The Effect of Beading and Permeable Axons on Water Diffusion Properties: A Monte Carlo Simulation of Axonal Degeneration and Its Effect on DTI and Q-space Contrasts

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Introduction: Diffusion tensor imaging (DTI) studies in animal models of axonal degeneration have reported that diffusion is increased perpendicular (⊥), and decreased parallel (//), to damaged white matter (WM) fibers [1-2]. Q-space imaging (QSI) has also shown that ⊥ diffusion is near Gaussian whereas // diffusion is non-Gaussian in damaged WM [3]. We hypothesized that two mechanisms that may account for these observations are the beading and increased permeability of the axon membrane. Axonal "beading" is characterized by multiple constrictions and enlargements of the axonal membrane and has been reported after axon stretching [4] and transection [5], and in multiple sclerosis [6] and Alzheimer's disease [7]. Additionally, injury can increase the permeability of the axon membrane [8]. Understanding the relationship between axon morphology, permeability, and the diffusion weighted imaging signal is therefore a vital step in the validation of DTI and QSI and in its application to neurodegenerative disease. Previously, Monte Carlo (MC) studies have modeled WM damage by varying the radius, permeability, and packing of cylinders [9-11]; and recent MC simulations of axonal beading have only considered intra-cellular (IC) diffusion [12]. Here we investigate the effects of axonal beading and membrane permeability in a tissue model with intra (IC) and extra-cellular (EC) compartments, and compare the effects on DTI and QSI contrasts currently used to study WM damage.

Methods: The Brownian motion of 100,000 spins was studied via MC simulation, using the *RandomWalkSimulator* [13], on an infinite lattice (6x6x20μm cell) containing healthy axons (cylinders of radius R_{cyl}) or degenerating axons (the union of cylinders of radius R_{cyl} with spheres of radius R_{sph}). Based on indications from histology that axoplasm is shifted from constricting to enlarging portions of axons [4], beading axons were modeled by decreasing R_{cyl} (7 steps from 1.91 to 1.62μm) while increasing R_{sph} (from 0 to 2.97μm) accordingly to maintain a constant axon volume (IC/EC fractions = 0.64/0.36). The bead separation was 20μm, consistent with histology [4-7]. Spins were assigned random initial positions, and simulations were performed with a diffusion time of 20ms, time step Δt = 0.2μs, and diffusion constant D = 2μm^2/ms (step length $l = \sqrt{6D\Delta t} = 0.05\mu m$). The DWI signal was simulated by computing the phase dispersion over all spins (PGSE, T2=100ms). Experiments were performed with membrane permeability of P_m= 0, 0.1, 1, and 10 x10^{-2} cm/s, which corresponded to empirical residence times of $\tau_e = \infty$, 95, 9.5 and 0.95 ms within a cylinder (R_{cyl} = 1.91μm). This agreed with analytical predictions ($\tau_e = R_{cyl}/2P_m$). Diffusion was assessed ⊥ and // to the axon. **DTI:** Perpendicular ($D_\perp$) and parallel ($D_{//}$) diffusivity, and fractional anisotropy (FA) were computed at b =1000 s/mm^2. **QSI:** The probability density function (PDF) was generated from the histogram of spin displacements, and the probability of zero displacement (PZERO), root mean square displacement (RMSD), and kurtosis excess (KE) were computed [14].

Results: A) shows geometries for [R_{cyl}, R_{sph}] = [1.91, 0] and [1.62, 2.97] μm. **B)** as the 3D RMSD for free diffusion is large (15μm over 20ms) compared to the confining geometry, the PDF for ⊥ diffusion within impermeable cylinders agrees with the autocorrelation function (ACF) for cylindrical geometry. The EC component is low and broad, but is distinct from free diffusion due to tortuosity. Thus the PDF for ⊥ diffusion of all spins (IC&EC) is tall with a broad base. For // diffusion, the PDFs for IC, EC and IC&EC agree with free diffusion (not shown). Subsequent results are for IC&EC diffusion. **C)** shows that increasing P_m produces PDFs for ⊥ diffusion that are lower and broader than PDFs with P_m = 0. In the case of R_{sph} = 0, P_m has no effect on // diffusion. Axonal beading results in increased ⊥ diffusion (lower, broader PDF) and decreased // diffusion (tall and narrow PDFs) relative to the PDF observed with R_{sph} = 0 and equal P_m. Notably, increased P_m dampens the effect of beading on // diffusion. **D)** presents the relationship between morphological parameters (R_{sph}, P_m) and diffusion contrasts. $RMSD_\perp$ and $D_\perp$ increase as a function of R_{sph}, however larger shifts in ⊥ diffusion are produced by increased P_m. The downward trend of $RMSD_{//}$ and $D_{//}$ as a function of R_{sph} is enhanced by low P_m. FA showed a strong dependence on both P_m and R_{sph} (due to its summary of the difference between // and ⊥ diffusion). $KE_\perp$ did not change substantially over the range of R_{sph} tested in this model; however, non-Gaussian ⊥ diffusion (KE≠0) was preserved over a wide range of membrane permeability. Notably, non-Gaussian // diffusion was only evident at large R_{sph} and low P_m.

Conclusion: The effects of axon beading and increased membrane permeability on diffusion properties were simulated. Axonal beading and increased membrane permeability can act in concert to produce increased perpendicular diffusion. On the contrary, the decreased, non-Gaussian, parallel diffusion caused by beading is mitigated by increased permeability. Future simulations of diffusion in biologically relevant geometries may aid the development and interpretation of DTI and QSI studies of WM damage.

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