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Simulation of the MRI Measurement of Diffusion in Realistic Neural Tissue Models

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Introduction In principle, the sensitivity of MRI to the diffusion of water in neural tissues provides a method for inferring local characteristics of the tissue structure and physiology by sampling the spatial (diffusion tensor imaging, DTI [1]) and spectral (q-space imaging [2]) variations of the diffusion weighted imaging (DWI) signal and relating this to a model of the signal behavior generated by a specific pulse sequence. Unfortunately, in practice the complexity of neural tissues precludes the formulation of analytical solutions for the DWI signal behavior, making investigation of diffusion in real neural tissues problematic. A promising approach to the problem is to numerically simulate the DWI experiment, including the construction of the tissue, the diffusion of water through the permeable membranes, and the influence of the pulse sequence. To date, this methodology has been primarily confined to analytical tissue models and grid based (i.e., finite difference) simulations [3]. Unfortunately, analytical tissue models have difficulty capturing the complexity of realistic neural tissues, and the simulation of fluid motion within more complex geometries by traditional grid-based methods is complicated by the computational complexity caused by the non-conformity of the tissue boundaries (individual fiber walls, inter-fiber spaces, cells, etc) and the computational grid. In this paper we describe a novel approach using Smoothed Particle Hydrodynamics (SPH) [4] in combination with ray tracing and complex tissue generation using parametric curves. Initial results in a standard geometry are shown to be consistent with theory.

SPH Theory SPH is a particle based method for solving the Navier-Stokes equations that simplifies the equations by assuming that particles have a limited region of influence that is described by an interpolating function $W(x,h)$ that allows the description of any function $A(x)$ in terms of its values at a set of arbitrary points defined by the neighboring particles: $A(x) = \int A(x')W(x-x',h)dx'$. The interpolating function is typically a Gaussian: $W(x,h) = (2h^2)^{-1/2} e^{-x^2/h^2}$ where the variance h defines the spatial scale of particle-particle interactions. Defining functions in terms of an interpolation kernel allows the construction of a differentiable interpolant function from its values at the neighboring particles. Our implementation is capable of solving the Navier-Stokes equations, each term in the N-S equations can be turned on or off separately, allowing investigation of separate effects (e.g., just diffusion) or the inclusion of additional physiological effects such as driven intercellular fluids. For the present study, however, we employed only a simplified diffusion model $x(p) = p \bullet x + v(p)t$ where the velocity $v(p)$ is that of Brownian motion.

Tissue Creation The geometry of neural tissues has a profound effect on the measured signal in diffusion weighted MRI, where the signal is an integral over the voxel volume. Because imaging resolutions (on the order of $3mm^3$) are typically much greater than the dimensions of neural fibers (approx 10um diameter), the signal averaging within a voxel combines the effects of the tissue geometry within any particular voxel. Restricted diffusion within a single neural cell produces anisotropic diffusion with the direction of highest diffusion along the neuron length. But within a typical voxel in human white matter there may be neurons pointing in several directions. Thus, while the diffusion is locally anisotropic, the diffusion weighted signal from the voxel, averaged over several neuron directions, can have an exceedingly complex structure. A primary goal of this study was thus to facilitate the generation of complex tissue geometries by building up fiber "bundles" from cylindrical structures packed together that possess curvature, one of the neural tissue properties known to exist but difficult to include in the standard DTI signal model. Moreover, individual fibers are separated by finite distances, thus creating an "inter-fiber" space that is extracellular and yet restricted, and has been implicated in the contribution to restricted diffusion DTI characteristics.

The creation of these multiple fiber bundles requires a computational organization capable of locally scaling the interactions in regions of high cell density. Octrees were employed to create hierarchically structured ellipsoidal "cells", within which are recursively generated additional internal structures that represent intercellular constituents. Ellipsoidal cross section "fibers" hierarchically organized into fiber bundles with user defined cross sectional area and fiber density. Fibers are generated using parametric curves using De Casteljau's algorithm which gives a numerically stable method of calculating the position along a Bezier spline. Parametric curves allow efficient generation of complex paths without the need for difficult triangle generation for individual surfaces. Moreover, they facilitate ray tracing complex geometries with little storage. An example is shown in Fig 1. The boundaries of the cells and fibers are permeable to a degree chosen by the user, as are the intra- and extra-cellular diffusion coefficients.

