The effect of axon shape and myelination on diffusion signals in a realistic simulation environment.

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Introduction:

The application of microstructure techniques in diffusion imaging, such as axon diameter (Alexander et al., 2010) and membrane permeability estimation (Sønderby et al., 2013), are often validated using Monte Carlo simulations. The geometric substrates are usually highly simplified cylindrical models that have a limited number of compartments. This work investigates a more realistic substrate derived from electron microscopy data and aims to showcase how the influence of shape and compartments on the diffusion signal can be investigated.

Methods:

Simulation substrates To create a realistic substrate, electron microscopy data was acquired from the corpus callosum of a mouse brain. A single section was segmented by manually tracing membranes (Figure 1). Six compartments were distinguished: unmyelinated (UA) and myelinated axons (MM + MA); glial bodies (GB) and processes (GP); extracellular space (ECS).
Two EM substrates were created with low and high ECS volume fraction (EM1/EM2). Cylindrical substrates were obtained by packing circles with equivalent radii, tightly (CT1/CT2) as well as matched to the EM1/EM2 packing densities (CM1/CM2). A substrate without myelin was created from EM1 by replacing myelinated with unmyelinated axons with the shape of the MM outer boundary.
Monte Carlo simulations Monte Carlo simulations were performed with DifSim (Balls and Frank, 2009) tracking the phase of the particles and calculating the diffusion MR signal. Compartmental diffusivities and concentrations were set according to Baxter and Frank (2013). Simulation step size was 1 μs. The effect of cross-sectional shape and myelination on the signal was assessed for a PGSE sequence using a range of diffusion times (Δ=[2-160] ms), b-values (100-32000 s/mm^2) and 30 diffusion gradient directions in a semicircle in the xy-plane. Two simulation experiments were conducted to assess the effect of geometry and permeability. (i) Shape: For assessing the effect of shape and volume fraction, substrates EM1, EM2, CT1, CT2, CM1 and CM2 were compared. In this experiment, membranes were impermeable. (ii) Permeability: Myelination has a profound effect on the exchange between axons and ECS, therefore permeability was included for the comparison between the myelinated and unmyelinated substrate.

