The Effect of Inflammation on DTI Derived Axial and Radial Diffusivity: A Monte Carlo Simulation Study

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Introduction:
Diffusion tensor imaging (DTI) has been successfully used to detect central nervous system (CNS) tissue injury. Increased radial diffusivity $\lambda_{\perp}$ and decreased axial diffusivity $\lambda_{||}$ have been used to detect demyelination and axon injury respectively. The presence of crossing fibers poses great difficulty to successfully apply DTI and directional diffusivity to detect white matter pathologies. Many novel diffusion MRI methods such as DSI, HARDI, and Q-Ball imaging, etc. have been proposed to resolve the complication of crossing fibers. One crucial yet less frequently discussed factor affecting all diffusion measurements is the axonal surroundings in physiological (partial volume effect of gray matter and CSF) or pathological (cell infiltration, edema, and axonal loss) conditions. To gain a better understanding of the surrounding environment on DTI measurements, a Monte Carlo (MC) simulation has been performed to model the impact of infiltrating cells, and edema on DTI derived $\lambda_{||}$ and $\lambda_{\perp}$ surrounding normal axon fibers.

Method:
In Silico Phantom: The space inside a sphere of 140 μm in diameter was defined as the random walk region (Fig. 1A). A bundle of 2-μm diameter 160-μm long axons arranged as a 10x10 square (i.e., a 20 μm × 20 μm fiber bundle) were simulated to allow the modeling of inter-fiber water diffusion (Fig.1C). The simulation temperature was 20º C leading to the average diffusion path length (with 40-ms diffusion time) of 13 μm. Thirty infiltrating cells with radius of 5 μm were distributed surrounding the axon fiber bundle (Fig. 1B). An isotropic image voxel of 80 x 80 x 80 μm^3 was selected at the center of the phantom (Fig.1 A).
Spin Random Walk: Similar to the previously reported study [1], $2.5x10^5$ spins were uniformly distributed in the 140-μm sphere (Fig. 1A). The stochastic spin motion was simulated as the conventional Brownian motion in the free space inside the sphere. At the boundary of axon fibers and infiltrating cells, the spin reflects elastically [1].
Simulated Spin Echo Sequence with Diffusion Weighting Gradient: A simple spin echo sequence with diffusion gradients (Fig.1D) was implemented to simulate the diffusion weighted MRI signals from the imaged voxel. A scheme of 99 distinct diffusion-weighting gradients expanding 3D grids was employed: [Gx,Gy,Gz] = [0,0,0], [1,0,0], [0,1,0], [1,0,0], [0,1,1], [1,0,1], [1,1,0], [1,1,1], … ,[3,0,0]. Maximal diffusion weighting factor b = 2000 (s /mm^2). TE=80ms, t_1^{--}=5ms, t_1^{+-}=35ms, t_2^{--} =45ms, t_2^{+-}=75ms,Δ= 40ms, δ=30ms.
Simulated Diffusion MRI signals for Different Configurations: The simulated diffusion MRI signals consist of three components (Fig. 1B): restricted anisotropic diffusion signals from axon fiber bundle (23%), restricted isotropic diffusion signal from infiltrating cells (45%), and hindered diffusion outside of the axon fiber bundle and cells within the image voxel (45%). We assume that there are no exchanges among the three components. Thus diffusion MRI signals from these components can be simulated independently and combined to examine four different scenarios of axonal surroundings mimicking CNS inflammation without axon or myelin injury: (1) Normal nerve bundle: Only the signal from axon fiber bundle analyzed; (2) Vasogenic edema + normal nerve: The signal from axon fiber bundle and hindered component combined and analyzed ; (3) Cell infiltration + normal nerve: The signal from axon fiber bundle and infiltrating cells combined and analyzed; (4) Cell infiltration +normal nerve + vasogenic edema: The signal from all three components and combined and analyzed.

