A Realistic DTI Simulation Environment

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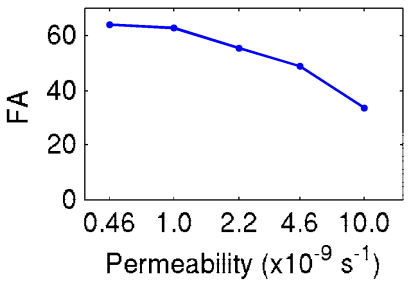
Introduction The sensitivity of MRI to the anisotropic diffusion of water within neural tissues provides some insight into the tissue structure. Spatial (diffusion tensor imaging, or DTI [1]) and spectral (q-space imaging [2]) variations of the diffusion weighted imaging (DWI) signal can be compared to the expected pulse signal response for simplified models of tissue structure. Analytical solutions are not available for structures with the complexity of real neural tissues, however. An alternative approach is to simulate the DWI experiment numerically, including diffusion, tissue effects, and the influence of the pulse sequence. Much work has already been done in this area, with simulations ranging from grid-based finite difference methods to smoothed particle hydrodynamics to Monte Carlo Brownian dynamics [3-7], but most simulations are limited to simplified tissue structures. We have created a computational environment capable of simulating the entire DTI experiment by embedding MCell, a sophisticated Monte Carlo simulator for cellular microphysiology, within an MRI simulator that tracks particle location, state, and signal amplitude and phase, and whose output is connected to a suite of analysis and visualization tools. The simulation environment is capable of modeling highly complex tissue structures, testing new pulse sequences, and developing new post-processing and analysis techniques. Here we demonstrate initial results testing the effects of fiber permeability and packing density on fractional anisotropy (FA).

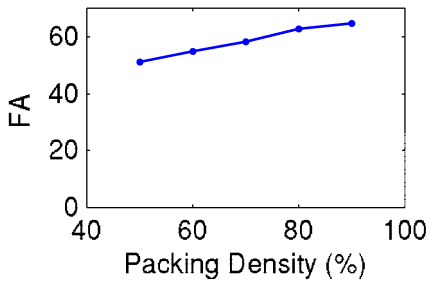
Monte Carlo Brownian Dynamics Simulator The Monte Carlo simulator MCell [8] was developed in the context of synaptic transmission and was designed to capture the stochastic effects of molecules interacting and reacting probabilistically according to reaction equations in highly complex geometries that possess the basic biophysical properties of real tissues. Geometries are modeled as polygonal surfaces, and these surfaces may reflect, transmit, absorb, or react with diffusing molecules. Multiple molecular species are allowed, each with its own diffusion constants. Particle locations and interactions are mediated by a ray-tracing algorithm that uses a binning method to reduce the number of polygons checked per ray-trace step. MCell is quite fast: a simulation with 1.25 million polygons can update over 150,000 particle locations per second on single-processor machines. With modifications added for our simulator, MCell can be run in parallel on multiple computers, allowing for even larger or faster simulations. Its flexibility allows for tissue models much closer to the complexity of real neural tissue, including biochemically-driven fluid flows.

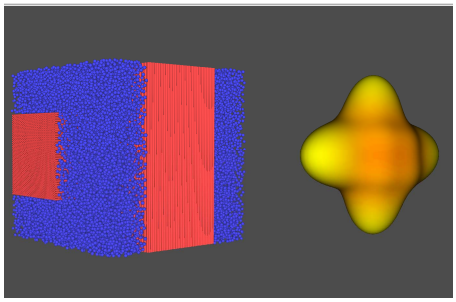
Tissue Simulation The interface to our simulator provides a way to create tubes around splines, packed together into fiber bundles. The user specifies diffusion coefficients for regions interior and exterior to the fiber, (corresponding to intra- and extra-cellular diffusion coefficients for white matter), the fiber packing density, and membrane permeability. The tissue generation tool can also create ellipsoidal cells in external or interstitial spaces. More complex geometries can also be generated by other methods (e.g. electron tomography [9]) and used as input to the simulation.

Pulse sequence simulation and MR signal generation The user interface allows the choice of the basic parameters associated with a standard DTI sequence (e.g. gradient strength, Δ, δ, voxel size, etc.) within a variety of pulse sequences. The b-value is calculated from these user inputs. The framework allows the flexibility to test a number of pulse sequences, from spin echo through general coherence pathway methods (e.g. hyperecho) diffusion weighted sequences or others specified by the user. The signal, *S*, is calculated by tracking each particle's location, *x*, generating the phase induced by its motion along the applied gradient directions G_j, and then averaging over all the spins in the voxel. For N_p particles and N_t timesteps of length *dt*, the signal is given by $S = (\sum_{N_p} \sum_{N_t} e^{i\gamma \vec{G} \bullet \vec{x} dt}) / (N_p N_t)$. This direct method will allow for the future inclusion of the effects of local field variations (such as those generated by local susceptibility changes due to blood oxygenation changes) and thus facilitates the study of diffusion-related signal changes in complicated physiological conditions. The simulator also incorporates a DTI analysis package, allowing the investigation of analysis methods for the difficult problem of high angular resolution DTI measurements in neural tissues.

Results and Conclusion For the results shown, we used the following parameters: G=4G/cm, Δ=60ms, δ=15.75ms, b=2003. The diffusion coefficient was set to 0.75×10^{-3} cm^2/s for both interior and exterior regions. Bundles were constructed of hexagonally packed straight fibers, with 1.2 μm diameter. Packing density was varied by adjusting the spacing between fibers. Signal was measured on a 100 μm^3 voxel centered in a 200 μm^3 simulated space, using 12 gradient directions oriented toward the vertices of an icosahedron. For our first simulation, fibers were packed to a density of 80%, and the permeability of the fibers was varied on a logarithmic scale from 4.6×10^{-9} s^{-1} to 2.2×10^{-8} s^{-1}. The calculated fractional anisotropy (FA) is shown below left. Next, keeping fiber permeability fixed at 1.0×10^{-9} s^{-1}, the density of the fibers was varied from 50% to 90% (near the maximum for hexagonally packed cylinders). The resulting FA is shown below center. Finally, crossing fiber bundles were simulated by filling 80% of the voxel volume, with half of the fibers oriented along the x-direction and half oriented along the y-direction and surrounding space filled with randomly oriented ellipsoidal cells with an average diameter of 2.0 μm. Permeability of both the fibers and the surrounding cells was set to 1.0×10^{-9} s^{-1}. The fibers and cells for this simulation are shown along with the resulting diffusion orientation transform (DOT) below right. Increasing permeability decreased FA, while increasing fiber density increased FA, as would be expected. Crossing fibers exhibit a crossed DOT.







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