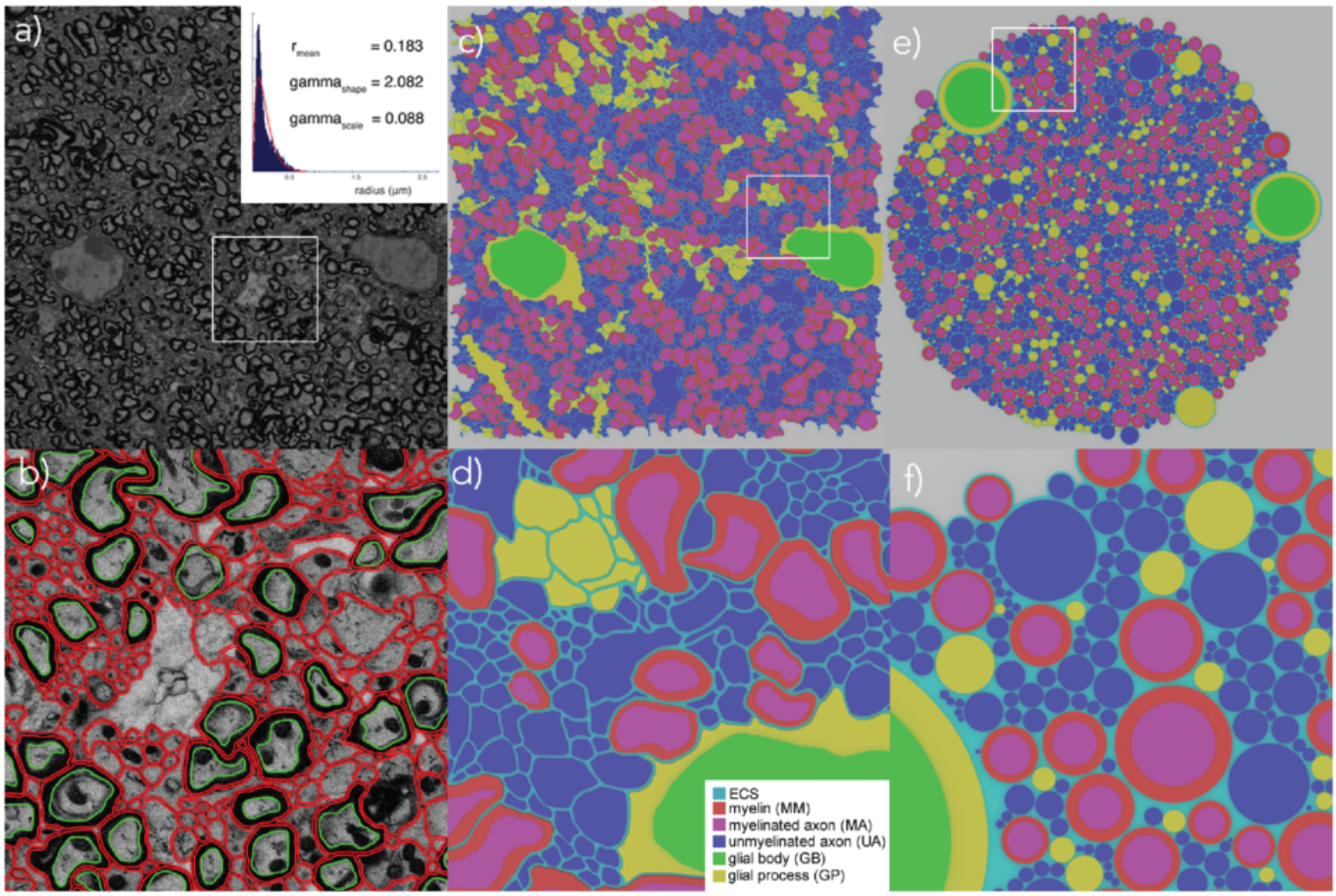

Figure 1. Electron microscopy segmentation.

a) Original section taken from a serial blockface electron microscopy dataset (4000x4000x460; 29.2x29.2x25.0 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. **b)** 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. Different extent of erosion yielded two EM-derived substrates EM1 and EM2 with volume fractions of of 0.19 and 0.23, respectively. **c)** 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 f). **d)** A closer look at the compartments (the region in c). **e)** Circle packing. Using the areas of the objects in the EM-derived substrates, homologue cylindrical substrates were created. First, tight packing of circles with equivalent radii yielded an ECS volume fraction of 0.14 (CT1/CT2). To achieve substrates with matched ECS volume the circles' centroids were shifted outward (CM1/CM2). **f)** A closer look at the compartments (the region in e). 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] $\mu m^2/ms$ and the base rate of 35 particles/μm^3 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 realistic model. Fortunately, these improvements are incorporated in the DifSim environment in a straightforward manner.

Results:

Shape The diffusion signal averaged over directions is similar for EM1/EM2 vs. CM1/CM2 substrates (Figure 2). The main variation is due to volume fraction, as also demonstrated by smaller attenuation for the CT substrates. The ECS signal is different between the two CM substrates, indicating that unequal spacing around objects interacts with volume fraction (arrow). Two regimes where shape might become a relevant factor (Figure 3: ALL): i) very short Δ, where lower signal in EM1 appears driven by restricted (quasi-)cylindrical compartments (MA/UA); ii) for the lower b-values across Δ's where the ECS signal is dominant.

Myelination With low permeability, no effect of myelination on the aggregate diffusion signal is seen (Figure 4: o). Higher permeability (+) induces loss of signal in the unmyelinated vs. myelinated substrate as there is both less restriction in intracellular compartments as well as increased diffusion across membranes.

