THREE-DIMENSIONAL MODELS OF TISSUE MICROSTRUCTURE FOR SIMULATING HIGH-PRECISION DIFFUSION MRI DATA

E. Panagiotaki[1], M. G. Hall[1], B. Siow[1,2], M. F. Lythgoe[2], and D. C. Alexander[1]

[1]Centre for Medical Image Computing, Dept. of Computer Science, University College London, London, United Kingdom, [2]Centre for Advanced Biomedical Imaging, University College London, London, United Kingdom

Introduction This abstract outlines a method to construct detailed three-dimensional geometric models of tissue microstructure using confocal laser scanning microscopy (CLSM) images. We use these models to simulate the diffusion MRI signal from the tissue by running random-walk simulations within the resulting mesh. Various studies use simple geometric models of white matter e.g. using cuboids [1], ellipsoids [2] or cylinders [3, 4], which grossly simplify the complexity of the tissue microstructure. The precise simulated data from our method provide a mechanism for evaluating the quality of simple parametric models and the parameter estimates they provide. Here we demonstrate the technique using a biological phantom (asparagus) and compare simulated measurements with both scanner measurements from the same sample and simulated measurements from much simpler parametric models of the microstructural geometry.

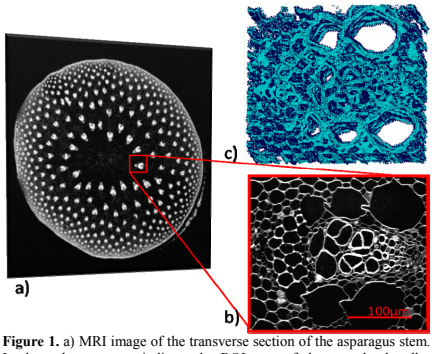

Figure 1. a) MRI image of the transverse section of the asparagus stem. In the red square we indicate the ROI, one of the vascular bundles appearing white in the MRI image. b) CLSM image of the same ROI. c) Reconstructed mesh model.

Methods We devise an acquisition protocol using a wide range of imaging parameters for diffusion sensitization both parallel and perpendicular to the asparagus stem and acquire diffusion-weighted data. We identify a region of interest (ROI) in the MRI data containing one of the vascular bundles (fig.1a), which we cut out and image with CLSM (fig.1b) to obtain a stack of images. We reconstruct a three-dimensional mesh model (fig.1c) from the CLSM image stack and use it as a substrate for Monte-Carlo simulation [6] to synthesise diffusion-weighted data. *Sample preparation*: We place a stem of green asparagus (*Asparagus officinalis*) in a syringe padded with cotton soaked in pure water. This keeps the sample hydrated, preventing tissue shrinkage and changes in the diffusion properties. *MRI acquisition*: We acquire diffusion-weighted MR images with a small bore 9.4T scanner (Varian) with maximum gradient strength 400mT/m and use a controlled air-flow mechanism to keep the sample temperature constant within ±1°C. The two-direction encoding scheme has one direction parallel to the asparagus stem and one perpendicular. We acquire 64 pulse-gradient spin-echo (PGSE) measurements with six diffusion times, Δ = 10, 30, 50, 70, 80, 100ms, three gradient durations δ = 3, 10, 30ms and gradient strength G varied from 40 to 400mT/m in ten steps of 40mT/m. The 64 measurements includes all combinations with $\Delta > \delta$ and $b < 6.5\text{x}10^9\text{s/m}^2$. We use the minimum echo time (TE) possible for each measurement and set the repetition time (TR) to 3s. The total acquisition time is approximately 40 hours. We correct for T2 dependence by acquiring separate $b = 0$ images for each parameter combination. The in-plane field of view is 16mm. The matrix size is 256x256 and the slice thickness is 0.5mm. *Confocal acquisition*: We use Vibratome to acquire 600μm thick samples from the stem that we stain with Eosin for 10 minutes and then thoroughly wash with phosphate buffered saline. We use a Leica SP2 AOBS confocal multi-photon laser scanning microscope. We image the specimens with a 40 x 1.25NA oil objective to give image dimensions of 375 μm x 375 μm. We acquire optical z-sections of 100 slices with 1μm thickness reaching a maximum depth of 100μm. Image averaging is set to 3 per z-slice. The image size is 1024x1024 pixels. *Mesh construction*: We downsample the confocal images to 100x100 pixels and use Otsu's method [7] to create binary images that separate the intra- and extra-capillary space. Subsequently, the marching cubes algorithm [5] reconstructs a mesh model of 376,260 triangles that describes the boundaries between the two compartments. *Simulation*: For all the simulations (see [6]) we use the same acquisition protocol as the MRI data. We use 100,000 spins, 5,000 timesteps and diffusivity $D = 2.1\text{x}10^{-9}\text{m}^2/\text{s}$.

