



Multi-compartment microscopic diffusion anisotropy imaging brought into clinical practice

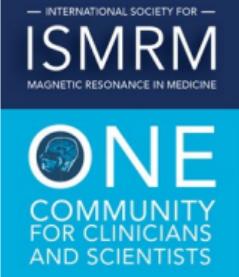
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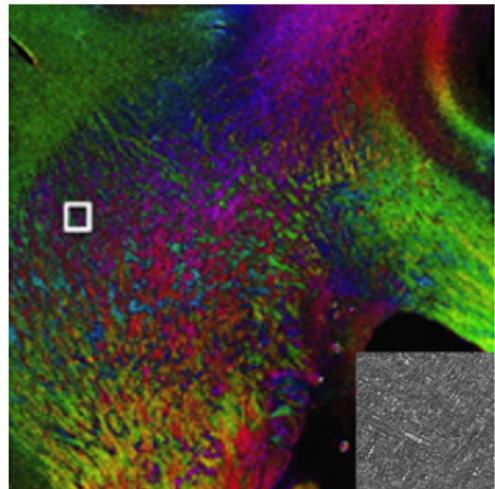
Declaration of Financial Interests or Relationships

Speaker Name: Enrico Kaden

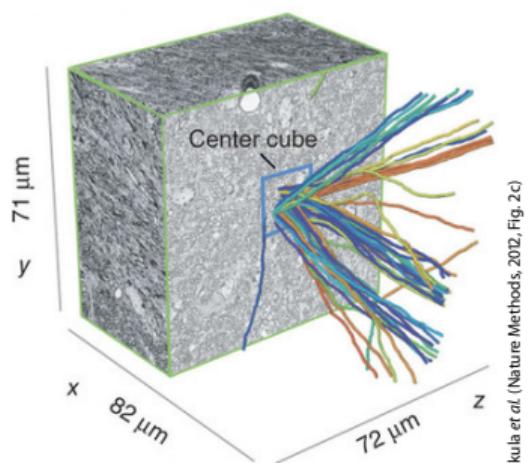
I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Fibre crossings and orientation dispersion are ubiquitous

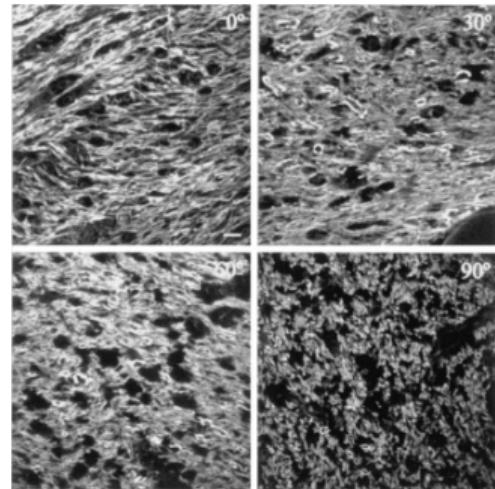
Fibre crossings



Orientation dispersion



Axon undulation



Fibre crossings, orientation dispersion and axon undulation in brain tissue give rise to complex orientation distributions at millimetre resolution.

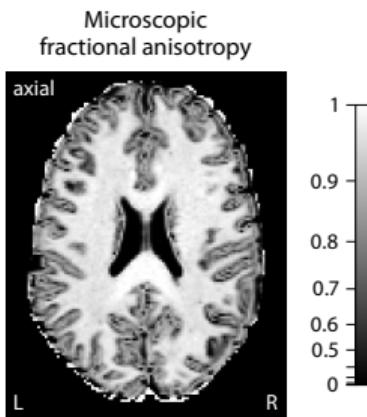
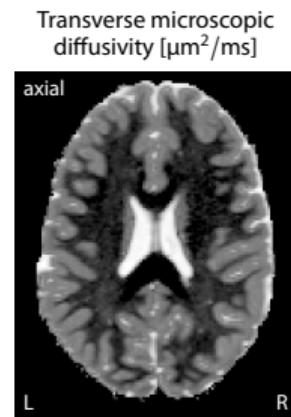
Spherical Mean Technique (SMT)

To disentangle the microscopic diffusion process from fibre crossings and orientation dispersion to uncover the microscopic tissue features.

