a) Approximately 50000 WM fibers were modeled in a circular bundle with a close random packing. White box shows a zoomed in illustration of the WM microstructure. Dark blue = extra-axonal space, green = myelin, red = axon. (b) The frequency map generated in presence of an external magnetic field $\boldsymbol{B_0}$. (c) Frequency histogram. (e) The resultant magnitude decay and phase evolution.

simulated over a FOV of 0.35 mm × 0.35 mm to calculate signal for an area roughly comparable to an MRI pixel. A high resolution grid space was used to ensure that the magnetic field perturbation pattern for each axon is sufficiently represented. After extensive testing of the trade-off between accuracy and computational feasibility, the grid was chosen such that 28×28 grid points covers 1×1 μm^2 (exactly framing an axon of median diameter) and the simulated FOV comprises approximately 7000×7000 grid points with 50,000 axons.

In this geometric model, we utilized the analytical solution for the magnetic field perturbation caused by an infinite cylinder (Haacke et al., 1999) to calculate the magnetic field change caused by each WM fiber at a given orientation to B_0. The analytical solution for the magnetic field perturbation at a given grid point due to one axon is given by Eqs. (1)–(3), where subscripts indicate compartments (ax = axonal, ea = extra-axonal, my = myelin), Δf is the change in resonance frequency in Hz, $\Delta\chi$ is the difference in magnetic susceptibility with respect to χ_{ea}, θ is the orientation of the cylinder's long axis to B_0, R is the radius of the compartment, ϕ and xtitr are the polar coordinates at each grid point with reference to the direction of B_0 and the centre of the axon. For a given grid point and axon, we select between Eqs. (1) and (3) depending on which compartment the grid point lies in with respect to that axon (i.e., Δf_{ea} is used for all grid points external to that particular axon, even if the grid point lies inside another WM fiber). WM fiber orientations were varied by changing θ, which is an approximate and simplistic method for adding some angular variation to an otherwise perfectly parallel fiber system. Thus, although the axons are simulated as perfect circles in the simulation, the field effects reflect a range of orientations. This