Monte Carlo simulations disambiguate the biophysical mechanisms of diffusion hindrance along tracts

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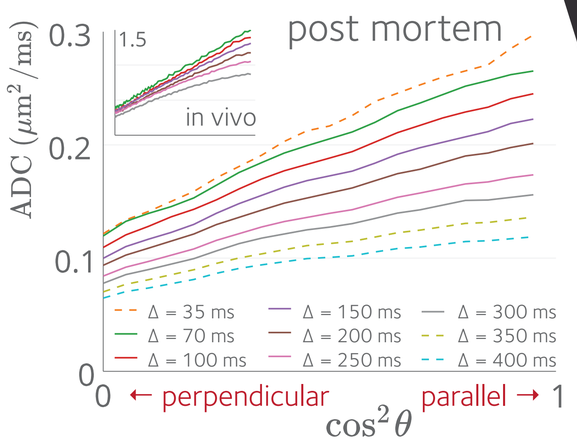
BACKGROUND

- Diffusion imaging at long diffusion times (Δ) informs on micro-structural tissue features up to the ~100 µm scale.
- Approximation of axons as straight cylinders might not hold, even for tissues that are generally assumed to be coherently organized, for example: the human corpus callosum (CC).
- Electron microscopy (Mikula 2012) and histology (Budde 2013) suggest that the CC is far from coherent: fibres bend, twist and undulate which might lead to specific signatures of hindrance along the tract.
- In this study, we investigated the diffusion time dependence of the apparent diffusion coefficient (ADC) along the fibres in the CC.
- Biophysical mechanisms of this dependence are explored by Monte Carlo simulations of various tissue models.

Diffusion time dependence of the ADC in the corpus callosum

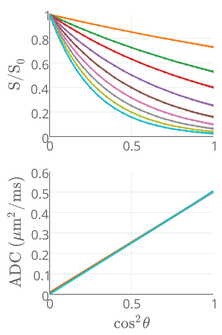
- The ADC in the corpus callosum decreases with diffusion time; to a comparable degree across and along the tract.
- This suggests considerable diffusion hindrance not only perpendicular to the fibres, but also in the tract direction.
- A model of infinitely long straight cylinders might thus be inappropriately simple, even for the (supposedly) most coherent WM tract.

Figure 1. ADC plotted against $\cos^2$ of the angle between the diffusion gradient direction and the primary diffusion direction.



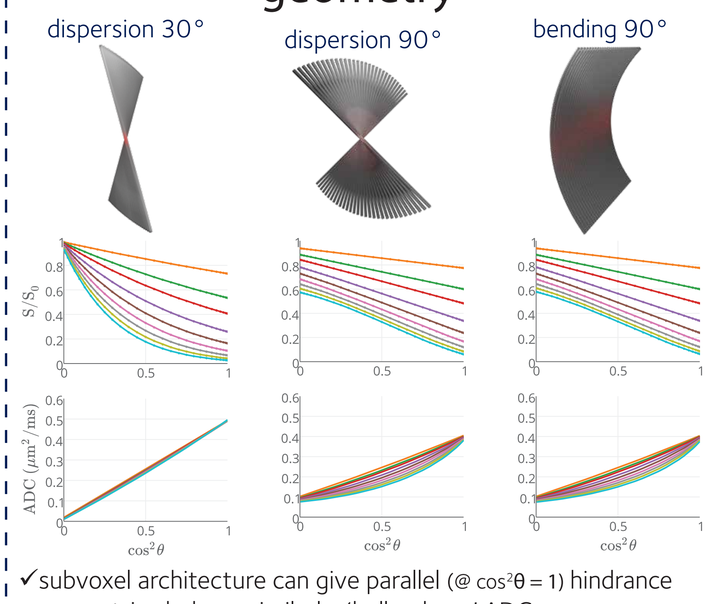
Monte Carlo simulations: which factors might explain these MR data?

