MEASUREMENT OF POST-MORTEM BRAIN MICROSTRUCTURE USING A CLINICAL MR SCANNER WITH OSCILLATING GRADIENTS

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Introduction Diffusion of water molecules in the presence of restricting boundaries reduces the apparent diffusion rates if the boundary geometry is of a similar order of magnitude to the diffusion distance. The ability to use this property to estimate the underlying restrictive geometry has long been recognized, for example, to yield estimates of axon diameter in white matter (1). While early approaches used standard gradient pairs, oscillating gradients at a particular frequency ω have also been proposed to estimate pore geometry (2). For example, cosine- and sine-modulated oscillating gradients have been explored, and the former has been used to measure intracellular diameter (3). The theory underlying oscillating gradient experiments predicts that the diffusivity of completely restricted spaces approaches zero at ω = 0, while hindered, but non-restricted, extracellular spaces have a finite diffusivity. We begin by considering simulations of these two compartments to understand their frequency dependence, which is poorly understood for the extracellular space. This motivates the combination of oscillating gradient waveforms and a modified signal model for estimating intra- and extra-cellular spaces. We present results in a post-mortem brain using a clinical scanner, suggesting the feasibility of in vivo measurement.

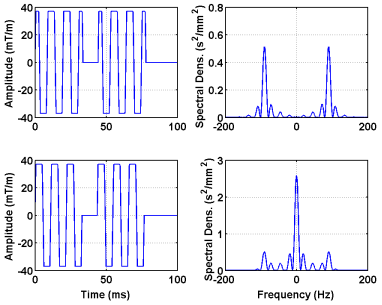

Fig. 1: Cosine- and sine-like diffusion-weighting gradients (left) and the spectral densities of their integrals (right).

Methods *Simulations*: Camino (4) Monte Carlo simulations were used to generate diffusion-attenuated signals inside and outside of square-packed, non-abutting cylinders with impermeable walls. Simulations of cylinders with 10 and 3 μm radii with 20.6 and 6.18 μm separation, respectively, were performed. Cosine-modulated oscillating gradients with frequencies of 4–600 Hz were simulated perpendicular to the cylinder axis. The signals were converted into diffusivity D using $D = -1/b \cdot \ln(S/S_0)$ where b is the diffusion weighting and S and S_0 are the simulated signals with and without diffusion weighting, respectively. Eq. [1] is a modification of an existing analytic model (2) for the intracellular diffusivity spectrum. Eq. [1] was used to fit both the intracellular diffusivity spectra $D_I(\omega)$ and extracellular diffusivity spectra $D_E(\omega)$. B_k and a_k depend on geometry (as in Ref. 2) except that the radius in B_k and a_k now refers to an effective intracellular radius R_I or extracellular radius R_E. D_{offset} is the diffusivity at ω = 0 (zero for $D_I(\omega)$). D_∞ is the asymptote and equivalent to the free diffusivity of water D_{free} for $D_I(\omega)$. *Experiment*: Diffusion-weighted sequences with cosine- and sine-like gradients (Fig. 1) were implemented on a 3 T MR scanner. Eight coronal slices centered on the splenium of a perfusion-fixed macaque brain were acquired using an 11" loop surface coil with FOV = 96 × 96 mm, thickness = 1.5 mm, TE/TR=150/1800 ms, 64 × 64 matrix, 63 averages, and four b = 0 scans. Oscillating frequencies for cosine were 18.3, 20.0, 45.0, 50.1, 55.0, 60.2, 63.9, and 90.0 Hz and for sine, 18.3, 20.0, 85.0, 90.0, and 91.0 Hz. The maximum number of oscillations was limited by the TE. The diffusion attenuation in an ROI containing only the splenium was fit to Eq. [2] and [3]. ν_I is the intracellular volume fraction, $b_{cos}(\omega)$ and $b_{sin}(\omega)$ are the diffusion weightings of the cosine- and sine-like diffusion gradients, and $D_I(\omega)$ is the intracellular diffusivity spectrum from Ref. 2. $D_I(\omega)$ includes the unknown intracellular effective radius R_I and free diffusivity of water D_{free}. $D_E(\omega)$ includes the unknown extracellular effective radius R_E, D_{offset}, and D_∞ as given in Eq. [1]. All fitting was done using Matlab.

