Inferring Axon Properties with double-PGSE MRI using Analytical Water Diffusion Model

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Introduction

We present an analytical water diffusion model for inferring axon properties using double-PGSE MRI (d-PGSE) accounting for finite gradient pulses. The MR signal attenuation obtained from single-PGSE (s-PGSE) reflects the underlying tissue structure that restricts the water molecules' diffusion within. However, high q-values must be applied to measure these tissue properties using s-PGSE, requiring high gradient strength and/or long pulse duration and diffusion times[1]. This inhibits the clinical applications of these methods. We propose to use low-q d-PGSE MRI for white matter tissue structure modeling in order to extract axon properties including axon caliber, water diffusivity and volume fraction of intra-axonal space.

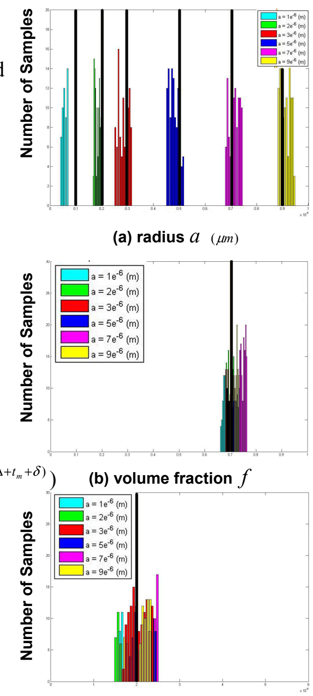
Method

The d-PGSE sequence is the simplest form of multi-PGSE[2] with two encoding intervals of gradients G_1 and G_2 with angle ψ. The two encoding intervals are separated by mixing time t_m, diffusion time Δ_1 and Δ_2, and pulse duration δ_1 and δ_2. Recently, Özarslan et al.[3] predicted the dependence of signal decay from d-PGSE sequence in confined geometries theoretically. Shemesh et al.[4] validated these dependencies of signal decay with well-controlled experimental parameters using water filled microcapillaries.

Model for MRI signal

We propose an analytical water diffusion model for estimating axon properties based on Özarslan's theory[3] using d-PGSE data. The model is composed of two compartments: (1) restricted diffusion in intra-axonal compartment within the axons that are modeled as cylinders (2) hindered diffusion in the extra-axonal compartment outside the axon. The two compartments are denoted with subscript *i* and *e*, respectively. The boundary of the cylinders representing the axon myelin is assumed to be impermeable. **The combined normalized MR signal attenuation** is then: $E = (1-f)E_e + fE_i$**,** where f is the volume fraction of the intra-axonal compartment. We model the **normalized MR signal attenuation in the extra-axonal compartment** with Gaussian distribution: $E_e = \exp(-\gamma^2\delta^2 D_e(G_1{}^2 + G_2{}^2)(\Delta - \frac{\delta}{3}))$. We decompose the **normalized MR signal attenuation in the intra-axonal compartment** into components parallel and perpendicular to the axon orientation: $E_i = E_{i//} \times E_{i\perp}$. By discretizing the gradient waveform, we can approximate it by train of impulses using a series of propagators and derive $E_{i//} = \exp(-\gamma^2\delta^2 D_i(G_1^2\cos^2\phi_1 + G_2{}^2\cos^2\phi_2)(\Delta - \frac{\delta}{3}))$ and $E_{i\perp} = C + A(G_1^2\cos^2\phi_1 + G_2{}^2\cos^2\phi_2) + B(G_1G_2\cos\phi_1\cos\phi_2)$, where