baseline



✓ free diffusion ||
@ $\cos^2\theta = 1$ with
$D = 5.0e^{-6}$ µm²ms⁻¹

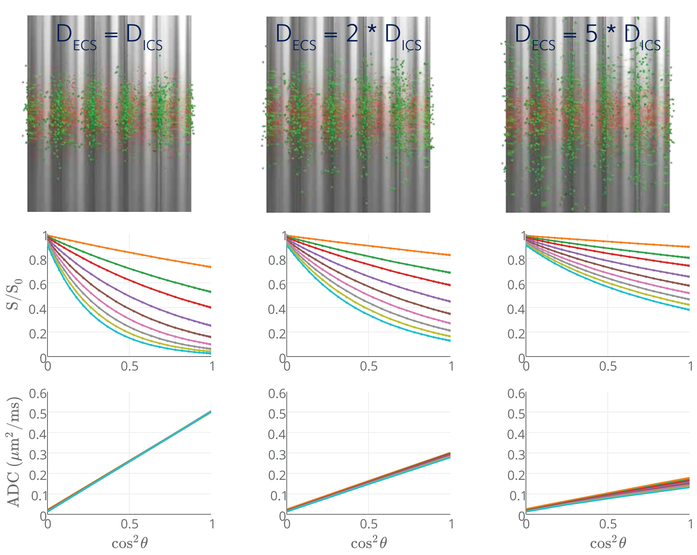
geometry



✓subvoxel architecture can give parallel (@ $\cos^2\theta = 1$) hindrance
- geometries behave similarly: 'belly-down' ADC curves

▶ axon arrangements unlikely to explain the pattern in the data

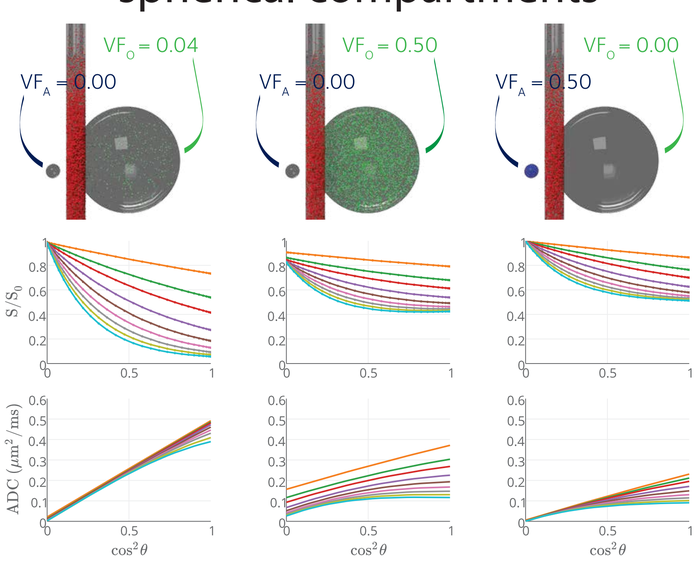
diffusivities



✓different ECS/ICS diffusivities result in parallel Δ-dependence
- need fixed b measurements to verify plausibility (forthcoming)

▶ only wildly different D's can account for the data ($D_{ECS} >> D_{ICS}$)

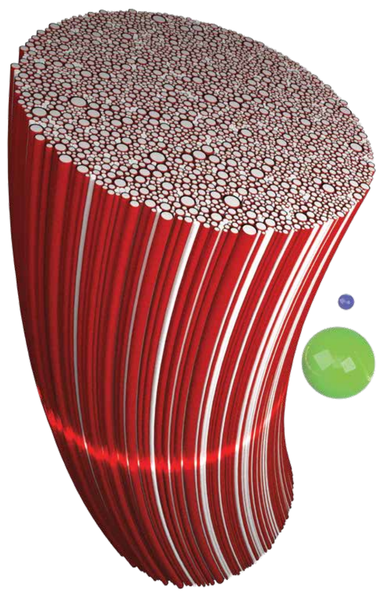
spherical compartments



✓inclusion of spheres introduces parallel restriction
- oligodendrocytes (VF_O; ø=20 µm) / astrocytes (VF_A; ø=2 µm)

▶ unrealistic volume fraction appear to be necessary (VF≈0.50)