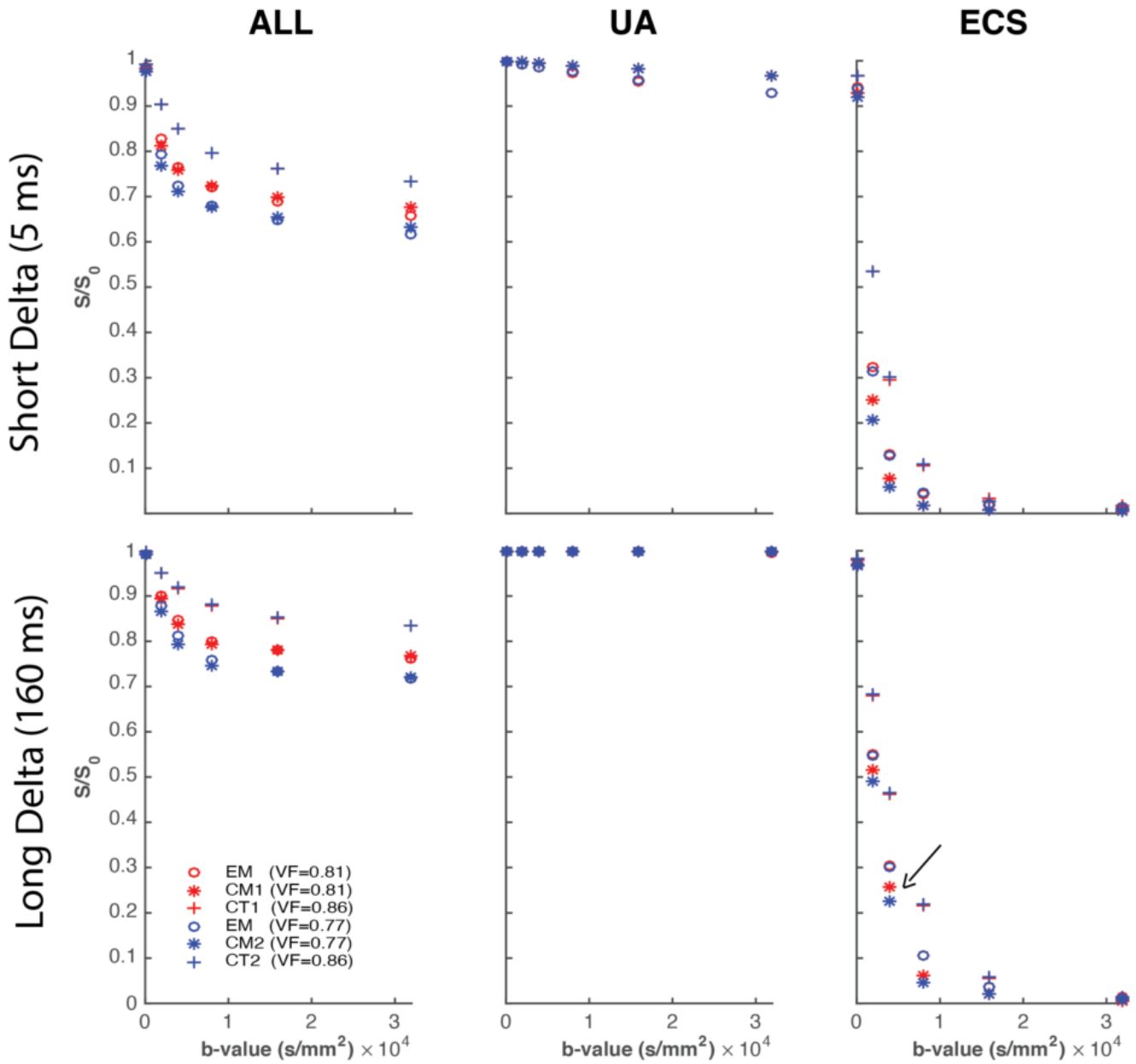

Figure 2. Effects of cross-sectional axon shape on the diffusion signal.
Simulated signals vs b-value averaged over perpendicular directions for EM and cylindrical substrates. Aggregate (ALL) and UA / ECS compartments signals are shown for long and short diffusion time. Red / blue traces are for EM substrates with different packing densities; symbols indicate the EM (o), CM (*) and CT (+) substrates.