- $C = 1 - A(G_1^2 + G_2{}^2) - B(G_1G_2\cos\psi)$, $A = 2\gamma^2a^2\sum_{n=1}^{\infty}S_n \times [\frac{2\delta}{\omega_n} - \frac{1}{\omega_n^2}(2 - 2e^{-\omega_n\delta} + e^{-\omega_n(\Delta-\delta)} - 2e^{-\omega_n\Delta} + e^{-\omega_n(\Delta+\delta)})]$
- $B = 2\gamma^2a^2\sum_{n=1}^{\infty}\frac{S_n}{\omega_n{}^2}(e^{-\omega_n(t_m-\delta)} - 2e^{-\omega_n t_m} + e^{-\omega_n(t_m+\delta)} - 2e^{-\omega_n(\Delta+t_m-\delta)} + 4e^{-\omega_n(\Delta+t_m)} - 2e^{-\omega_n(\Delta+t_m+\delta)} + e^{-\omega_n(2\Delta+t_m-\delta)} - 2e^{-\omega_n(2\Delta+t_m)} + e^{-\omega_n(2\Delta+t_m+\delta)})$
  - $S_n = \frac{1}{\alpha_n^4 - \alpha_n^2}$, $\omega_n = \frac{\alpha_n^2(D_i + D_e)}{a^2}$, α_n are the roots of the derivatives of the first order Bessel function $J'(\alpha_n) = 0$. We approximated A and B using the most important lowest 6 roots. For simplification, $\Delta_1 = \Delta_2 = \Delta$ and $\delta_1 = \delta_2 = \delta$.
- The axon properties are axon caliber a, volume fraction of the intra-axonal compartment f, water diffusivity of intra- and extra-axonal compartment D_i and D_e, and we account for the axon orientation with relative angle ϕ_1 and ϕ_2 with respect to gradients G_1 and G_2.



(a) radius a (μm)

(b) volume fraction f

(c) Diffusivity D ($m^2/2$)

Figure 2: Histogram of 100 samples from posterior distribution on a, f and D using MCMC.

Experiments

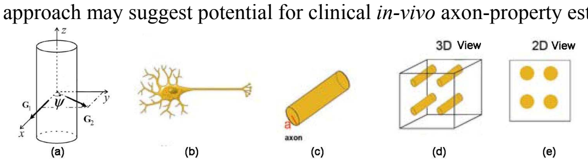
Our model was fitted into 4 diffusion experiments using Monte-Carlo random walk simulation. We used a geometric model of rectangular arrangement of cylinders (Fig. 1d) aligned on the z-axis (Fig. 1a) with the following axon properties as defined above: $a = [1,2,3,5,7,9](\mu m)$; $f = 0.7$; and $D_1 = D_2 = D = 2e^{-9}(m^2/s)$. We set our experimental parameters to be: $\delta_1 = \delta_2 = 2(ms)$; $\Delta_1 = \Delta_2 = [10,10,20,40,60,110](ms)$; $t_m = 3(ms)$; and $G_{1\max} = G_{2\max} = [0.5,0.5,0.5,0.5,0.3,0.3](T/m)$ for $a = [1,2,3,5,7,9](\mu m)$ respectively, with SNR = 16. We held G_1 direction constant on the x-axis and varied G_2 direction on the x-y plane ranging ψ from 0° to 360° with 18 increments to probe diffusion signals that are most sensitive to restricted diffusion (Fig. 1a).

Results

We used a Markov Chain Monte Carlo (MCMC) procedure to get samples of the posterior distribution of the model parameters given the data. Fig. 2 is our main estimation results showing the estimation-sample histograms of: (a) axon caliber a; (b) volume fraction of the intra-axonal compartment f; and (c) water diffusivity D. Each histogram combines a total number of 100 samples and the true value for each parameter is indicated with a black line. Overall, we were able to extract accurate estimates of these axon properties. It is worth noticing that when axon caliber gets smaller ($a \le 2\mu m$), we observed an underestimation of the axon caliber dimension.

Conclusions

Our estimation results demonstrate the feasibility inferring axon properties using d-PGSE that utilizes signal intensity dependency on gradient-pair direction to compensate for high-q requirement in s-PGSE experiments. Since many gradient directions can be acquired in rather short time in the current MRI scanner, this approach may suggest potential for clinical *in-vivo* axon-property estimation.



References
[1] Assaf et al., Magn. Reson. Med.59: 1347—1354, 2008 [2] Cory et al., Polym. Preprints, 31: 149, 1990 [3] Özarslan et al., J. Chem. Phys. 128: 154511, 2008 [4] Shemesh et al. J. Magn. Reson., 198: 15:23, 2009

Figure 1: (a) Experimental setup. (b) Schematic view of axon. (c) single cylinder representing axon with caliber a. (d-e) 3D and 2D view of rectangular arrangement of cylinders representing axons in white matter fiber.