ESTIMATION OF MICROSTRUCTURAL PROPERTIES OF FIXED CORPUS CALLOSUM FROM OGSE MEASUREMENTS

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Introduction Conventional diffusion MRI provides exquisite sensitivity to tissue microstructure, but often lacks clear biological interpretation. Improved specificity may be possible with diffusion "spectrum" measurements, in which tissue micro-geometry is reflected in the diffusive movement of water at different temporal frequencies ω. Diffusion within simple restricting geometries is straightforward to calculate[1], enabling one to model axons in white matter as simple cylinders and calculate the diffusion spectrum of the intra-axonal space (IAS). We recently presented a model for the diffusion spectrum of hindered diffusion around randomly packed cylinders[2], enabling us to also calculate the diffusion spectrum for the extra-axonal space (EAS). Here, we combine and simplify the models for the IAS and EAS diffusion spectra and compare predictions with simulated spectra over a range of packing geometries as well as measured spectra from corpus callosum specimens.

Model The IAS and EAS are modeled as two non-exchanging compartments with signal attenuation spectra $E_{\text{int}}(\omega)$ and $E_{\text{ext}}(\omega)$. The effective total spectrum due to both compartments is given by Eqs. 1–2, where f_{int} is the axon volume fraction. $E_{\text{int}}(\omega)$ is the volume-weighted mean across the attenuation spectrum of each axon with radius R_{int} (Eqs. 3–4), where $D(\omega)$ is the diffusion spectrum of particles within an impermeable cylinder[1] and F the radius distribution with mean $\mu_{R_{\text{int}}}$ and SD $\sigma_{R_{\text{int}}}$. $E_{\text{ext}}(\omega)$ is calculated similarly (also Eqs. 3–4) for each EAS "pore" with radius R_{pore}, where $D(\omega)$ is the EAS diffusion spectrum[2] and F the radius distribution with mean $\mu_{R_{\text{pore}}}$ and SD $\sigma_{R_{\text{pore}}}$. We expect this model to be over-parameterized if a relationship between R_{int} and R_{pore} were not assumed since the IAS and EAS coexist in the same space and, in this idealized model, are the only compartments. Randomly packed axons were simulated over a wide range of size distributions to establish empirical relationships between the parameters of the EAS and IAS, leading to model simplifications (Eqs. 5–6).

IAS and EAS Diffusion Spectrum Model

$$D(\omega) = -\frac{1}{b}\ln E(\omega) \quad [1]$$

$$E(\omega) = f_{\text{int}}E_{\text{int}}(\omega)+(1-f_{\text{int}})E_{\text{ext}}(\omega) \quad [2]$$

Attenuation Spectrum

$$E(\omega) = \int A(R)\exp[-bD(\omega)]dR \quad [3]$$

$$A(R) = F(R)R^2/\int F(r)r^2dr \quad [4]$$

Model Simplification

$$\mu_{R_{\text{pore}}} = 0.63p\cdot\mu_{R_{\text{int}}} \quad [5]$$

$$\sigma_{R_{\text{pore}}} = p\cdot\sigma_{R_{\text{int}}} \quad [6]$$

Methods Simulations: We conducted Monte Carlo simulations[3] of spins diffusing in and around parallel, impermeable, randomly packed cylinders with a gamma distribution of radii[4] and spanning a range of f_{int}. Cosine oscillating gradients from 2 Hz–1 MHz were applied perpendicular to the cylinder axes with b = 1 ms/μm^2. The simulations used a free diffusion coefficient D_f of 2 μm^2/ms and no noise was added. Eqs. 5–6 were found to agree well with simulated spectra. p is the fractional cylinder separation[2] given by $p = (f_{\text{int,max}}/f_{\text{int}})^{-1/2}$, where $f_{\text{int,max}}$ is the volume fraction under the tightest possible packing (determined numerically to be ~0.84 for the simulations). These simulations were compared to forward predictions of our analytic model (Eqs. 1–6). Experiments: Diffusion-weighted images of fixed porcine brain specimens from the genu, mid body, and splenium of the corpus callosum were acquired with a 9.4 T animal scanner (Varian, Inc., Yarnton, UK) using a spin echo sequence with linescan readout. A PGSE scan (Δ/δ = 59/1 ms) and OGSE scans from 29–304 Hz (30 ms waveform duration) were performed with b = 0.6 ms/μm^2 and gradients parallel and perpendicular to the axons. The other parameters were: TE = 74 ms, field of view = 20 mm × 20 mm, slice thickness = 1 mm, matrix = 64 × 64, and averages = 9. The TR was varied linearly between 1200 ms at the lowest gradient frequency to 4600 ms at the highest to reduce gradient heating. The model parameters f_{int}, EAS tortuosity λ, $\mu_{R_{\text{int}}}$, and $\sigma_{R_{\text{int}}}$ were fitted using Bayesian techniques to the diffusion spectra measured perpendicular to the axons. R_{int} was assumed to be a gamma distribution and D_f to be $D(\omega)$ measured parallel to the axons at the highest frequency.

