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The effect of axon shape and myelination on diffusion MRI signals in a realistic Monte Carlo simulation environment

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Abstract:
Diffusion MRI (dMRI) microstructure techniques, e.g. axon diameter and membrane permeability estimation, are often validated using Monte Carlo (MC) simulations. The geometric substrates are usually oversimplified cylindrical models. This work investigates more realistic geometry derived from electron microscopy (EM) data and aims to showcase how subtle microstructural features can be explored.
An EM section from mouse corpus callosum was segmented into 6 compartments: unmyelinated/myelinated axons; myelin; glial bodies/processes; extracellular space (Figure1a). MC simulations were performed using MCell (Stiles et al., 1996), with DifSim (Balls and Frank, 2009) calculating the dMRI signal from the phase of protons diffusing under a PGSE sequence with diffusion times Δ=2-160 ms, b-values 100-32000 s/mm2 in 30 perpendicular directions.
The effects of two tissue features were assessed:
(A) Shape, by comparing EM-derived vs. cylindrical geometry with equivalent radii (Figure1b): The aggregate dMRI signal averaged over directions is similar for EM-derived vs. cylindrical geometry, lending validity to modeling axons in cross-section as circles. Two regimes where shape is relevant: i) short Δ, where lower signal in EM-derived geometry appears driven by irregularly-shaped cell processes; ii) lower b-values, where higher signal in EM-derived geometry might be due to more tortuous diffusion in ECS around realistic cell packings.

(B) Myelination, by comparing EM-derived vs. geometry with myelinated axons replaced by unmyelinated axons under various permeability conditions (Figure 1c): at low permeability, only a modest effect of myelination on the dMRI signal is seen, suggesting myelination does not contribute much to signal attenuation in healthy tissue.

The EM-based geometry and simulation environment presented here has been developed to provide researchers with a flexible tool for investigating the role of a range of tissue features. Here, we have presented two examples: shape and myelination. Ongoing work extends these realistic simulations in full 3D using SBFSEM.

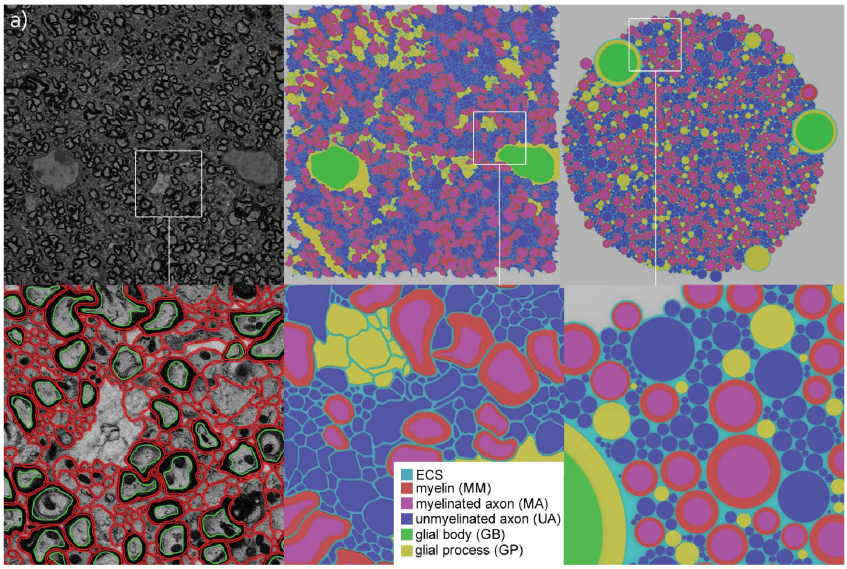
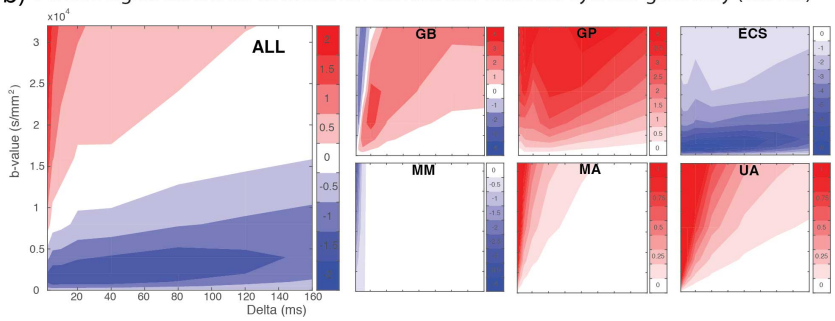
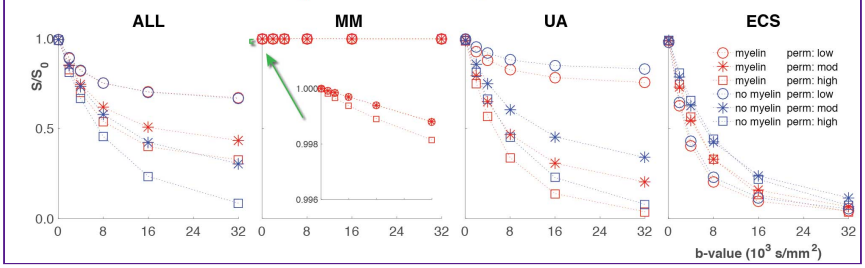


Figure 1a. Electron microscopy segmentation.
top-left) Original section taken from a serial blockface scanning electron microscopy dataset (4000x4000x469; 29.2x29.2x23.5 µm) from the genu of the corpus callosum of a mouse brain in sagittal sections. Acquisition used a Zeiss Merlin Compact Scanning Electron Microscope with a Gatan 3View system. The single section was segmented manually. **bottom-left)** Membranes in contact with ECS (MM/UA/GB/GP: red) and myelinated axons (MA: green). Extracellular space (ECS) was enforced around all objects (no abutting fibres) by eroding objects where they touched. ECS volume fraction is 0.19. **top-middle)** Final segmentation of the section (object counts: 3329 UA; 445 MM/MA; 2 GB; 461 GP). Dilation of the filled mask of all objects in the substrate by 0.0292 µm resulted in an ECS container fitting tightly around the substrate (see bottom-right). **bottom-middle)** A closer look at the compartments (the region in top-middle). **top-right)** Circle packing. Using the areas of the objects in the EM-derived substrate, a homologue cylindrical substrate was created. First, tight packing of circles with equivalent radii yielded an ECS volume fraction of 0.14. To achieve substrates with matched ECS volume the circles' centroids were shifted outward. **bottom-right)** A closer look at the compartments (the region in top-right).
Substrates had a z-dimension (10 µm) to meet the 3D nature of the simulation environment, but diffusion was periodic and free in the constant z-dimension. Diffusivities for ECS, intracellular compartments and myelin were set to [2.0; 0.75; 0.03] µm²/ms and the base rate of 35 particles/µm³ was scaled by concentration factors [0.95; 0.88; 0.50]. The EM-derived substrate is somewhat oversegmented as connections between objects occuring outside the segmented section were ignored. Future 3D tissue modeling efforts will address this shortcoming. Further compartmentalisation and variations in compartment properties (e.g. mitochondria and separate permeabilities of glia and neurons) will add to the accuracy of this model. Fortunately, these improvements are incorporated in a straightforward manner by DifSim.

b) Percent signal difference between EM-derived and matched-cylinder geometry (CM-EM)



c) dMRI signal behaviour with myelin and without myelin for three permeabilities (Δ=160 ms)



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