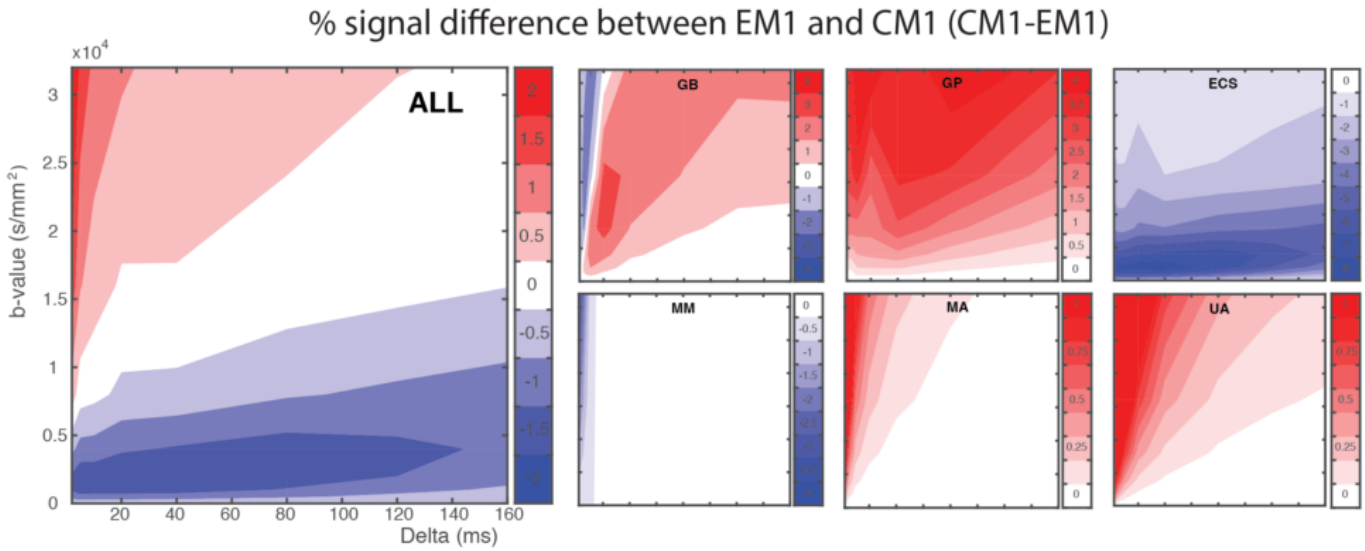

Figure 3. Signal differences between the EM-derived and cylindrical substrate.
Signal difference between shaped (EM1) and matched cylinder (CM1) model for the aggregate signal and the signal from the six compartments.