For any fixed gradient timing and gradient magnitude (thus fixed b -value):

- ▶ The spherical mean of the diffusion signal over the gradient directions does *not* depend on the orientation distribution.
- ▶ In particular, the mean diffusion signal is *only* a function of the microscopic diffusion signal.

Microscopic diffusion tensor imaging



Microscopic diffusion anisotropy maps, which have factored out the effects due to the intra-voxel neurite orientation distribution.

Kaden et al. (ISMRM, 2015), Kaden et al. (MRM, 2016)

- ▶ Intra-neurite domain: Microscopic “stick” model

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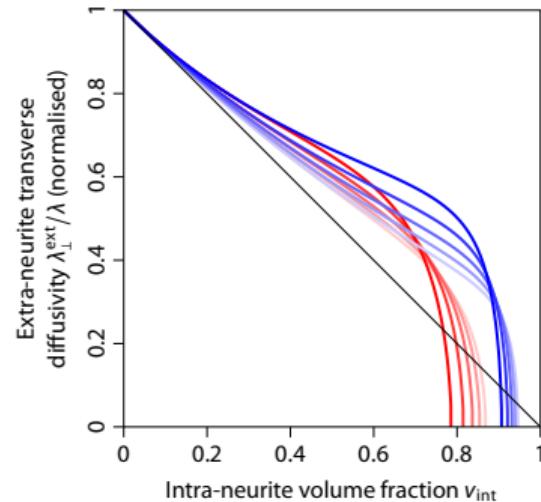
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- Assumptions

- No myelin water pool
- Intrinsic water diffusivity: $\lambda = \lambda_{\parallel}^{\text{int}} = \lambda_{\parallel}^{\text{ext}}$
- Tortuosity effect: $\lambda_{\perp}^{\text{ext}} = (1 - v_{\text{int}})\lambda$

Tortuosity model (Bruggeman, 1935)



-  **Square lattice of cylinders** with fixed diameter (Perrins *et al.*, 1979)
-  Square lattice of small cylinders with large cylinders added for $\xi = \{0, 0.2, 0.4, 0.6, 0.8\}$ (Novikov & Fieremans, ISMRM, 2012)
-  **Hexagonal lattice of cylinders** with fixed diameter (Perrins *et al.*, 1979)
-  Hexagonal lattice of small cylinders with large cylinders added for $\xi = \{0, 0.2, 0.4, 0.6, 0.8\}$ (Novikov & Fieremans, ISMRM, 2012)
-  **Randomly placed cylinders** of variable diameter (Bruggeman, 1935)

Bruggeman's approach $\lambda_{\perp}^{\text{ext}} = (1 - v_{\text{int}})\lambda$ is a first-order approximation of the tortuosity effect.

Step 1: Formulate a diffusion signal model for a single microdomain, e.g. multi-compartment microscopic model:

$$h_b(g, \omega | v_{\text{int}}, \lambda) = \underbrace{v_{\text{int}} h_b^{\text{int}}(g, \omega)}_{\text{intra-neurite}} + \underbrace{(1 - v_{\text{int}}) h_b^{\text{ext}}(g, \omega)}_{\text{extra-neurite}}$$