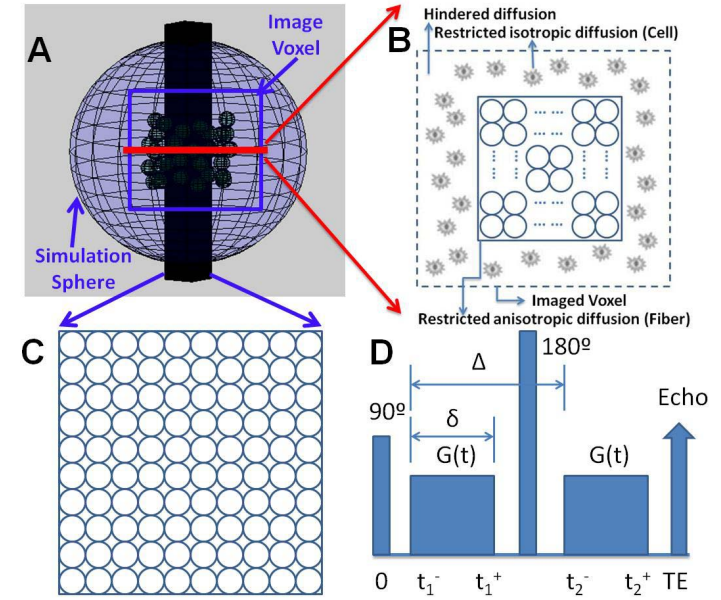

Figure 1. (A) Sphere for simulated random walk. (B) Cross sectional view of image voxel. (C) Cross sectional view of axon fiber bundle. (D) Diffusion weighted spin echo sequence timing diagram.

Results and Discussion:
Conventional DTI was applied to the simulated diffusion MRI signals under 4 different environments surrounding a normal axon fiber bundle (Table 1). The simulated DTI of the normal axon fiber bundle without extra outside signal served as the baseline. In the presence of vasogenic edema simulated as the increased diffusion weighted MRI signal originating from the hindered isotropic component with 66% of edematous water and 34% of normal fiber bundle $\lambda_{||}$ and $\lambda_{\perp}$ increased by 9% and 246% respectively. In the presence of infiltrating cells without edema with 58% of cells and 42% of axon fiber bundle, $\lambda_{||}$ and $\lambda_{\perp}$ decreased by 70% and 30% respectively. When both vasogenic edema and cell infiltration were present at 45% edema, 32% cells, and 23% axon fiber bundle, $\lambda_{||}$ decreased by 48% and $\lambda_{\perp}$ increased by 111%. The current simulation findings suggest that edema exerts significant effect in $\lambda_{\perp}$ resulting in significant overestimation of its value while cell infiltration imposes more profound effect on $\lambda_{||}$ resulting in significant underestimation of its value. Thus, it is likely vasogenic edema could lead to a false positive estimation of demyelination while cell infiltration will lead to false negative conclusion of axonal injury based on the DTI derived directional diffusivity. When both edema and cell infiltration coexist as commonly seen in CNS inflammation, the overall effect will largely dependent on the volume ration of each component. A more refined simulation has been pursued with graded volume ratios of each component to determine the extent of each component on the assessment of CNS white matter pathology as well as to identify the limit at which DTI derived directional diffusivity is still capable of correctly identifying axonal injury and demyelination.

Table1: DTI derived directional diffusivity and mean apparent diffusion coefficients in μm^2/ms

	Normal Axon Fiber	Normal Axon Fiber + Edema	Normal Axon Fiber + Cell Infiltration	Normal Axon Fiber + Cell Infiltration + Edema
DTI Axial Diffusivity $\lambda_{||}$	1.49	1.63	0.45	0.77
DTI Radial Diffusivity $\lambda_{\perp}$	0.26	0.90	0.18	0.55
DTI Mean ADC (MADC)	0.67	1.14	0.27	0.62

References:
[1] Chunlei L. Magnetic Resonance in Medicine 51:924–937 (2004)