An Open Source Monte Carlo Framework for Simulating Diffusion in Biologically Relevant Geometries including Broken, Crimped and Bulging Axons

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Introduction: The signal in diffusion weighted (DW) MRI experiments is exquisitely sensitive to tissue architecture on a micrometer scale. Yet, current contrasts, whether from diffusion tensor imaging (DTI), q-space formalism, high angular resolution diffusion imaging (HARDI) or other higher-order analysis methods, are non-specific for distinguishing between broad classes of pathological processes in white matter, especially when multiple types of damage may be concomitant (i.e., myelin loss, axonal loss, edema, inflammation, etc.). Determining whether it is possible to infer the specific mechanisms that underlie changes in the DW-MRI signal is an intense area of investigation and could lead to new modeling approaches for generating DW-MRI contrasts that are specific to particular white matter degeneration processes [1]. Yet, analytic models of restriction environments are only available for simple geometries (e.g., ellipsoids, plates, and cylinders) [2,3]. To date, simulations have been primarily restricted to ellipsoidal and cylindrical geometries (often in 2-D) due to complexity of modeling these compartments [4-5] and have rarely included the effects of T2 relaxation [6]. Here, we present an efficient, cross-platform 3-D computational framework for simulating diffusion in restriction compartments. The Random Walk Simulator software (RWS) is available in open-source through the Neuroimaging Informatics Tools and Resources Clearinghouse (www.NITRC.org: project name: "DW-MRI Random Walk Simulator") under the Lesser GNU Public License (LGPL). To demonstrate the utility of our approach and the vast potential for continuing exploration, we compare diffusion (and its impact on the DW-MRI signal) in broken, crimped, and bulging axons.

Simulation Framework: RWS is composed of an object oriented Monte Carlo simulator (written in Java, Sun Microsystems, Santa Clara, CA) and a simple front end for specifying the experimental design and rendering results (written in Matlab, MathWorks, Natick, MA). The simulator considers the interaction between the motion of individual, non-interacting particles (spins) and the boundaries of restriction compartments (which lie within an infinite rectangular lattice). Spin position may be initialized uniformly at random in a lattice block either inside all compartments, outside all compartments, or both. The compartments and the extra-compartmental space have independently defined unrestricted diffusivities (i.e., the diffusion coefficient in the absence of barriers, D) and transverse relaxation time constants (T2); compartments also have boundary permeabilities (P). To simulate diffusion, the simulator executes a finite, user defined time step (Δt) in which each spin selects a random direction and takes a step corresponding to $l = \sqrt{6D\Delta t}$. If a spin encounters a compartment boundary, the spin is either specularly reflected or transmitted according to the permeability of the boundary and the diffusivities on either side of the boundary (as to ensure no net flux across the boundary). RWS includes basic compartment geometries for spheres, cylinders, and arbitrary polyhedral meshes. Advanced compartment geometries may be generated by constructing the union, intersection, set difference, or affine transformations of existing basic or advanced geometries. The framework may be easily extended for new compartments by extending a compartment class. T2 signal loss for each spin is computed based on the relative proportion of time spent in each compartment, while spin phase change is calculated based on the net change in position (i.e., short pulse approximation). Ensemble magnitude and phase effects are computed by integrating T2 signal loss and phase changes over all spins.

Methods and Results: Four models of axon geometry were studied in a 20x10x10 μm lattice (**Fig. 1**): (a) healthy axon – a single infinite cylinder with a 1.5 μm diameter, (b) bulging axon – an infinite length of beads on a string with cylinder diameter of 1.5 μm and a spherical bulge diameter of 4 μm, (c) crimped axon – an infinite length of repeating crimp injuries with an axon diameters of 1.5 μm with two 4 μm sphere reducing the minimum diameter to 60% of the original, and (d) a broken axon – an infinite set of 15 μm cylindrical segments of 1.5 μm diameter separated by 5 μm. All compartments were impermeable with a diffusivity of 2 $\mu m^2/ms$ and T2 of 100 ms. 100,000 spins were initialized within each compartment and were studied for diffusion times of 2 ms and 20 ms with a time step of 1 μs. Simulations executed in approximately 650,000 spin-steps/s on a 2.5 GHz 64 bit computer. **Fig. 2A&3A** show the empirical probability distributions for diffusion parallel or perpendicular to the axis of the axon. **Fig. 2B&3B** show the excess kurtosis (a measure of non-Gaussianity) of each corresponding curve. To project these results to more familiar measures, **Fig. 2C&3C** show the fractional anisotropy that would be observed in a diffusion tensor imaging (DTI) experiment at a b-value of 1000 s/mm^2.

Discussion: We see that the empirical probability distributions (i.e., as would be observed with q-space or diffusion spectrum imaging) clearly disambiguate each axonal restriction environment from each other and from that of free diffusion. Furthermore, excess kurtosis and (to a lesser extent) fractional anisotropy can reveal these differences. These results could be used to investigate and design contrast mechanisms that maximize specificity and sensitivity to changes of biological interest using a minimum number of acquisitions. RWS could readily be extended (at the cost of additional computational complexity) to relax the short pulse approximations. Since the full system is available in open source, anyone may use or adapt this system for their particular needs. In summary, RWS enables efficient, quantitative comparison of diffusion in biologically relevant restriction geometries that are not analytically accessible. This simulation framework may aid in the interpretation DTI, q-space, and higher order DW-MRI methods as well as the optimized development of new higher order analysis techniques targeted at specific white matter injuries.

References: [1]Song SK, *et al*, NeuroImage 2003, 20:p1714. [2]Stanisz GJ, *et al*, MRM 1997, 37:p103. [3]Pfeuffer J, *et al*, NMR Biomed. 1998, 11:p19.[4]Fieremans E, *et al*, JMR 2008, 190:p189. [5]Hall M, *et al*. MICCAI/CDMRI 2008 p.9 [6]Balls G, *et al*. MICCAI/ CDMRI 2008 p.249. **Funding**: NIH/NCRR-P41RR15241