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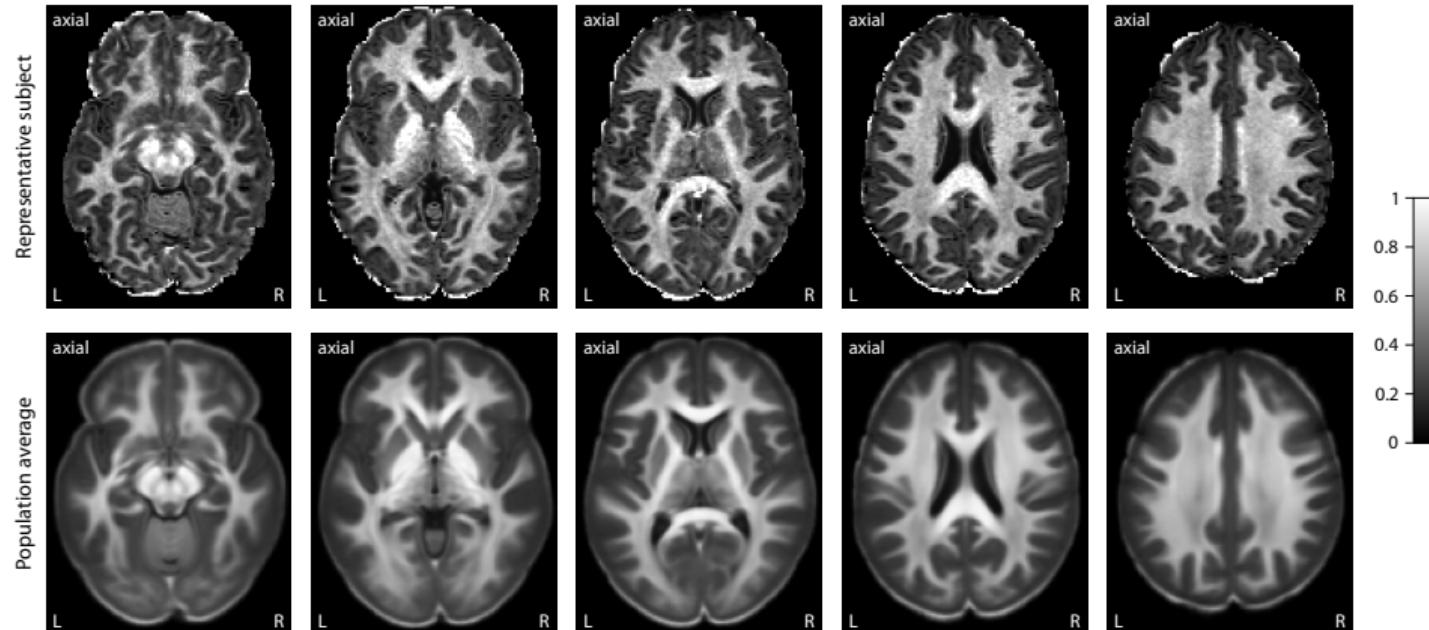
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Step 3: Fit the spherical mean version of the microscopic diffusion model to measured mean signals:

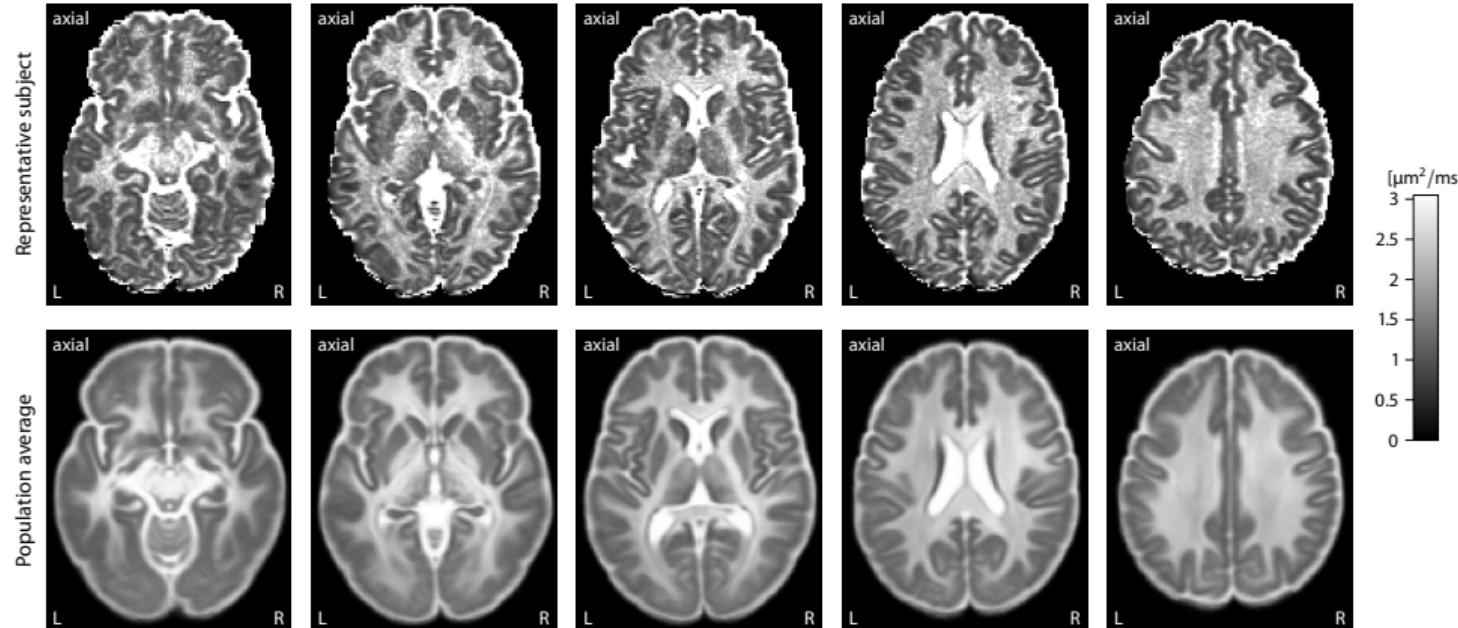
$$\bar{e}_b(v_{\text{int}}, \lambda) = \underbrace{v_{\text{int}} \frac{\sqrt{\pi} \operatorname{erf}(\sqrt{b}\lambda)}{2\sqrt{b\lambda}}}_{\text{intra-neurite}} + \underbrace{(1 - v_{\text{int}}) \exp(-b\lambda_{\perp}^{\text{ext}}) \frac{\sqrt{\pi} \operatorname{erf}(\sqrt{b[\lambda - \lambda_{\perp}^{\text{ext}}]})}{2\sqrt{b[\lambda - \lambda_{\perp}^{\text{ext}}]}}}_{\text{extra-neurite}}$$

Intra-neurite volume fraction



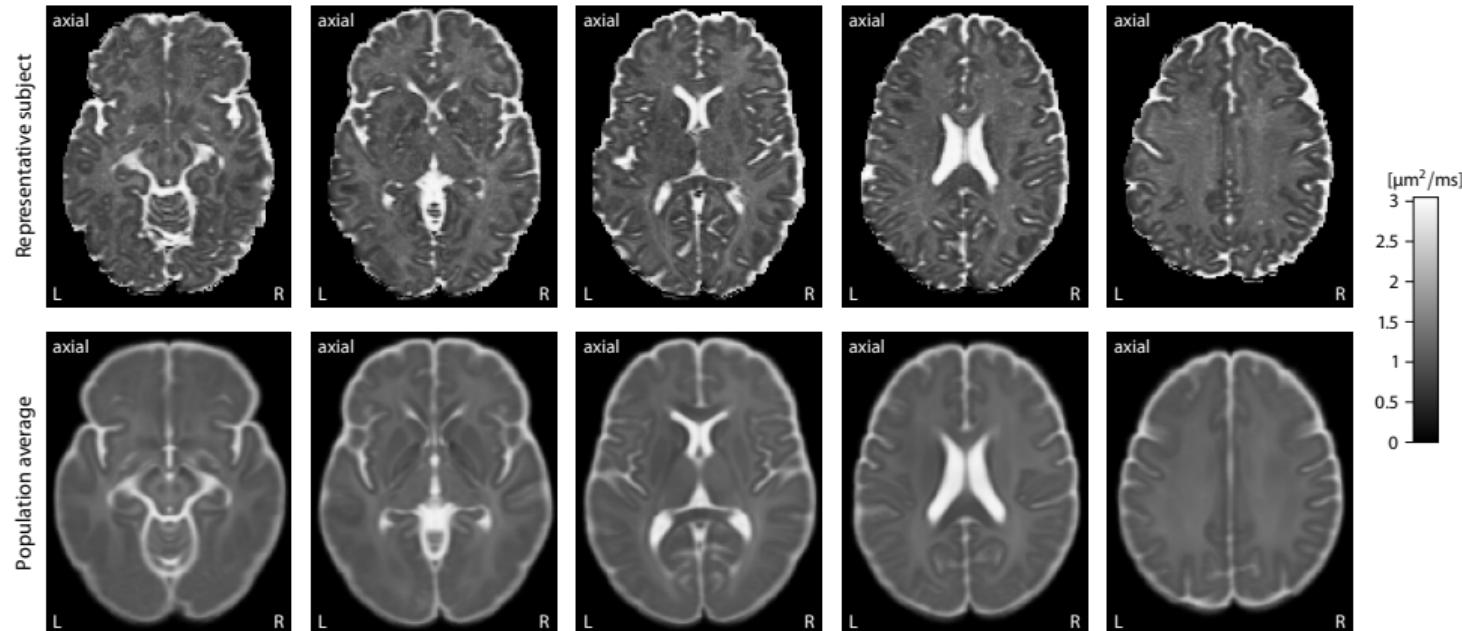
The key feature of these neurite density maps is that the confounding effects due to fibre crossings and orientation dispersion have been factored out.

