Monte Carlo Simulation of White Matter as a Composite Porous Medium

Gregory T Baxter[1] and Lawrence R Frank[1]
[1]*Radiology, UCSD, La Jolla, CA, United States*

Introduction Biological tissues are composed of complex cellular structures and multiple media. Diffusion-weighted (DW) MRI measures an apparent diffusion coefficient (ADC) which represents a bulk average, obscuring the effects of membrane permeability, structure tortuosity, and tissue heterogeneity. Theoretical models are only available for idealized tissues with simple geometries, generally omitting these complicating effects. Sen and Basser[1,2] developed a theoretical model for diffusion in white matter in the brain, representing the tissue as a composite porous medium. While the geometry remains simple—a periodic array of coated cylinders—the model includes distinct diffusion coefficients and concentrations for the axonal core, the myelin sheathing, and the surrounding bath medium. Their model gives the longitudinal and the transverse ADC in the long-time limit. The result for such a model in the context of diffusion tensor (DT) MRI remained an open question. Previously, Hwang et al.[3] demonstrated a finite-difference based simulation of arrays of coated cylinders, but they could only compare results to the theoretical models for diffusion confined entirely within a cylinder and for diffusion in an array of impermeable cylinders. We have reproduced the white matter model of Sen and Basser within a Monte Carlo diffusion simulator[4] to measure variations in ADC as the *b*-value, the diffusion time τ (Δ-δ/3), and the pulse width δ are modified, thus extending their results to incorporate realistic DT-MRI parameters typically used in human imaging studies.

Theory The composite porous medium model used here allows for different spin concentrations and diffusion coefficients in the axonal core, the myelin sheathing, and the surrounding bath medium. The diffusion characteristics of this model in the long-time limit are analogous to a similarly constructed problem in electrostatics, for which an analytical solution was developed by Nicorovici et al.[5], and Sen and Basser base their theoretical model on that result, representing the transverse effective ADC as a multipolar expansion. Here we are using the result truncated to third order. Sen and Basser give the longitudinal effective ADC as an average of the three diffusion coefficients, weighted by spin concentration and volume fraction. We adapted the numerical simulator used here[4], to allow particle transitions between media. To maintain the discontinuities of spin concentrations at the boundaries between media in a quasi-steady state, the flux from a medium with high concentration must be limited to match the flux from a medium with low concentration. We adjust the probability, *p*, of transition between regions to maintain quasi-steady state concentrations: transitions from regions of low concentration happen with $p = 1$ (completely permeable boundary), but transitions from regions of high concentration occur with probability $p = (C_l/C_h)\ \mathrm{sqrt}(D_l/D_h)$ (non-transmitted spins are reflected). We use the simulated signal *S* to compute ADC as $-\ln(S)/b$.

Simulations We use geometry and parameters similar to those used by Sen and Basser[1,2]. Our model incorporates periodic boundaries (at the dashed lines in Fig. 1) by storing locations in two coordinate systems: one relative to the boundaries (and periodic) and one absolute. This approach reduced the number of surfaces in the model while avoiding artifacts due to domain boundaries. The simulated hexagonal array of coated cylinders has an axonal core diameter $r_c = 6$ µm and cylinder spacing $L = 18.2$ µm. We varied the sheathing thickness from 0.2 to 3.0 µm: a thickness of 3.1 µm would be the maximum possible for hexagonally packed cylinders spaced and sized as described. We set the diffusion coefficient for the core, sheath, and bath regions to be $(D_c/D_s/D_b)$ = (7.5E-4/3.0E-5/2.0E-3) mm^2/s, and the relative concentrations for the three regions to be $(C_c/C_s/C_b)$ = (0.88/0.50/0.95). We calculated the longitudinal ADC, $D_{l,\mathrm{eff}}$, and the transverse ADC, $D_{t,\mathrm{eff}}$, for simulations with a *b* value of 1333 s/mm^2 ($1/D_c$) varying τ from 0.2 to 5 times r_c^2/D_c (9.6, 48, and 240 ms) but keeping a narrow pulse, with $\tau/\delta = 1200$. For the thickest sheath (3.0 µm), we simulated both permeable and impermeable membranes using clinically realistic pulse sequence values, fixing the gradient strength at 4 G/cm and keeping a short spacing between pulses (Δ-δ = 3 ms) over a range of *b* values (1000, 4000, and 8000 s/mm^2). Finally, we repeated these simulations with a lower concentration of spins in the sheath region ($C_s = 0.15$) which better matches the normal myelin water fraction (10-20%)[6].

