VALIDATION OF EXTRA-AXONAL DIFFUSION SPECTRUM MODEL WITH FREQUENCY-DEPENDENT RESTRICTION

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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. Recently, a model for the diffusion spectrum hindered diffusion around randomly packed cylinders was presented[2] enabling one to calculate the diffusion spectrum for the extra-axonal space (EAS), but it was not validated by physical measurement. Here, we compare measured diffusion spectra from an EAS phantom[3] to simulations and model predictions.

Model The model considers EAS water to be "exchanging" between regimes of restricted diffusion (when trapped in the spaces between cylinders) and free diffusion (when diffusing through gaps, with free diffusion coefficient D_{f}). This two-component (restricted and free) rapid exchange model is given by Eqs. 1–7, where the fraction of time spent in each regime depends on tortuosity λ (free fraction $f_{\mathrm{f}} = 1/\lambda^2$). The restricted compartment is modeled as an impermeable cylinder with diffusion spectrum[1] $D_{\mathrm{cyl}}(R(\omega),\omega)$ and apparent radius $R(\omega)$, which smoothly transitions from R_0 at low ω to R_∞ at high ω (Eqs. 4–7). At low frequencies, molecules fully sample the space and R relates to the mean distance R_{pore} between the pore centroid and perimeter. For randomly packed cylinders, R_{pore} is a distribution. At high frequencies, the spins remain close to their initial positions, and R is primarily driven by the pore surface-to-volume ratio S/V. R is modulated by λ and fractional cylinder separation p (Eqs. 5–6). $p = (f_{\mathrm{int,max}}/f_{\mathrm{int}})^{-1/2}$, where f_{int} is the cylinder volume fraction and $f_{\mathrm{int,max}}$ is that under the tightest possible packing.

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

$$E_{\mathrm{ext}}(\omega) = \int A_{\mathrm{ext}} \exp\{-b[f_{\mathrm{f}}D_{\mathrm{f}} + (1-f_{\mathrm{f}})D_{\mathrm{cyl}}(R(\omega),\omega)]\} dR_{\mathrm{pore}} \quad [2]$$

$$A_{\mathrm{ext}} = F_{\mathrm{ext}}R_{\mathrm{pore}}^2 / \int R_{\mathrm{pore}}^2 dR_{\mathrm{pore}} \quad [3]$$

$$R(\omega) = (R_0 - R_\infty)\exp(-\omega/\omega_{\mathrm{d}}) + R_\infty \quad [4]$$

$$R_0 = R_{\mathrm{pore}}(1 - 1/\lambda^2)p^2 \quad [5]$$

$$R_\infty = 3(S/V)^{-1}(1 - 1/\lambda)p \quad [6]$$

$$\omega_{\mathrm{d}} = 2\pi(2D_{\mathrm{f}}/R_0^2) \quad [7]$$

Methods Experiments: Diffusion-weighted images of the phantom (consisting of ~50,000 parallel solid fibres[3]) were acquired with a 9.4-T animal scanner (Varian, Inc., Yarnton, UK) using a spin echo sequence with linescan readout. A PGSE scan ($\Delta/\delta = 79/1$ ms) and OGSE scans from 22–350 Hz (40 ms waveform duration) were performed with $b = 0.5$ ms/μm^2 and gradients parallel and perpendicular to the axons. The other parameters were: field of view = 20 mm × 20 mm, slice thickness = 5 mm, matrix = 64 × 64, and averages = 2. The TR was varied linearly between 1200 ms at the lowest frequency to 4600 ms at the highest to reduce gradient heating. Experiments were performed at two TE values, 90 and 110 ms, to investigate possible eddy current effects. The R_{pore} distribution was assumed to be gamma variate with mean $\mu_{R_{\mathrm{pore}}}$ and standard deviation $\sigma_{R_{\mathrm{pore}}}$. The model parameters λ, $\mu_{R_{\mathrm{pore}}}$, $\sigma_{R_{\mathrm{pore}}}$, and R_∞ were fitted using Bayesian techniques to the diffusion spectra measured perpendicular to the axons. D_{f} was assumed to be $D(\omega)$ measured parallel to the axons. Simulations: We conducted Monte Carlo simulations[4] of spins diffusing around parallel, impermeable, randomly packed cylinders with a gamma distribution of radii (mean ± SD: 8.5 ± 1.3 μm)[5] and f_{int} matched to those of the phantom and averaged over eight trials. Cosine oscillating gradients from 2 Hz–1 MHz were applied perpendicular to the cylinder axes with $b = 1$ ms/μm^2. The simulations used $D_{\mathrm{f}} = 1.8$ μm^2/ms and no noise was added.

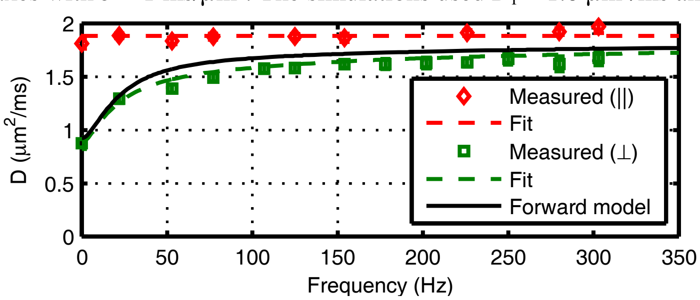

Fig. 1: Measured (TE = 90 ms; markers), fitted (dashed lines), and model predicted (solid line) diffusion spectra for the EAS phantom.

	$1/\lambda$	$\mu_{R_{\mathrm{int}}}$ (μm)	$\sigma_{R_{\mathrm{int}}}$ (μm)	R_∞ (μm)
Fit to experimental data				
TE = 90 ms	0.69 ± 0.02	8.1 ± 1.9	4.4 ± 2.5	3.9 ± 0.2
TE = 110 ms	0.67 ± 0.02	7.1 ± 2.2	5.1 ± 2.5	3.5 ± 0.2
Fit to mean of eight simulations				
	0.70 ± 0.01	9.9 ± 0.1	4.5 ± 0.2	6.3 ± 0.1
From segmentation of simulated geometry (assuming $1/\lambda = 0.7$ and $f_{\mathrm{int,max}} = 0.7$ to calculate R_∞)				
	-	8.2 ± 0.2	6.0 ± 0.4	5.6 ± 0.1

Table 1: Fitted and simulated values (mean ± SD) of the model parameters for the EAS phantom. 1/λ was calculated from $D(\omega = 0)$ and fixed before fitting the remaining parameters.

Results & Discussion Measured, fit, and model-predicted EAS spectra are shown in Fig. 1 demonstrating excellent agreement. $D(\omega)$ had outliers at four frequencies (see $D(\|)$ in Fig. 1) when diffusion gradients were applied parallel to the bore, likely due to mechanical resonances. $D(\omega)$ had artifacts consistent with eddy currents when diffusion gradients were applied along the readout direction, but not when applied along the phase encoding direction. The latter is shown as $D(\perp)$ in Fig. 1 and used for calculations. Model parameters from fitting to the measured and simulated diffusion spectra as well as those calculated from segmentation of the simulated geometry are listed in Table 1 and show reasonable agreement. In another abstract, we discuss how our EAS model can be merged with existing expressions for the intra-axonal space to provide a more accurate model of white matter microstructure.

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References: [1]Stepišnik Physica B 1993. [2]Lam MRM 2014. [3]Fieremans JMR 2008. [4]Cook ISMRM 2006. [5]Burcaw ISMRM 2013.