Intrinsic water diffusivity



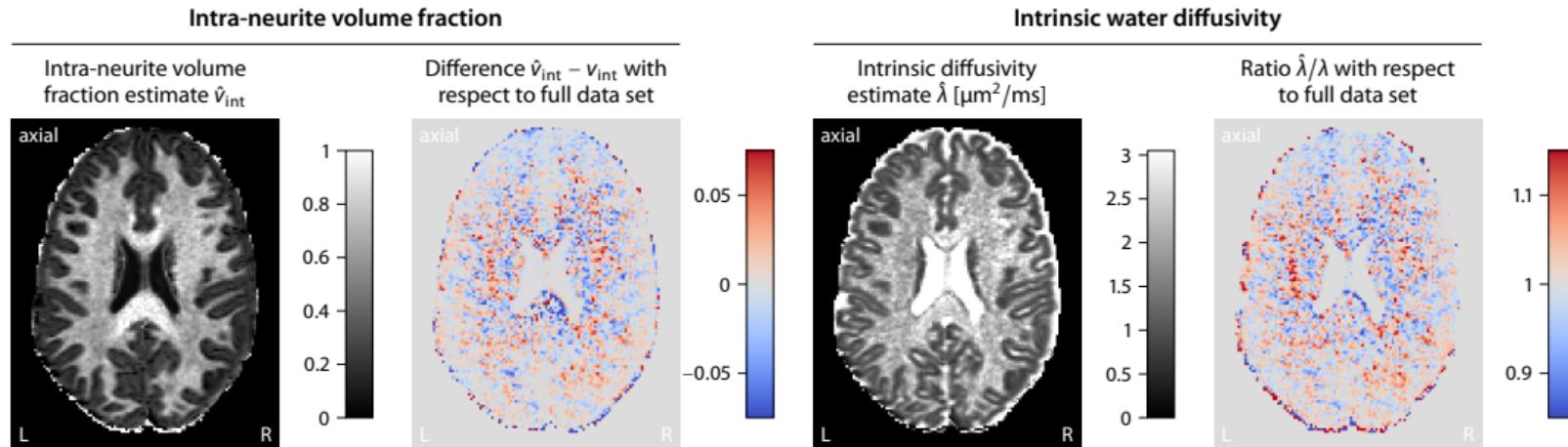
We do not assume fixed diffusivities. Indeed, our results demonstrate that the intrinsic diffusivity, if released, varies substantially over the brain.

