LONGITUDINALLY HINDERED DIFFUSION OF IN VIVO HUMAN WHITE MATTER AT LONG DIFFUSION TIME

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Introduction Conventional diffusion MRI provides exquisite sensitivity to tissue microstructure through models of restricted and hindered diffusion within and around axons, respectively. These models often idealize axons as parallel, infinite and impermeable cylinders, where diffusion is often assumed to be free along the direction of axons. However, quantification of the degree of diffusion hindrance parallel to axon bundles, or the permeability of axon walls, may be possible with measurements at a range of diffusion times longer than those in typical experiments. At longer diffusion times, spins have an opportunity to probe longer length/time scales. Here, we present long diffusion time measurements of in vivo white matter using stimulated echoes and compare the fitting quality of successively simpler models of the diffusion attenuation accounting for overfitting.

Methods Experiment: STEAM[1] was used to measure diffusion attenuation in five healthy adults (three males; mean age ± SD: 26 ± 3) using a 3-T clinical scanner (MAGNETOM Verio, Siemens AG, Healthcare Sector, Erlangen, Germany). A 32-channel head coil was used to acquire images containing the entire corpus callosum (≈ 50 min). A constant q (0.08 rad/μm), 30-diffusion-direction protocol was applied with $\delta = 20$ ms and $\Delta = 70, 100, 150, \ldots, 300$ ms. The q value was chosen such that the scans would have a mean b value of 0.9 ms/μm^2, which balances the needs for sufficient diffusion contrast and SNR. At each Δ, the TR (in the range 4.2-11.1 s) was chosen to minimize scan time. The other parameters were: TE = 63.2 ms, 30 slices, field of view = 190 mm × 190 mm, slice thickness = 2 mm, matrix = 96 × 96, partial Fourier factor = 6/8, GRAPPA ($R = 2$), and averages = 2. A diffusion tensor was fitted to each voxel with *dtifit*[2] using the direction-specific b values calculated from the full b matrices[3] (including the effect of the imaging gradients – significant at long Δ). Models: The diffusion attenuation for voxels with FA > 0.8 was fitted to several nested models of varying complexity (Table 1). The most complex was that of Stanisz et al.[4]: axons as parallel, prolate ellipsoids and glia as spheres with exchange between them and the extracellular space. The models were compared using the Bayesian Information Criterion (BIC), where smaller values indicate a more appropriate model given the data.

Model	Description	Free parameters
1	Ellipsoidal axons, spherical glia (permeable)	9
2	Ellipsoidal axons, spherical glia (impermeable)	7
3	Ellipsoidal axons (permeable)	6
4	Ellipsoidal axons (impermeable)	5
5	Infinite cylindrical axons (permeable)	5
6	Infinite cylindrical axons (impermeable)	4

Table 1: List of models ordered by decreasing complexity.

Results The measured ADC (FA > 0.8) of a representative subject is plotted in Fig. 1, showing that the ADC parallel to the axons exhibits a marked dependence on Δ and thus hindered diffusion, which is consistent with literature[5]. The BIC values for the models are plotted in Fig. 2. Although Models 1–3 have the lowest BIC values, their parameters displayed instability during fitting, suggesting Model 4 (Fig. 3) is the most appropriate. This model has five free parameters: the intra- and extra-ellipsoidal diffusion coefficients D_{int} and D_{ext}, respectively; ellipsoid minor and major axes $a(\perp)$ and $a(\parallel)$, respectively; and the ellipsoid volume fraction V. The measured and fitted diffusion attenuation for a representative subject is plotted in Fig. 4 and shows excellent agreement. The fitted model parameters are listed in Table 2 and largely display reasonable consistency across subjects and small uncertainties ($a(\perp)$ is driven by diffusion perpendicular to the axons and its accurate estimation requires higher q values than those used). Although we used measurements at long Δ, the exchange parameters had unstable fits and are only expected to be constrained at higher b values[4].