Results The anisotropy, defined here as $D_{l,\mathrm{eff}}/D_{t,\mathrm{eff}}$, matches the analytical model[1,2] for long diffusion times, but shorter diffusion times (<= 48 ms) result in markedly decreased measured anisotropy for thick sheathing, as seen in Fig. 2. Models with impermeable membranes show lower anisotropy than models with permeable membranes (Figs. 3a & 3b). Simulations with permeable boundaries and a high sheath spin concentration exhibit less anisotropy than is usually found: the signal is anisotropic, but signal in the longitudinal direction is still significant even at the highest *b* value. Simulations using a lower sheath spin concentration (within the normal range for myelin water fraction) show more anisotropy, specifically exhibiting reduced signal in the longitudinal direction, giving the signal a more "peanut"-like shape, as seen in Fig. 3c.

Conclusion The Monte Carlo simulation method used here provides a means to test models of myelinated axons under clinically realistic DWI pulse sequences. We found that signal anisotropy matches the long-time limit model proposed by Sen and Basser when the diffusion time is long ($\tau = 5\ r_c^2/D_c$ = 240 ms) but is greatly reduced at shorter diffusion times (<= 48 ms): clinical scans using short diffusion times may not capture the full anisotropy of myelinated axons. For models with a thick myelin sheath and a high spin concentration in the sheath region, membrane permeability does not necessarily decrease anisotropy, but on the contrary can increase anisotropy: spins in the sheath region diffuse slowly and contribute significantly to the signal for a sheath spin concentration of 0.5. Models with a thick myelin sheath and a sheath spin concentration closer to the normal range result in the expected "peanut"-shaped DW signals. Increased myelin water fraction coincides with decreased anisotropy, even when myelin thickness remains fixed. These simulations show the care that must be taken when inferring tissue properties from DWI data.

References 1. Sen & Basser, Mag Res Im 23:(2005); 2. Sen & Basser, Biophys Jour 89:(2005); 3. Hwang et al., MRM 50:(2003); 4. Balls & Frank, MRM 62:(2009); 5. Nicorovici et al., Proc R Soc A 422:(1993); 6. Whittall et al., MRM 37:(1997).

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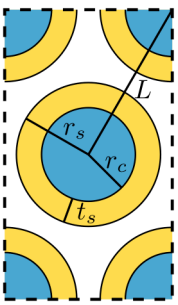

Fig. 1: Model geometry (periodic boundaries).

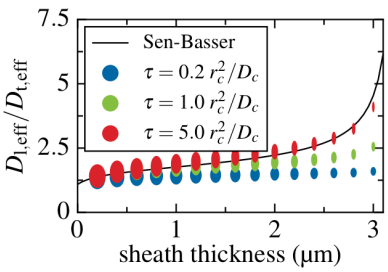

Fig. 2: Anisotropy vs. sheath thickness: measured anisotropy is reduced for short diffusion times.

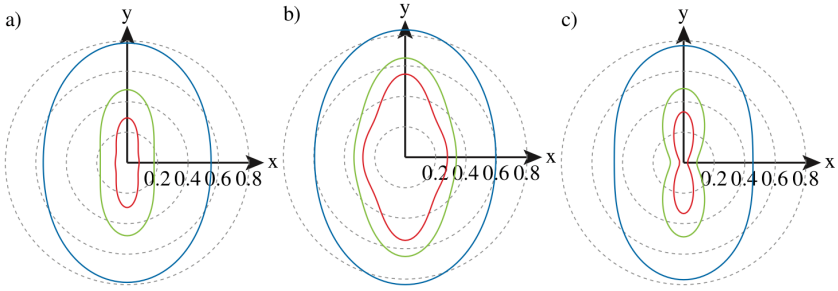

Fig. 3: a) Signal for simulations with high sheath spin concentration. b) Same, but with impermeable boundaries. c) Permeable boundaries and normal sheath spin concentration.