Measurement of axon radii distribution in orientationally unknown tissue using angular double-pulsed gradient spin echo (double-PGSE) NMR

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Introduction

We present an analytical diffusion model for measuring axon radii distribution in orientationally unknown tissue using angular d-PGSE NMR. S-PGSE NMR reflects the underlying axon properties that restrict internal diffusion. 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 are the first to demonstrate that using angular d-PGSE experiments, clinically feasible acquisition is sufficient to accurately reconstruct quantitative measurements of axon properties in tissue of unknown orientation in typical human brain tissue range $(1-5\mu m)$. In addition to axon radii distribution, we were also able to infer other important axon properties such as axon orientation and axon volume fraction.

Method

Imaging Protocol The double-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. Özarslan et al.[4] gave a theoretical solution of the angular dependence of the signal decay in restricted geometries. Shemesh et al.[5] validated these signal-decay sensitivities in well controlled experiments using water-filled microcapillaries.

Analytical Model Based on histological observations[6], we construct a geometric model 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. These two compartments, denoted ***i*** and ***e*** below, have no water exchange. We extend previous model[7, 8] based on Özarslan's theory [4] to incorporate axon radius variation from a distribution of fiber sizes and to account for unknown fiber orientation. We model the **combined normalized MR signal attenuation** from the two compartments in the geometric model as: $E=(1-f)E_e+f\sum_n \omega_n(\alpha,\beta)E_i(a_n)$, where f is axon volume fraction, and the weights ω_n of different axon radii are modeled by a normalized two-parameter gamma distribution. We model the normalized MR signal attenuation in the extra-axonal compartment with the Gaussian diffusion distribution: $E_e=\exp(-\gamma^2\delta^2 D_e(G_1^2+G_2^2)(\Delta-\frac{\delta}{3}))$. 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[9] 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

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

Experiments Our model was fitted to diffusion experiments using Monte-Carlo simulation in Camino toolkit[10, 11]. The experiments were repeated with five different gamma-distributed axon radii with mean values $a=[1,2,3,4,5]\mu m$. The rest of the axon parameters in the simulation are: axon orientation $\vec{u}=(1,\pi/9,\pi/4)$, axon volume fraction $f=0.7$, and water diffusivity $D=1.6e^{-9}m^2/s$. Data were collected with the following experimental parameters: pulse duration $\delta=15ms$; diffusion time $\Delta=35ms$; diffusion gradients $G_{1\max}=G_{2\max}=0.07T/m$; mixing time $t_m=20ms$; ψ varied in 10° increments.

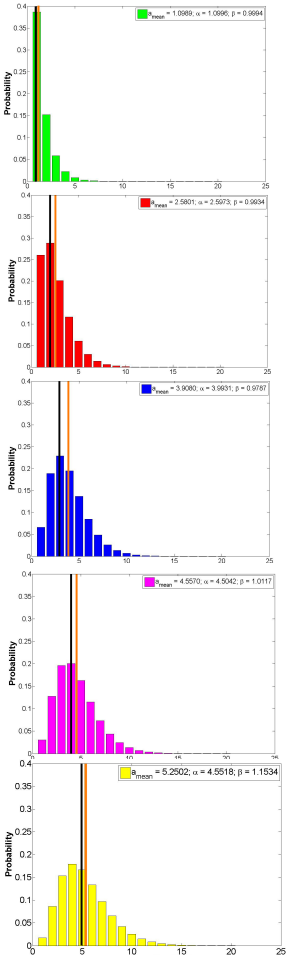

Fig. 1: Estimated axon radii distribution

Results Table 1 and Fig. 1 show our main results from simulation data using a Levenberg-Marquardt fitting process. The estimated axon properties including axon radii distribution a, axon orientation $\vec{u}=(1,\theta,\phi)$, and axon volume fraction f are summarized in Table 1. Fig. 1 shows the estimated axon radii distribution for each simulation experiment. The black vertical lines indicate ground truth for the mean axon radius and the orange vertical lines show the estimated mean values $(a_{mean}=\alpha\beta)$. Overall, we were able to extract the underlying axon properties accurately.

Conclusions We have demonstrated for the first time the feasibility of estimating axon radii distributions in the typical human range without prior knowledge of axon orientation using low-q angular double-PGSE experiments in clinically feasible settings; other important underlying axon properties such as axon volume fraction and orientation were accurately extracted from the analytical model as well.

Mean Axon Radius (μm)		Axon Orientation (rad)		Volume Fraction
Ground truth	Estimate	$\theta=0.3491$	$\phi=0.7854$	$f=0.7$
1	1.0989	0.3490	0.7866	0.6944
2	2.5801	0.3507	0.7886	0.7161
3	3.9080	0.3545	0.7915	0.7329
4	4.5570	0.3637	0.8020	0.6635
5	5.2502	0.3859	0.8283	0.5605

Table 1: Summary of estimated mean values of axon parameters

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