Extra-neurite microscopic diffusivity



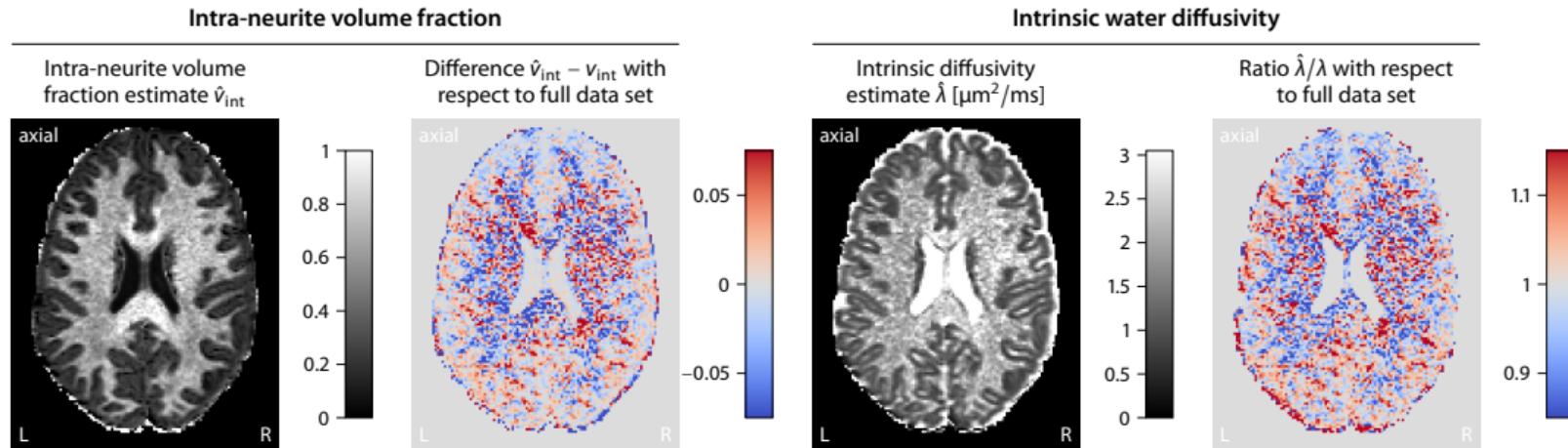
This imaging biomarker provides unique insight into the extra-neurite microstructure, which is crucial for a better understanding of developmental and pathological processes.

Sparse sampling: 180 (from 270) diffusion gradients



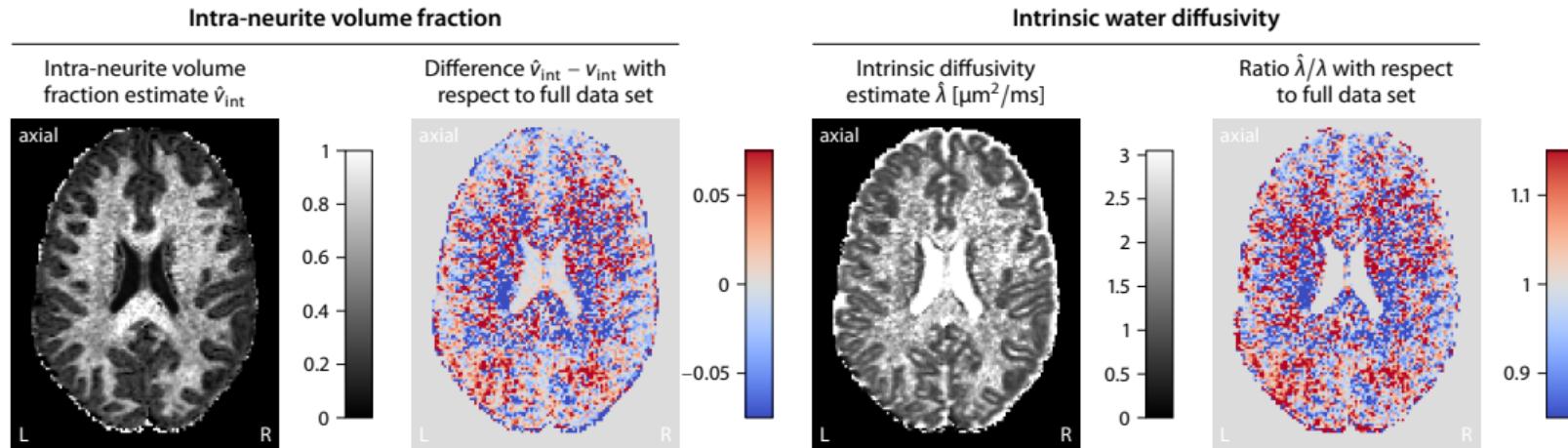
Estimation accuracy for 180 diffusion gradients evenly distributed over three b -shells, here 1000, 2000 and 3000 s/mm^2 (i.e. 66.7% of full HCP S500 data set).

