Accurate Estimation of Intra-axonal Water Diffusion Requires Proper Modeling of Surrounding Cellularityμμ

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Introduction

Although diffusion tensor imaging (DTI) has been successfully used to measure the apparent directional diffusivity in white matter [1], it does not provide insight into the intra-axonal water diffusion. Most recently, an idealized two-compartment, no-exchange diffusion model of white matter was proposed, diffusion kurtosis imaging (DKI) [2], to estimate the intra- and extra-axonal diffusivities, as well as the intra-axonal water fraction from the clinically feasible diffusion measurements. However, DKI does not model isotropic cellular component, which is commonly observed in the central nervous system (CNS). Diffusion of water molecules in these cellular components is highly restricted similar to those inside of the axonal membrane. Therefore, it is not yet clear whether or how these cellular components, particularly prominent after inflammatory cell infiltration in CNS injury, affect the accuracy of intra-axonal water diffusion estimates. We recently developed diffusion basis spectrum imaging (DBSI) to better account for both crossing fibers and inflammation induced cellularity and water content changes without separating intra- and extra-axonal diffusion [3]. To examine the effect of cellularity changes on intra-axonal water diffusion estimates, we previously included intra-axonal component in DBSI analysis to model the non-Gaussian restricted intra-axonal water diffusion, close agreement between DBSI and DKI was seen in normal mouse trigeminal nerves [4]. In this study, we applied DBSI with intra-axonal component to analyze data generated using Monte Carlo simulation mimicking axonal bundle with various cellularity to assess the role of cellularity on the intra-axonal water estimation. Results indicated that neglecting cellularity tends to overestimate the intra-axonal water fraction, and underestimate the intra-axonal axial diffusivity, the higher cellularity leading to the worse estimate error.

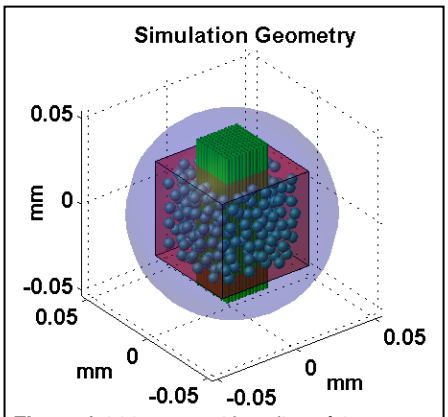

Figure 1 144 axons with radius of 1 μm were organized into a 12x12 arrayed bundle (green cylinders). Different amount of cells with radium of 3 μm (blue spheres) were randomly placed surrounding the axon bundle to simulate various extent of cell infiltration. Imaging voxel (50μm^3 red cube) was placed in the center of the simulation domain (light blue outer sphere).

Method

In Silico Phantom: Within a sphere of 90 μm in diameter (Fig. 1, light blue sphere), axonal bundle of 2 × 84 μm cylinders tightly arranged in 12 rows x 12 columns was simulated to model inter-axonal water diffusion. The average diffusion path length (with 13-ms diffusion time) of 7.4 μm was set to reflect simulation temperature of 20º C. Five different amounts (0, 50, 100, 150, and 200) of cells (Fig. 1, small blue sphere) with radius of 3 μm were introduced surrounding the axonal fiber bundle. An isotropic image voxel of 50μm^3 was selected at the center of the phantom. ***Spin Random Walk:*** Similar to the previously reported study [5], 2.5x10^5 spins were uniformly distributed in the 45-μm radius sphere for the conventional Brownian motion simulation. At the boundary of axon fibers and cell membranes, the spin reflects elastically [5]. ***Simulated Spin Echo Sequence with Diffusion Weighting Gradients:*** A simple spin echo sequence with 99 distinct diffusion-weighting gradients expanding 3D grids was employed [3] to simulate the diffusion weighted MRI signals from the imaged voxel. Rician noise was added to maintain SNR=50.

$$S_k = \tilde{S}\, e^{-\left|\vec{b}_k\right|\tilde{\lambda}_\perp} e^{-\left|\vec{b}_k\right|\left(\tilde{\lambda}_\parallel-\tilde{\lambda}_\perp\right)\cos^2\theta} + \bar{S}\, e^{-\left|\vec{b}_k\right|\bar{\lambda}_\parallel\cos^2\theta} \quad [1]$$

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DBSI Intra-axonal Water Diffusion: As suggested previously [2], the radial diffusivity of intra-axonal water can be approximated as zero due to the small axonal diameter comparing with thediffusion path length. For coherent nerve fiber bundles, Eq. [1] (the model without restricted intracellular isotropic diffusion), and Eq. [2] (the model with restricted intracellular isotropic diffusion) can be solved by fitting the simulated 99 diffusion-weighted signals using global nonlinear optimization and NNLS analysis. The first term on the right side of Eq. [2] describes the anisotropic extra-axonal water diffusion, and the second term describes the intra-axonal water diffusion. For Eq. [2], the restricted isotropic components with mean ADC close to zero were assigned to cells, while the rest of the isotropic components were assigned to isotropic extra-axonal water.

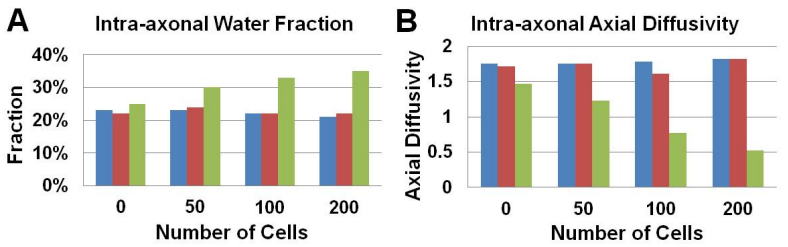

Figure 2 (A) Neglecting cellular component caused overestimation of intra-axonal water fraction (green bars) with respect to true value (blue bars). The deviation became worse with the increase of cell number. Such overestimation can be corrected with proper modeling of cellular component (red bars). (B) In compared to true value (blue bars), intra-axonal axial diffusivity was progressively underestimated (green bars) with the increased cell content. Both intra-axonal water content and axial diffusivity can be accurately estimated by considering cellular component (red bars).

Results and Discussion

The intra-axonal water fraction was overestimated when intra-cellular component is not included in the diffusion modeling (Fig. 2, panel A, green bars) due to the similarly highly restricted intra-cellular and intra-axonal radial diffusion. The inadequate modeling for the cellularity caused the overestimated intra-axonal fraction that reflected restricted diffusion components resulting from confounding cellular components. Similarly, intra-axonal axial diffusivity derived by the model without considering cellular component would in fact average restricted intracellular diffusivity with intra-axonal axial diffusivity, resulting in underestimating intra-axonal diffusivity (Fig. 2, panel B, green bars). Current results suggest that properly modeling cellular component is critical for the accurate estimation of intra-axonal water diffusion, especially for CNS regions with high cellularity. The current finding cautions the interpretation of axon diameter distribution, or intra-axonal water fraction derived by modeling intra-axonal water diffusion without taking into account the effect of the surrounding cells [6], [7].

References [1] Song, SK. *et al. Neuroimage*. 2002; 17:1429. [2] Fieremans, E. *et al. Neuroimage*. 2011; 58:177-188; [3] Wang,Y. *et al. Brain*. 2011; 134:3590; [4] Wang,Y. *et al. ISMRM*. 2011; 5904; [5]Chunlei L. *et al. MRM*. 2004; 51:924–937;[6] Assaf,Y. *et al. Neuroimage*. 2005; 27: 48-58; [7] Alexander,D. *et al. Neuroimage*. 2010; 52: 1374-89;