MODELLING EXTRA-AXONAL DIFFUSION SPECTRA FOR OSCILLATING GRADIENT MEASUREMENTS

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Introduction Diffusion has enormous potential to probe tissue microstructure in a more interpretable manner than is currently feasible. One approach is based on the apparent diffusivity spectrum, which characterizes diffusion based on vibrational modes at different frequencies. This spectrum reflects the environment of the particles, in which boundaries to diffusion impart shape to the spectrum. Closed-form expressions exist for restricted diffusion within simple structures such as infinite cylinders (1), which have been proposed as a model for parallel axons (2). While considerable attention has been given to the intra-axonal compartment, hindered diffusion in the space between such structures has received less attention and is generally assumed *not* to exhibit frequency dependence. However, simulations have shown that diffusion in this space in fact bears a striking resemblance to the spectrum of restricted compartments. Here, two simple models for signal attenuation from diffusion in the space between periodically packed cylinders are proposed and their predictions are compared with spectra generated by Monte Carlo simulations.

Models Both approaches build on existing models for restricted diffusion within a cylinder, which is adapted to the concept of an "extra-cylinder radius". R_{extra} is calculated as the radius of a circle with area equal to the area of the space between cylinders (increasing with the separation between cylinders). Both models consider this radius as restricting for some particles, while others manage to diffuse beyond this radius; the models differ in how this behavior is encapsulated.

Model 1 This model consists of two compartments (Fig. 1a). The first compartment contains particles that diffuse in a cylindrical space of radius R_{extra}. The spectrum for these particles is given by Eq. [1], which is the traditional cylinder model modified to include a constant term to account for hindered diffusion (D_0, the diffusivity at $\omega = 0$). D_{free} is the free diffusivity and B_k and a_k are given in Ref. 1 for cylindrical geometry. The tortuosity α determines $D_0 = D_{free}/\alpha$ and is a function of the cylinder volume fraction and packing type (3), with $\alpha = 1$ in the case of free diffusion and $\alpha \to \infty$ for pure restriction. The fraction of particles $f_{cyl}(\omega)$ within the cylindrical compartment is given by the probability of diffusing a distance up to R_{extra} during one period of frequency ω (Eq. [2]). The second compartment experiences hindered diffusion that is constant across all frequencies. The diffusion attenuation $E(\omega)$ is that of each compartment weighted by the fraction of particles in each (Eq. [3]).

Model 2 This model consists of N nested cylindrical compartments with restricted diffusion and one with free diffusion. Conceptually, particles that diffuse into adjacent compartments are treated as having a larger extra-cylinder radius (circles in Fig. 1b). Each cylinder is characterized by the diffusion spectrum for a restricted cylinder of that radius (i.e., Eq. [1] with $D_0 = 0$). The innermost cylinder has radius $R_1 = R_{extra}$ and subsequent cylinders have radii that are multiples of the pore-to-pore spacing. Using $r_{free}(\omega) = \sqrt{(2D_{free}(2\pi/\omega))}$ as the mean path length of a particle over time ω^{-1}, then $C_n(\omega) = 1 + [r_{free}(\omega) - R_n]/(2R_n)$ is the number of times a particle can travel between the center and edge of a compartment. Using $1/\alpha$ as the probability that a particle will escape past the radius of the current compartment in any given "collision" with its boundary, then Eq. [4] gives the probability that a particle will stay in compartment n after travelling a path length $r_{free}(\omega)$. The number of compartments N is given by the number of compartments that can be traversed by particles with the longest oscillatory period. The remaining particles experience free diffusion (Eq. [5]). As above, $E(\omega)$ is the signal attenuation of each compartment weighted by the fraction of particles in each (Eq. [6]).

$$D_{cyl}(\omega) = D_0 + \sum_k B_k \frac{a_k (D_{free} - D_0)\omega^2}{a_k^2 (D_{free} - D_0)^2 + \omega^2} \quad [1]$$

$$f_{cyl}(\omega) = \frac{2}{\sqrt{4\pi D_0 (2\pi/\omega)}} \int_0^{R_{extra}} e^{-\frac{x^2}{4\pi D_0 (2\pi/\omega)}} dx \quad [2]$$

$$E_{model\,1}(\omega) = f_{cyl}(\omega) e^{-bD_{cyl}(\omega, R_{extra})} + [1 - f_{cyl}(\omega)] e^{-bD_0} \quad [3]$$

$$f_n(\omega) = \left(1 - \frac{1}{\alpha}\right)^{C_n(\omega)} - \sum_{k=1}^{n-1} f_k(\omega) \quad [4]$$

$$f_{free}(\omega) = 1 - \sum_{n=1}^{N} f_n(\omega) \quad [5]$$

$$E_{model\,2}(\omega) = \sum_{n=1}^{N} f_n(\omega) e^{-bD_{cyl}(\omega, R_n)|_{D_0=0}} + f_{free}(\omega) e^{-bD_{free}} \quad [6]$$

