Inferring Axon Diameter Sizes using Monte Carlo Simulations and Oscillating Gradient Spin Echo Sequences

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Introduction Oscillating gradient spin echo (OGSE) sequences have been used to make measurements at short diffusion times[1-6]. OGSE probes the shortest possible diffusion time scales so that the transition from restricted to hindered diffusion within the smallest structures can be detected. Here we simulate a cylindrical geometry using OGSE sequences and AxCaliber[7] to determine the ability of the OGSE sequences to distinguish cylinder diameter distributions for small diameters and to understand better the physical factors affecting *ADC* measurements. We vary the frequency of the gradient ($f \sim 1/\Delta$) from very small to very large to approach free diffusion in the larger simulated axons.

Methods A Monte Carlo computer simulation was conducted using a gamma distribution of non-overlapping parallel cylinders surrounded by extracellular water (D_e = 2.5 μm^2/ms) with lattice periodicity. This geometry aims to model the axon environment in healthy white matter regions[8]. Figure 1 shows 100 non-overlapping parallel cylinders and an intracellular packing fraction of ~0.81. A cosine gradient spin echo sequence[3] was used to generate 400 signals with different cosine frequencies (from .05 to 10 kHz) and gradient strengths (from 0 to 72580 mT/m). Ten simulations were run back to back with 114688 particles and 42000 time steps. Gaussian noise with σ = .02 (SNR = 50) was added to both components of the transverse magnetization. The cylinders were impermeable and the water within the cylinders had D_i = 1.0 μm^2/ms. The simulations were programmed in CUDA C/C++ and run on a HP Z240 workstation containing a Intel® Xeon® Processor E5-1650 6-core 3.20GHz CPU. The HP Z240 workstation contained two graphics cards, a Tesla C2075 (Fermi 2.0) graphics card for dedicated CUDA computation and a Quadro 600 (Fermi 2.1) graphics card handling the display.

The mean signal was then fitted using χ^2 minimization to the AxCaliber analytical model for the signal[9]:

$$S = (1 - f_h)\sum_i \frac{D(r_i,\vec{\theta})r_i^2}{\sum_k D(r_k,\vec{\theta})r_k^2} e^{-\beta_i(r_i,D_{free})} + f_h e^{-bD_h},$$

where, r_i is the radius of the ith cylinder, $D(r_i, \vec{\theta})$ is the axon density distribution with parameter $\vec{\theta}$. f_h and D_h are the hindered packing fraction and hindered diffusion coefficient respectively, b is the diffusion weighting, D_{free} is the free diffusion coefficient in each of the cylinders and β_i is the analytical signal attenuation for diffusion in a cylinder with a cosine gradient spin echo sequence[4]. We assumed $D(r_i, \vec{\theta})$ was a gamma distribution with fixed limits on the minimum (0.25 μm and maximum 4.9 μm) radius and with D_{free} fixed to its actual value in the fit.

Results The results of the fit to simulated data from the OGSE sequence are shown in black in Figure 2. The fitted data agree fairly well with the input model indicating our method can be used to infer axon diameter distributions. Axon numbers for axon diameters between 0.5 μm and 1.75 μm are underestimated whereas for those 3 μm and larger, the axon numbers are overestimated. The mean radius of 1.57±0.01 μm measured from the fitted gamma distribution agrees within ~6% of the actual mean radius of 1.67μm.

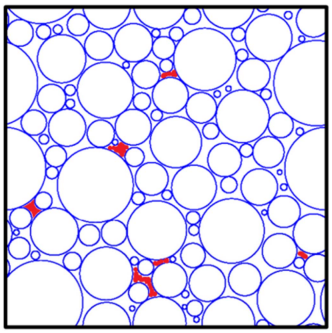

Figure 1. Cross-section of Gamma distribution of non-overlapping parallel cylinders used in this work. The red regions indicate examples of regions of restricted diffusion in the extra-cellular space. The lattice square has a width of .0365 mm

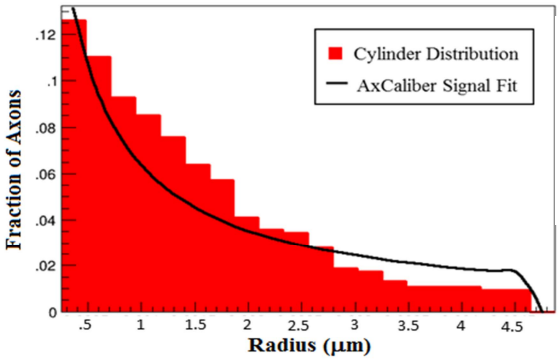

Figure 2. Actual (red) and fitted (black) axon diameter distributions for the geometry shown in Figure 1.

Discussion and Conclusion With the high intracellular volume fraction (0.81) and correspondingly low extracellular volume fraction (0.19) there were many extremely hindered regions (examples shown in red in Figure 1) which are not accounted for in the basic CHARMED model[9]. This could account for some of the discrepancy in the distribution and mean diameter measurements from the fit. Small intracellular volume fractions need to be studied in order to more closely match the CHARMED model or a new model accounting for the restricted extracellular space needs to be made. Also, because the signal is proportional to r^2, the larger axons contribute more to the signal than the smaller axons. With noise added to the simulation, the smaller axons are harder to identify. A modification is necessary to the CHARMED model so that the volume fraction is used in the signal calculations and the number fraction of axons is calculated from the volume fraction. This work is the first step toward combining OGSE measurements with axon diameter distribution models to infer distributions of small axon diameters in tissues. Distributions of non-parallel axons, less ideal cosine pulse sequences and more diffusion gradient directions will be needed to make a more complete model.

References 1. Gross *Messtechnik* 77, 171–177 (1969). 2. Schachter JMR. 2000; 147(2):233-237. 3. Does MRM 49:206–215 (2003). 4. Gore NMR in Biomed 2010; 23: 745–756. 5. Kershaw ISMRM: 409 (2011) 6. Xu MRI 29 (2011) 380-390 7. Assaf MRM 59:1347-1354 (2008) 8. Hall Medical Imaging IEE Transactions 2009 1354-1364. 9. Assaf MRM 59 (2008) 1347-1354. **Funding** NSERC, MHRC, CFI, and MRIF.