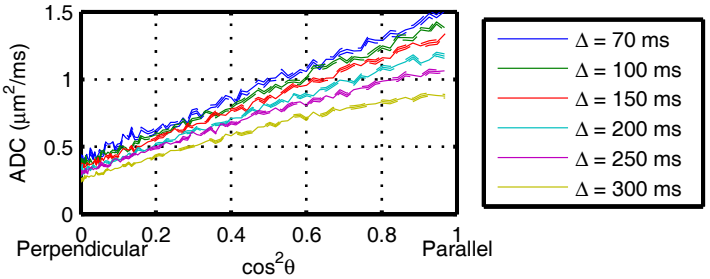

Fig. 1: ADC versus the squared cosine of the angle θ between the diffusion direction and the principal diffusion direction for a representative subject.

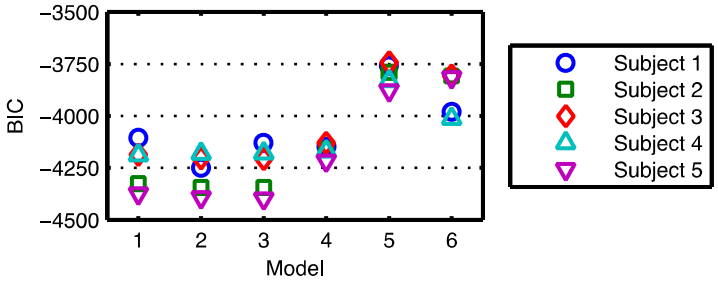

Fig. 2: BIC values of the models in Table 1.

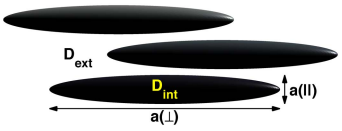

Fig. 3: Schematic of Model 4.

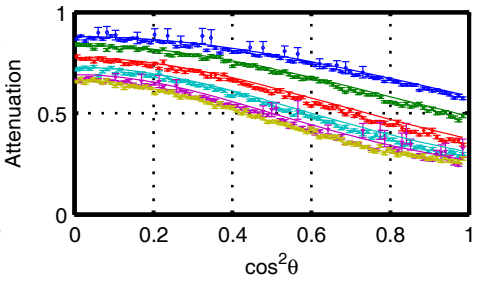

Fig. 4: Attenuation measured (markers) and fitted (lines) to Model 4 for a representative subject. The legend is as in Fig. 1.

Subj.	D_{int} (μm²/ms)	D_{ext} (μm²/ms)	$a(\perp)$ (μm)	$a(\parallel)$ (μm)	V
1	1.13 ± 0.11	1.72 ± 0.06	0.5 ± 0.4	57.4 ± 3.4	0.53 ± 0.01
2	1.35 ± 0.03	2.29 ± 0.08	4.0 ± 1.2	45.9 ± 0.6	0.63 ± 0.01
3	1.55 ± 0.06	2.05 ± 0.03	5.4 ± 1.1	40.3 ± 0.4	0.59 ± 0.00
4	1.33 ± 0.04	1.83 ± 0.05	0.7 ± 0.6	46.4 ± 0.9	0.55 ± 0.01
5	1.53 ± 0.03	1.84 ± 0.02	1.2 ± 0.7	42.2 ± 0.4	0.56 ± 0.00

Table 2: Parameters from fitting to Model 4.

Discussion Our major observation from these unique long diffusion time measurements is the dependence of ADC on the diffusion time along axons (much more than across them). This contradicts models that assume longitudinal free diffusion (e.g., white matter modeled as infinite parallel cylinders). An alternative model that does assume infinite cylinders could be one where the cylinders are not aligned and exhibit fanning. However, our calculations (not shown) indicate that at least 70º of fanning is necessary to produce greater Δ dependence parallel to the axons than perpendicular. This may appear excessive, but is consistent with findings from electron microscopy that axons in the mouse corpus callosum can fan with 80º[6]. This observation can also be due to the wiggling effect (i.e., microscopic fanning but macroscopically consistent axonal orientation). Future work will attempt to validate this idea using comparisons between long diffusion time measurements and microscopy in tissue samples.

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References: [1]Merboldt MRM 1991. [2]Smith NeuroImage 2004. [3]Sigmund NMR Biomed 2014. [4]Stanisz MRM 1997. [5]Burcaw ISMRM 2014. [6]Mikula Nat Methods 2012.