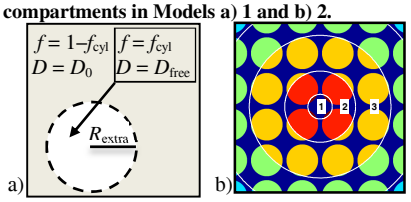

Fig. 1: Schematic representations of the compartments in Models a) 1 and b) 2.

Simulation Monte Carlo simulations in Camino (4) were used to generate the signal attenuation from water diffusing between parallel, impermeable cylinders. Cylinders of radius 1 µm were arranged in square and hexagonal lattices separated by distance L = 2.00–2.24 µm (5). Camino was used to simulate signal for cosine-modulated oscillating gradients (6) from 2 Hz–1 MHz (perpendicular to the cylinder axes). Sufficiently long gradient durations were chosen in order that each gradient would sample the diffusivity spectrum closely around one frequency. The gradient amplitude was adjusted such that each gradient had b = 1000 s/mm^2.

Results The simulated and predicted signal attenuations are shown in Fig. 2 (× markers and lines, respectively). For abutting cylinders (L/R = 2), the RMS error is 2.6% for the square lattice and 7.3% for the hexagonal lattice (same prediction from each model). This discrepancy is likely due to the use of a cylindrical model for non-cylindrical pores. In the case of non-abutting cylinders (L/R > 2), the RMS error is 1.9–3.0% for Model 1 and 3.1–5.3% for Model 2. The predictions for non-abutting cylinders by Model 2 have an offset from simulations for low gradient frequencies where a large number of compartments n is required.

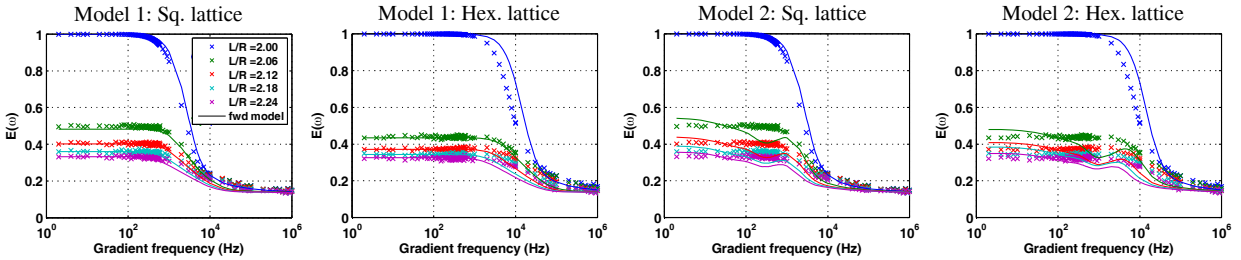

Fig. 2: Simulated and predicted signal attenuation from hindered diffusion between periodically packed, parallel cylinders.

Discussion Our goal is to provide a simple, empirical description of diffusion in a highly structured, hindered space by building on established theory of restricted diffusion. The ideal model would capture the relevant features of the spectra: a similar shape to restricted diffusion but including signal attenuation at low frequencies, which does not occur under true restriction. Indeed, other models that fail to account for these features cannot provide a reliable estimate of the extra-axonal volume fraction. It would additionally be gratifying for such a model to correspond to an intuitive and simple geometric picture of diffusion between a series of inter-connected "pores". The two-compartment hindered model provides superior agreement with the simulated signal behavior and is relatively simple; however, we have been unable to provide a clear interpretation of the source of the offset term D_0 in Eq. [1]. By comparison, the nested cylinder model is arguably a more intuitive picture of the process of diffusion, but in its current form it is less successful at describing signal behavior. Future work will aim to resolve these shortcomings. Finally, it is not clear how feasible estimates of brain tissue will be given the high frequencies required to cover the salient features of the diffusion spectrum (~kHz).

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