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

Introduction

We present an analytical water diffusion model for inferring axon properties using low-q angular double-pulsed gradient spin echo (d-PGSE) NMR, taking into account finite gradient pulses. Estimating these properties using s-PGSE, however, requires prior knowledge of tissue orientation and high q-values, inhibiting clinical application of these methods[1]. Emerging methods for estimating orientationally invariant fibers using s-PGSE requires protocol optimization for the specific axon radius being estimated[2]. Our simulation results demonstrate that using low-q d-PGSE MRI, important axon properties including axon caliber, water diffusivity and axon volume fraction can be extracted in both orientationally known and unknown tissue.

Method

Imaging Protocol The d-PGSE sequence is the simplest form of multi-PGSE, first proposed by Cory[3]. Two pairs of diffusion gradients G_1 and G_2 are applied at any direction with angle ψ between them. The two encoding intervals are separated by mixing time t_m with diffusion time Δ_1 and Δ_2 and, pulse duration δ_1 and δ_2. In angular double-PGSE experiments, the diffusion time, pulse duration, and mixing time are fixed and we vary the angle ψ. Shemesh et al.[5] validated Özarslan's[4] d-PGSE signal-decay dependency theory in well controlled experiments using water-filled microcapillaries.

Analytical Model

We propose an analytical water diffusion model for estimating axon properties based on Özarslan's theory[4] with two compartments: 1) The *intra-axonal compartment* – the space inside the axons with radius *a* represented by parallel non-abutting cylinders exhibits restricted diffusion, and (2) the *extra-axonal compartment* – the homogeneous substrate space outside the axons exhibits hindered diffusion. The two compartments have no water exchanged and denoted with subscript *i* and *e*, respectively. We model the **combined normalized MR signal attenuation** from the two compartments in the geometric model as: $E = (1-f)E_e + fE_i$, where f is axon volume fraction. We model the normalized MR signal attenuation in the extra-axonal compartment with the Gaussian diffusion distribution: $E_e = \exp(-\gamma^2\delta^2 D(G_1^2 + G_2^2)(\Delta - \frac{\delta}{3}))$. The two encoding intervals have the same diffusion time and pulse duration. We further decompose the normalized MRI signal in the intra-axonal compartment E_i into two components: parallel and perpendicular to the axon orientation: $E_i = E_{i//} \times E_{i\perp}$. We use a discretization scheme for the gradient waveform[6] to approximate it by a train of impulses using a series of propagators and derive

$E_{i//} = \exp(-\gamma^2\delta^2 D\ (G_1^2\cos^2\beta_1 + G_2^2\cos^2\beta_2)(\Delta - \frac{\delta}{3}))$ and $E_{i\perp} = C + A(G_1^2\cos^2\beta_1 + G_2^2\cos^2\beta_2) + B(G_1G_2\cos\beta_1\cos\beta_2)$, where

- $A = 2\gamma^2 a^2 \sum_{n=1}^{\infty} S_n \times [\frac{2\delta}{\omega_n} - \frac{1}{\omega_n^2}(2 - 2e^{-\omega_n\delta} + e^{-\omega_n(\Delta-\delta)} - 2e^{-\omega_n\Delta} + e^{-\omega_n(\Delta+\delta)})]$; $C = 1 - A(G_1^2 + G_2^2) - B(G_1G_2\cos\psi)$
- $B = 2\gamma^2 a^2 \sum_{n=1}^{\infty} \frac{S_n}{\omega_n^2}(e^{-\omega_n(t_m-\delta)} - 2e^{-\omega_n t_m} + e^{-\omega_n(t_m+\delta)} - 2e^{-\omega_n(\Delta+t_m-\delta)} + 4e^{-\omega_n(\Delta+t_m)} - 2e^{-\omega_n(\Delta+t_m+\delta)} + e^{-\omega_n(2\Delta+t_m-\delta)} - 2e^{-\omega_n(2\Delta+t_m)} + e^{-\omega_n(2\Delta+t_m+\delta)})$
- $S_n = \frac{1}{\alpha_n^4 - \alpha_n^2}$, $\omega_n = \frac{\alpha_n^2 D}{a^2}$, α_n are the roots of the derivatives of the first order Bessel function $J'(\alpha_n) = 0$.

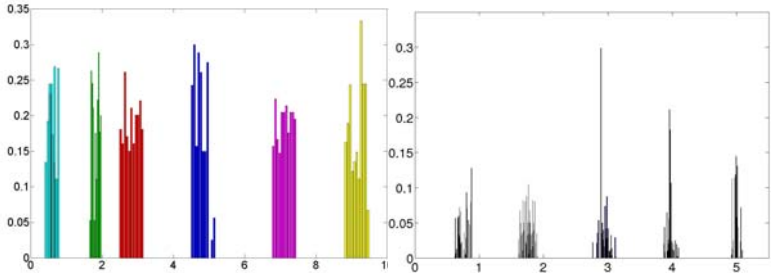
Experiments

Our model was fitted into two diffusion experiments with Monte-Carlo simulation using Camino [7, 8]. In the first experiment, we assumed a known axon orientation aligned in the z-axis and repeated for axon radii $a = [1,2,3,5,7,9](\mu m)$ and $G_{\max} = 0.5(T/m)$. In the second experiment, we assumed an unknown orientation for axon radii $a = [1,2,3,4,5](\mu m)$ with orientation $\vec{u} = (1, \pi/6, \pi/3)$ and $G_{\max} = 0.4(T/m)$. The axon volume fraction $f = 0.7$ and water diffusivity $D = 2e^{-9}m^2/s$ in both experiments.

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. 1 is our main estimation results showing the estimation-sample histograms of axon radius a. Along with axon caliber, we also extracted axon volume fraction f and water diffusivity D (data not shown)[9, 10]. 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 without prior knowledge of tissue orientation. We conclude that modeling microstructural properties using d-PGSE acquisition may be advantageous in extracting underlying microstructural properties as it utilizes signal intensity dependency on gradient-pair direction to compensate for high-q requirement in s-PGSE experiments.



References

[1]Assaf et al., Magn. Reson. Med.59: 1347—1354, 2008 [2]Alexander et al., NeuroImage, 52: 1053-8119, 2010 [3]Cory et al., Polym. Preprints, 31: 149, 1990 [4]Özarslan et al., J. Chem. Phys. 128: 154511, 2008 [5]Shemesh et al. J. Magn. Reson., 198: 15:23, 2009 [6]Özarslan et al., J. Magn. Reson., 188(2): 285-294, 2007 [7]Hall et al., ISMRM, 2006 [8]Cook et al., ISMRM, 2006 [9]Zhou et al., ISMRM, 2010 [10]Zhou et al., CDMRI at MICCAI, 2010

Figure 1: Histogram of posterior distribution on axon radius a. Left: estimation in orientationally known tissue. $a = [1,2,3,5,7,9](\mu m)$ **Right: estimation in orientationally unknown tissue.** $a = [1,2,3,4,5](\mu m)$