A MODEL FOR EXTRA-AXONAL DIFFUSION SPECTRA

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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[2]. While considerable attention has been given to intra-cellular compartments, hindered diffusion outside cells, such as the extra-axonal space (EAS), has received less attention[2]. Hindered diffusion is often assumed not to exhibit frequency dependence; however, simulations have recently demonstrated strong frequency dependence akin to restricted compartments[3]. Here, we present a model for the EAS diffusion spectrum and compare predictions with simulated spectra for a range of packing geometries.

Model The EAS is often characterized in terms of its "tortuosity" (λ), which reflects the packing geometry and density. For abutting cylinders (infinite λ), EAS water is trapped in restrictive pores, while looser packing (reduced λ) creates gaps between cylinders through which water occasionally diffuses. We can thus consider 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 in Eq. 1, where the fraction of time spent in each regime depends on tortuosity (free fraction $f_f = 1/\lambda^2$). The primary challenge, then, is to find a model for the "pores" between cylinders to describe the restricted component, $D_r(R,\omega)$. We propose to model this compartment as a restrictive cylinder with an apparent radius R that smoothly transitions from R_0 at low ω to R_∞ at high ω (Eqs. 2–5). At low frequencies, molecules fully sample the space, and the apparent radius relates to the mean distance between the pore centroid and perimeter, R_{pore}. At high frequencies, the spins remain close to their initial position, and the apparent radius is primarily driven by the surface-to-volume ratio (S/V). We empirically determined that this apparent radius is accurate if modulated by the tortuosity (λ) and fractional cylinder separation (p), as in Eqs. 3–4. The change in radius with frequency is inversely related to the diffusion time required to displace a distance R_0 ($\omega_d = 2\pi\tau^{-1}$, $\tau = R_0^2(2D_f)^{-1}$). For random packing, R_{pore} is given by a distribution and the diffusion spectrum is a weighted sum of the attenuation spectrum per pore. The expression for $D_r(R,\omega)$ is that of an impermeable cylinder[1].

$$D_{EAS}(\omega) = (1-f_f)D_r(R(\omega),\omega) + f_f D_f \quad [1]$$

$$R(\omega) = (R_0 - R_\infty)\exp(-\omega/\omega_d) + R_\infty \quad [2]$$

$$R_0 = R_{pore}(1 - 1/\lambda^2)p^2 \quad [3]$$

$$R_\infty = 3(S/V)^{-1}(1 - 1/\lambda)p \quad [4]$$

$$\omega_d = 2\pi(2D_f/R_0^2) \quad [5]$$

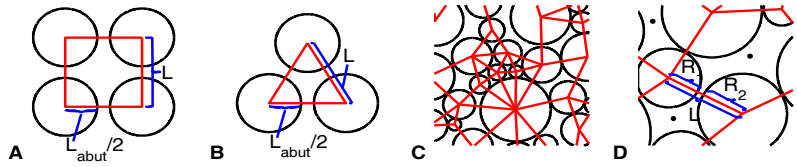

Fig. 1: Cross-section of square, hexagonal, and random packings (D is a magnified view of C). Actual cylinder distance (L) is related to the abutting case (L_{abut}) by $p = L/L_{abut}$. Pore boundaries are indicated by straight lines and pore centroids by dots. For random packing, L_{abut} for any given boundary is the sum of the radii (R_1 and R_2) of the two cylinders through which the boundary passes.

Methods We conducted Monte Carlo simulations[4] of spins diffusing around parallel, impermeable cylinders, including square, hexagonal and random packing (Fig. 1). Periodic (square and hexagonal) geometries covered p = 1–2 and ~0.1–10 µm. Random packing of a gamma distribution of radii[5] spanned a range of cylinder volume fractions (f_{cyl}). Oscillating gradients[6] from 2 Hz–1 MHz were applied perpendicular to the cylinder axes with b = 1000 s/mm^2. Simulations used D_f = 2 µm^2/ms and no noise was added. These simulations were compared to forward predictions of our two-compartment model for all geometries (Eqs. 1–5). For periodic packing, all model parameters can be calculated analytically from the cylinder geometry, while random packing requires a different approach, as follows. S/V was calculated analytically. Tortuosity is defined by the reduced diffusion distance under hindrance, and is thus calculated from the apparent diffusion at zero frequency: $\lambda^2 = D_f/D(\omega = 0)$. Distributions of R_{pore} and p were calculated numerically by segmenting the EAS using boundaries drawn between all cylinder pairs (Fig. 1C–D).

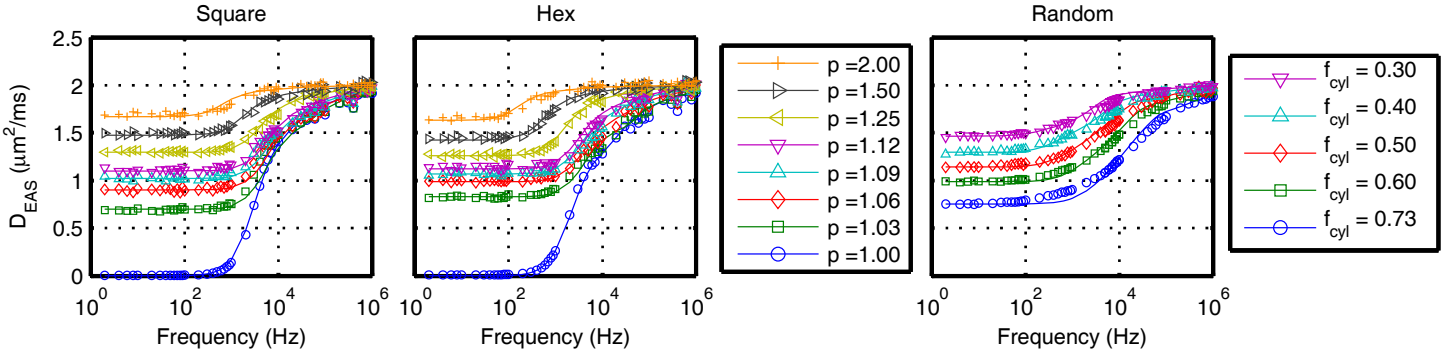

Fig. 2: EAS spectra demonstrating good agreement of model prediction (lines) with Monte Carlo simulations over a range of packing densities.

Results & Discussion Simulated EAS spectra are shown in Fig. 2 along with the model prediction, demonstrating remarkable agreement across a diverse range of packing geometries (an intermediate radius is shown, but results were similar at all radii spanning two orders of magnitude). The spectra exhibit a similar shape to restricted diffusion, but do not in general asymptote to zero diffusion at low frequencies, the one exception being the truly restricted spectra for abutting cylinders (p = 1). This model clearly improves on previous estimates of the EAS, which assume a flat spectrum (D_f/λ^2) that is only accurate at low frequencies. Our EAS model can be merged with existing expressions for the intra-axonal space to provide a more accurate model of white-matter microstructure. Ultimately, this approach 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), placing serious demands on gradient hardware.

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