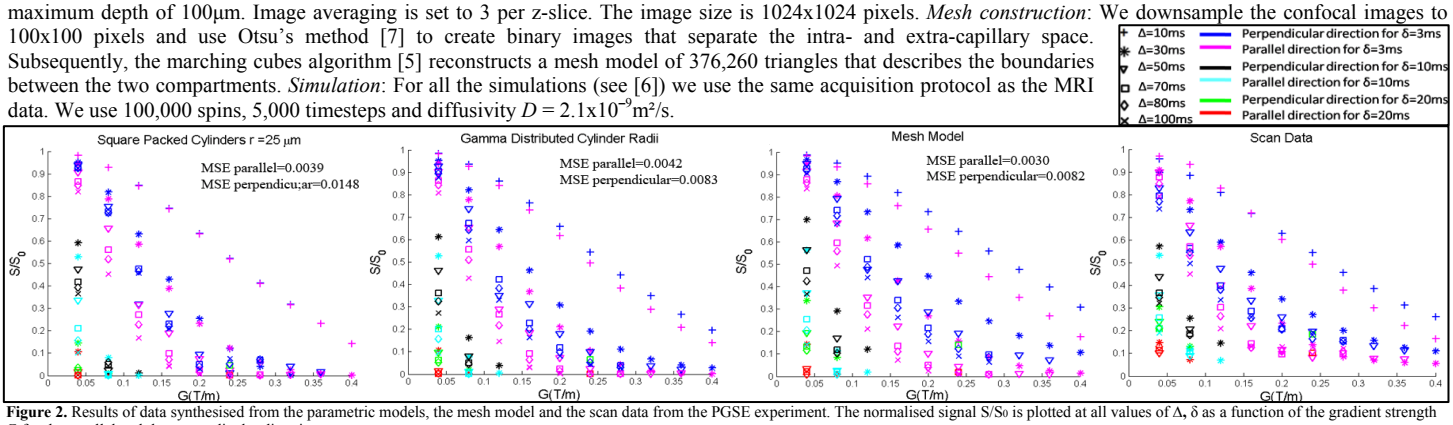

Figure 2. Results of data synthesised from the parametric models, the mesh model and the scan data from the PGSE experiment. The normalised signal S/S_0 is plotted at all values of Δ, δ as a function of the gradient strength G for the parallel and the perpendicular direction.

Experiments To study the parallel and perpendicular signal attenuation we average each signal over all 114 MRI voxels in our ROI. For comparison, we generate three sets of synthetic data: The first comes from the mesh model and the other two from packed-cylinder substrates with parametric distributions radii. The first parametric model has square packed-cylinders with radius 25μm. The choice of single radius comes from the mean capillary radius in the mesh weighted by capillary volume, because the contribution to the signal is proportional to the volume. The second parametric model has gamma distributed radii derived from the histogram of capillaries in the ROI. In both parametric models, we pick the packing density so that the intra-capillary volume fraction is 0.65, which is consistent with the mesh model. We synthesise diffusion-weighted data from the parametric models and the mesh model using the Monte-Carlo simulation, and add independent Rician noise at approximately the level in the scan data over 500 iterations, and take the mean to incorporate Rician noise bias.

Results Figure 2 compares data synthesised from the three models to the scan data by plotting the normalised signal S/S_0 at all values of Δ and δ as a function of the gradient strength G for the parallel and perpendicular direction. The prediction from the simulation with the cylinders of constant radii captures the data least well, for example not capturing differences in parallel and perpendicular signals with Δ = 10ms. The gamma distributed radii model and the mesh model agree closely and both capture the broad trend of the MRI data. The mean squared error (MSE) is lower for the mesh model in both directions (see fig.2) which suggests that although the gamma distributed cylinders provide a good model, the mesh model captures some added subtleties. In particular, the fit to the data improves in the parallel direction, most likely because the mesh model can capture heterogeneity in capillary orientations and shape.

Discussion & Conclusions This work introduces a method for constructing a detailed tissue mesh model using CLSM to generate realistic diffusion MRI data. We test the simulated data from the mesh model against scan data and simulated measurements from simple parametric models. Results show that the mesh model matches the data better than the parametric models in the parallel direction. Previous studies investigating the diffusion signal in the brain with analytic models found that additional restriction is needed in the parallel direction [8]. Our results are encouraging since the mesh model captures part of this parallel restriction in a natural way. We speculate that further restriction comes from binding of the water to the tissue surface and not the microstructure itself. Future work will test the method with white matter tissue and experiment with the CLSM image resolution and the segmentation process. The Monte-Carlo simulation approach with a tissue model of high fidelity can potentially capture subtle effects such as permeability and surface-particle interactions that simple parametric models of the signal generally ignore.

References and Acknowledgements [1] Szafer, MRM (1995), [2] Stanisz, MRM (1997), [3] Assaf, MRM (2008), [4] Alexander, MRM (2008), [5] Lorensen, Comp Graph (1987), [6] Hall, TMI (2009), [7] Otsu, Trans Sys Man Cyber (1979), [8] Panagiotaki, MICCAI (2009).

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