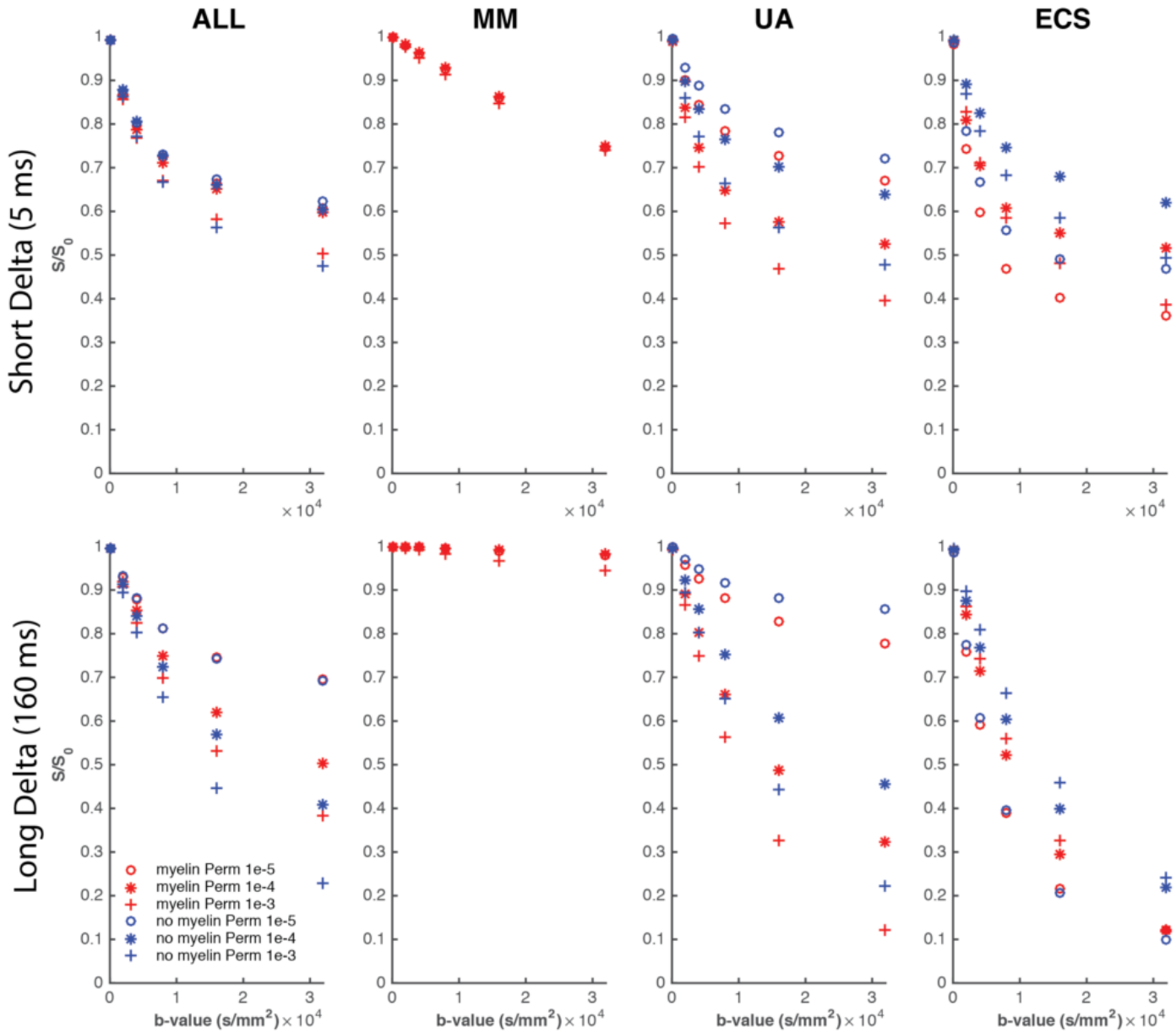

Figure 4. Effects of myelination and permeability on the diffusion signal.
Signal behaviour for diffusion in substrate EM1 with myelin (red) and without myelin (blue). Different symbols indicate various permeabilities: Transition probabilities of [1e-5,1e-4,1e-3] for UA to ECS with other transition probabilities adapted accordingly. Exchange into the myelin sheath was chosen two orders of magnitude lower than for unmyelinated axons.

Conclusions:

The EM-based substrate 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 present the two examples of shape and permeability.
Considering the modest change in signal between EM-derived and cylindrical substrates, our results suggest that a circular cross-sectional shape is a valid approximation for white matter, e.g. as deployed for axon diameter mapping. On the other hand, the minor effect myelination had at low permeability suggests higher exchange rate estimates in grey vs. white matter (Sønderby et al., 2013) might be due to abundance of permeable glia, rather than degree of myelination.

Imaging Methods:

Diffusion MRI

Modeling and Analysis Methods:

Diffusion MRI Modeling and Analysis [1]
Methods Development [2]

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WHITE MATTER IMAGING - DTI, HARDI, DSI, ETC

[1|2]Indicates the priority used for review

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Please indicate which methods were used in your research:

Other, Please specify - electron microscopy, Monte Carlo simulation

Which processing packages did you use for your study?

Other, Please list - ITK-SNAP, DifSim

Provide references in author date format

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