SPH Implementation Particles are stored in an octree to speed up the evaluation of the SPH kernels and allow neglect of intersections of distant surfaces. SPH simulation within this neural tissue model is complicated primarily by the requirement of satisfying the boundary conditions for permeability imposed by the complex geometry. The permeability is defined as the probability that a particle will pass through a surface of permeability P and normal $\boldsymbol{n}$. The necessity of determining how each particle's trajectory intersects with a functionally defined surface was solved

using the methods of ray tracing which allows that particle path, defined by its velocity, to be traced and thus determine its intersection with an arbitrary boundary in a similar fashion as the simulation of light through a dielectric.

Pulse sequence simulation and MR signal generation One of the great strengths of MRI is the ability to modulate the diffusion sensitivity of the diffusion weighted experiment by manipulation of the pulse sequence parameters. However, the effect of gradient strengths, durations, and separations, and the influence of radio-frequency (RF) pulses is difficult to assess in the presence of complex geometries. Therefore, the program includes not only the simulation of molecular diffusion, but the influence of the gradient and RF pulses as well, thereby allowing the user to construct and play out a variety of diffusion weighted pulse sequences in the presence of diffusion within the model neural tissue system. The user interface allows the choice of all diffusion imaging parameters (e.g., gradient strength, diffusion gradient sampling pattern, b, Δ, δ,), the imaging parameters (e.g., voxel size, SNR), the pulse sequence (e.g., spin echo). The phase of each particle generated by its motion along applied gradient directions is tracked and the resulting projection through the voxel generates the signal. The resulting signal is mapped onto the gradient sampling pattern to allow construction of the angular variations in ADC (relative to a reference sphere of b=0 [Fig 3]), which is then available to our DTI analysis routines [5].

Results and Conclusion The final particle distribution from an SPH diffusion simulation in a straight fiber bundle in a spin echo experiment with G=4G/cm, b=8300, Δ=100 ms, δ=10 ms is shown in Fig 2. The calculated ADC (Fig 3) from 162 diffusion encoding directions determined from spherical tessellations matches closely the "peanut" expected from anisotropic, single fiber diffusion [5], suggesting the efficacy of the SPH approach to the efficient and accurate simulation of diffusion in realistic neural tissue models. Future work will focus on the generation of more realistic tissue models, including the modeling of water transport across tissue boundaries, and parallel implementation of the code to allow the simulation of a more realistic number of diffusing water molecules.

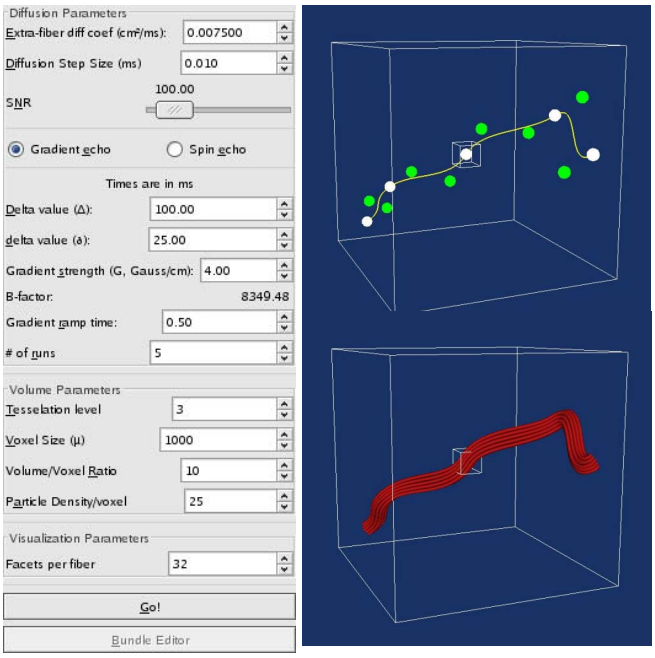

Fig 1: (Left) The diffusion and pulse sequence parameter interface. (Right) Fiber bundle generation along parametric curve

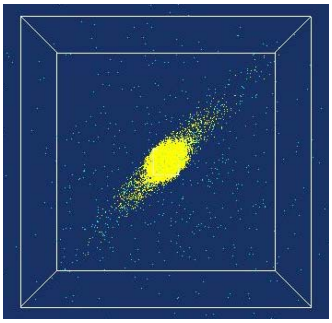

Fig 2: SPH simulation in straight fiber (not Fig 1)

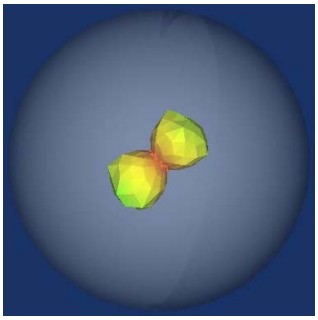

Fig 3: Peanut shape ADC consistent with theory

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