$$D(\omega) = D_{offset} + \sum_k B_k \frac{a_k (D_\infty - D_{offset})\omega^2}{a_k^2 (D_\infty - D_{offset})^2 + \omega^2} \quad [1]$$

$$E_{cos}(\omega) = S_{cos}/S_0 = \nu_I e^{-b_{cos}(\omega) D_I(\omega)} + (1-\nu_I) e^{-b_{cos}(\omega) D_E(\omega)} \quad [2]$$

$$E_{sin}(\omega) = S_{sin}/S_0 = \nu_I e^{-b_{sin}(\omega) D_I(\omega)} + (1-\nu_I)\left[e^{-b_{sin}(0) D_E(0)}\, e^{-b_{sin}(\omega) D_E(\omega)}\right] \quad [3]$$

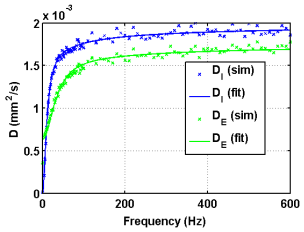

Fig. 2: Simulated and fitted diffusivity spectra for cylinders with R_I = 10 μm.

Results *Simulations*: Both the intracellular and extracellular diffusivity spectra provided an excellent fit to the simulations (Fig. 2). For cylinders with 10 μm and 3 μm, Eq. [1] estimated intracellular effective radii R_I of 9.8 and 3.0 μm, respectively, and extracellular effective radii R_E of 4.3 and 1.32 μm, respectively. Circles inscribed in the extracellular space would have radii of 4.6 and 1.37 μm, respectively, consistent with the fit values. *Experiment*: The fitting (Fig. 3) to Eq. [2] and [3] returned values of ν_I = 0.60, R_I = 9.5 μm, R_E = 5.4 μm, $D_{free} = 0.65 \times 10^{-3}$ mm²/s, $D_{offset} = 3.7 \times 10^{-3}$ mm²/s, and $D_\infty = 8.6 \times 10^{-3}$ mm²/s. These values are in broad agreement with known intracellular volume fraction (0.7–0.8) and free water diffusion ($D = 2.0 \times 10^{-3}$ mm²/s), although the axon diameters are larger than expected from histology (~1 μm).

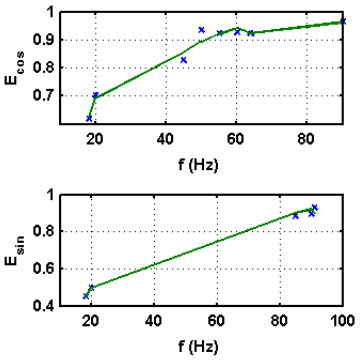

Fig. 3: Diffusion attenuation of measured and fitted values for cosine- (top) and sine-like (bottom) diffusion gradients.

Discussion We demonstrate the estimation of intracellular volume fraction, radius and effective radius of the extracellular compartment (related to packing density) using a novel set of cosine and sine oscillating gradient measurements. The fitted values for ν_I, R_I, R_E, and D_{free} are broadly consistent with those of fixed white matter measured with conventional techniques on high-performance pre-clinical scanners, as well as being consistent with our simulated diffusion spectra for the separate compartments. The diameter estimates are higher than expected based on histology, which is a general trend in reported measurements due to long diffusion times. D_{offset} likely relates to the tortuosity of the extracellular space and is similar to the tortuosity term in the intracellular model (2); however, we were unable to obtain reasonable fits of this model to our simulated extracellular signal curves. The oscillating gradients in our experiment utilize trapezoidal approximations to maximize the diffusion weighting while mainly preserving the frequency content. The gap in measurement frequencies in the sine-like gradients (Fig. 3) were due to spectral side lobes that make a single frequency assignment inappropriate. The fitted line does not contain any points in the gap since the fitting is dependent on the b-value at each measurement frequency. Future work will consider methods to attenuate these side lobes through careful design of the gradients and whether the combination of cosine and sine waveforms is critical.

Conclusions A model that fits the extracellular diffusivity spectrum of square-packed, non-abuttting cylinders was developed and validated with simulation. The combination of sine and cosine gradients provided sensitivity to the extracellular compartment at ω = 0. Values for intracellular volume fraction, effective intracellular and extracellular radii, and diffusivity spectra of the splenium of a post-mortem brain were acquired using a clinical MR scanner.

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