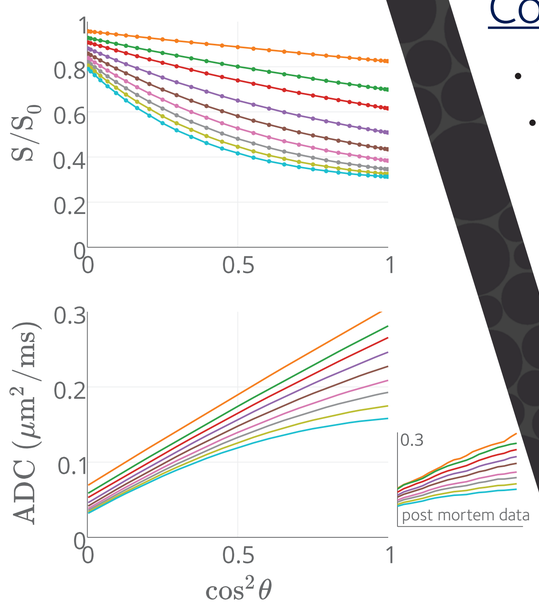
Combining factors for a biophysically plausible model



- sensible combination of all of the above approximates the data

MODEL:
gamma-distributed cylinders
N=3573; <Ø>=0.5 µm; g-ratio=0.8
bending of 30°
compartments:
25% ECS ($D=5.0e^{-6}$µm²/ms)
10% myelin ($D=1.0e^{-6}$µm²/ms)
40% axons ($D=4.0e^{-6}$µm²/ms)
10% oligodendrocytes ($D=D_{ECS}$)
10% astrocytes ($D=D_{ECS}$)
5% mitochondria ($D=1.0e^{-6}$µm²/ms)

- glial volume fractions might still be too high

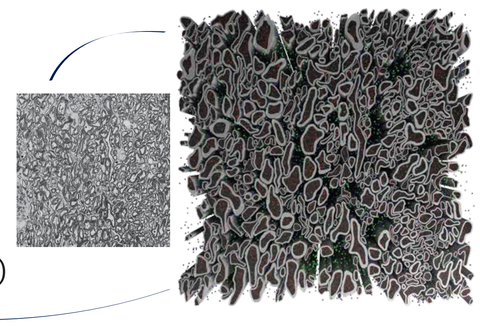


Conclusions

- The ADC parallel to the bundle is diffusion time dependent
- Monte Carlo simulations suggest the explanation has to involve a combination of microstructural factors
- This work demonstrates a framework for assessing micro structure MRI: from simple cylinders to complex geometry

Outlook: using EM data

- electron microscopy as ground truth for µ-dMRI
- realistic geometries for MC simulations (2½D&3D)

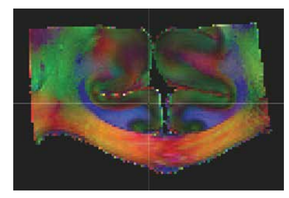


METHODS

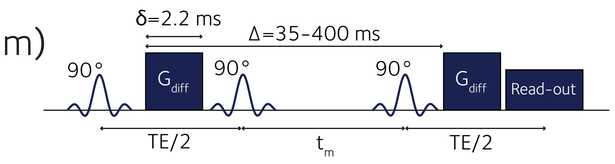
MR measurements (post mortem)

- 3x2 cm coronal block of a human corpus callosum
- soaked in PBS for 72h
- scanned in Fluorinert on a Varian 9.4T


sample as scanned

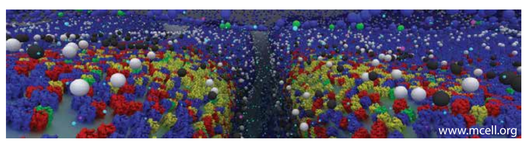

spin echo DTI fit

- acquiring DW-STEAM data with:
  - 9 diffusion times: 35-400 ms
  - 30 directions
  - fixed q-value (0.14 rad/µm)
  - TE=16 ms, TR=2.4-4.1 s
  - 10 slices, 400 µm voxels



Monte Carlo diffusion simulations

- Geometries created with CellBlender: blender
  - L_{axon} = 160 µm
  - d_{axon} = 3 µm
- Particle trajectories from MCell (Stiles 1996): MCell
  - $D = 0.5$ µm²/ms
  - dt = 100 µs
  - 400000 particles
  - impermeable walls



- dMRI signals calculated with DifSim (Balls 2009):
  - STEAM MR protocol (as above)
  - T2 decay not simulated

RESULTS

CONCLUSION

Balls, G.T., MRM 2009; Budde, M.D. FiIN 2013;
Lam, W.W. DPhil thesis 2015; Mikula, S. Nat. Meth. 2012;
Nilsson, M. NMR Biomed. 2012; Stiles, J.R. PNAS 1996.

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