An Analytical Model of Diffusion and Exchange of Water in White Matter from Diffusion-MRI and its Application in Measuring Axon Radii

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Introduction

We present an analytical model of diffusion and water exchange in white matter to estimate axon radii. Direct measurement of important biomarkers such as the axon radii, density, and permeability are important for early detection of diseases. We use a model for white matter with two compartments between which there is exchange of water molecules. Our analytical formulas examine the derivation of axonal parameters that affect the signal attenuation of diffusion-weighted MR experiments in white matter. The model is fitted to Monte Carlo simulation data. The parameters obtained are compared with known ground truth from simulation data and prove the feasibility of recovering underlying axonal radii using the model.

Method

The model is composed of two compartments: one cylindrical restricted and one hindered. The cylindrical restricted compartments are surrounded by partially permeable membranes. The free diffusion coefficients D_1 and D_2 are assumed to be the same. We use indices 1 and 2 to denote intra-axonal and extra-axonal compartments. MR signal attenuation reflects the water diffusion in white matter in two processes: restricted water diffusion in the intra-axonal space and hindered water diffusion in extra-axonal space. The combined normalized MRI signal is then: $E(q,\Delta) = fE_1(q,\Delta) + (1-f)E_2(q,\Delta)$, where f is the volume fraction of the intra-axonal compartment, Δ is the time between pulses, and q is the wavenumber.

Water Diffusion in Intra-axonal Space:

The motion of molecules undergoing diffusion can be described with the conditional propagator, $P_s(\vec{r} \mid \vec{r}_0, t)$, an ensemble-averaged probability density for spin displacement from $\vec{r}_0$ to $\vec{r}$ over a time, t. $P_s(\vec{r} \mid \vec{r}_0, t)$ obeys:

- Ficks's Law: $\frac{\partial P_s^{(1)}}{\partial t} = D_1 \nabla^2 P_s^{(1)}$, Initial Condition: $P_s^{(1)}(\vec{r} \mid \vec{r}_0, 0) = \delta(\vec{r} - \vec{r}_0)$
- Boundary Condition: $D\frac{\partial P_s^{(1)}}{\partial \rho}|_{\rho=a} + MP_s^{(1)}|_{\rho=a} = 0$, Boundary Relationship: $D_1 \frac{\partial P_s^{(1)}}{\partial \rho}|_{\rho=a} = D_2 \frac{\partial P_s^{(2)}}{\partial \rho}|_{\rho=a}$
- Define: Transport rate through interface $h = \frac{Ma}{D_1}$, M is the permeability coefficient

The solution to the diffusion problem posed above, given rotational symmetry about the direction of the field gradient, is written in terms of the corresponding eignfunctions [1]. In a typical experiment, only the eigenvalue $\alpha = \alpha_{01}$ is important [3]. Our solution to the **normalized MRI signal in the intra-axonal compartment** is:

- $E_1 = 4\exp(\frac{-\alpha_{01}^2 D_1 \Delta}{a^2}) \frac{[hJ_0(2\pi qa) - 2\pi qaJ_1(2\pi qa)]^2}{[(2\pi qa)^2 - \alpha_{01}^2]^2}$, with boundary condition: $\alpha_{01}J_1(\alpha_{01}) - hJ_0(\alpha_{01}) = 0$

Where a is the axon radius, J_n is the Bessel functions, and α_{nm} are the positive roots of the equation $\alpha_{nm}J_n'(\alpha_{nm}) / J_n(\alpha_{nm}) = -h$

Water Diffusion in Extra-axonal Space:

We model the hindered diffusion surrounding the axons with Gaussian distribution. By assuming a sufficiently long diffusion time $\frac{\Delta \cdot D_{in}}{a^2} \geq 1$, the apparent diffusion coefficient of the extra-axonal compartment can be approximated as $D_{2app} = D_2 + \frac{1}{q^2\tau}$, where τ is the exchange time between the two compartments [2].

Thus, the **normalized MRI signal in the extra-axonal compartment** is then:

- $E_2 = \exp(-q^2 D_2 \Delta - \frac{\Delta}{\tau})$

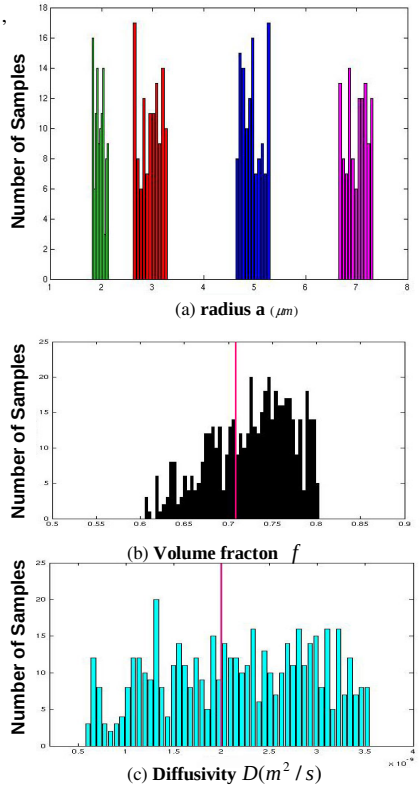

Figure 1: (a) Axon radius estimation result. (b, c) Volume fraction and diffusivity estimation results at radius = 5 (μm). Histogram of 500 samples from posterior distribution on a, f and D using MCMC.

Experiments

Our Model is fitted to 6 constant-gradient experiments using Monte Carlo simulation in CAMINO [7] with the following axonal parameters: various cylindrical radii: R = [1.9, 3, 5, 7] (μm); transport rate $h = 5.788e^{-4}$; diffusivity value $D = 2e^{-9}(m^2/s)$; and intra-axonal volume fraction $f = 0.708$. We set our experimental parameters to be: δ = 2ms; diffusion time is chosen from 20 to 500 ms with 13 linear increments; diffusion gradients were applied only perpendicular to the axon axis and each simulation was repeated for 6 linear gradient amplitudes of 200-700 (mT/m) with SNR = 16.

Results

We use a Markov Chain Monte Carlo (MCMC) procedure to get samples of the posterior distribution of the model parameters given the data. Figure 1 is our main result. Figure 1(a) shows the histograms of the marginal posterior distribution on axon radius a. Figure 1(b, c) shows the histogram of the marginal posterior distribution of the other model parameters: f (volume fraction) and D (diffusivity). Each histogram combines a total number of 500 samples. Overall, the estimate of the axonal parameters is accurate and demonstrated the feasibility of recovering underlying axonal radii.

Discussion

Previous work on axon radii estimation [4, 5] has assumed no exchange between intra- and extra-axonal compartments. Recent work [6] has demonstrated that if diffusion is modeled as two compartments, of which one is restricted, exchange must be included in the model. Our estimation results of axon radii based on simulation data is a first towards recovering axonal features incorporating water exchange. In the near future, we plan to apply our model for axon radii measurement in vivo with macaque data. Our method will be validated with radii distribution measured from photomicrographs on the corpus callosum and the cingulum bundle.

References

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