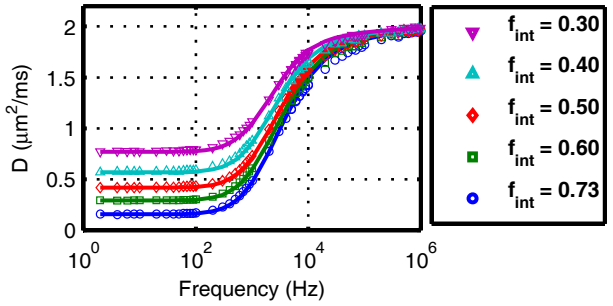

Fig. 1: Axonal diffusion spectra from simulations (markers) and model predictions (lines) over a range of packing densities.

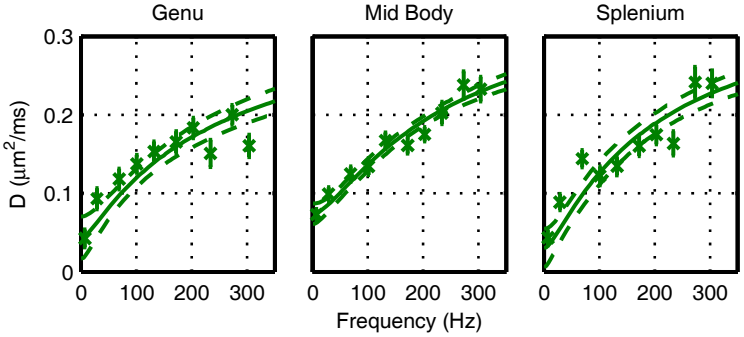

Fig. 2: Diffusion spectra measured (markers) perpendicular to axons in specimens and the means (solid lines) and SD (dashed lines) of the fitted posterior distributions.

Results & Discussion Axonal diffusion spectra from simulations and model predictions are shown in Fig. 1 and demonstrate good agreement across a range of f_{int}. Measured and fitted diffusion spectra of the specimens are shown in Fig. 2 (PGSE data are plotted at 7 Hz). The fitted parameters are given in Table 1. The data are broadly in agreement with literature values. Although λ could in theory be calculated from $D(\omega \approx 0)$ (i.e., the PGSE measurement) instead of being fitted, this was found to significantly decrease the fitted f_{int} to ~0.5–0.6. This could be due to violations of the parallel or impermeable axon assumptions. In addition, $D(\omega)$ measured parallel to the axons was unexpectedly not constant across frequency, indicating hindered diffusion and consistent with literature[6]. This could also be due to axon orientation dispersion. Ultimately, the model presented may enable one to quantify axonal packing and radius distribution properties. However, measurements remain challenging due to the need for measurements at high frequency (~kHz).

Specimen		f_{int}	λ	$\mu_{R_{\text{int}}}$ (μm)	$\sigma_{R_{\text{int}}}$ (μm)
Genu	Fit	0.78 ± 0.07	2.1 ± 1.8	0.33 ± 0.21	0.30 ± 0.06
	Lit.	0.74 ± 0.01	1.8 ± 0.2	0.55	0.24
Mid Body	Fit	0.74 ± 0.04	1.2 ± 0.1	0.62 ± 0.22	0.31 ± 0.08
	Lit.	0.74 ± 0.01	-	0.72	0.42
Splenium	Fit	0.80 ± 0.08	2.7 ± 2.2	0.56 ± 0.29	0.34 ± 0.10
	Lit.	0.74 ± 0.01	2.0 ± 0.2	0.63	0.28

Table 1: Model parameters from fits and literature[4–6].

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References: [1]Stepišnik Physica B 1993. [2]Lam MRM 2014. [3]Cook ISMRM 2006. [4]Aboitiz Brain Res 1992. [5]Vořišek J Neurophysiol 1997. [6]Aggarwal MRM 2012.