Sparse sampling: 90 (from 270) diffusion gradients



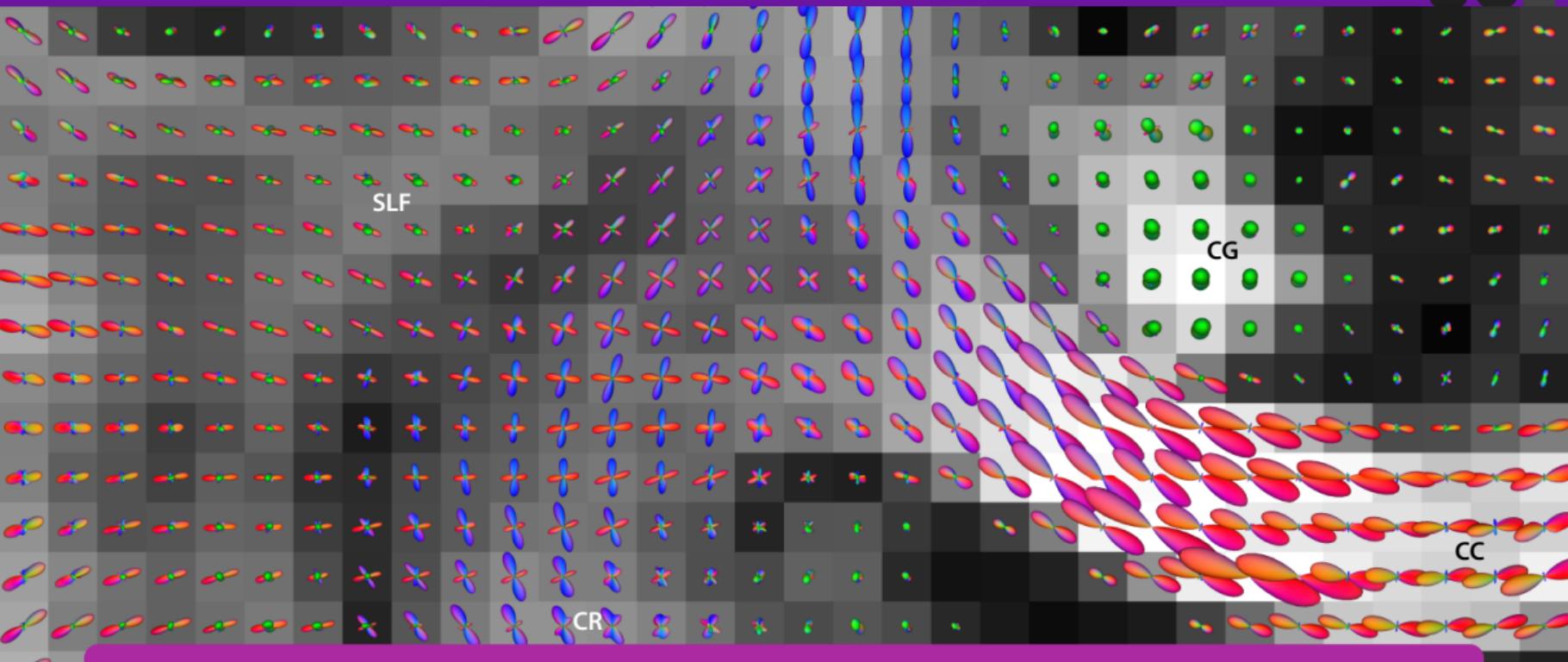
Estimation accuracy for 90 diffusion gradients evenly distributed over three b -shells, here 1000, 2000 and 3000 s/mm^2 (i.e. 33.3% of full HCP S500 data set).

Sparse sampling: 45 (from 270) diffusion gradients



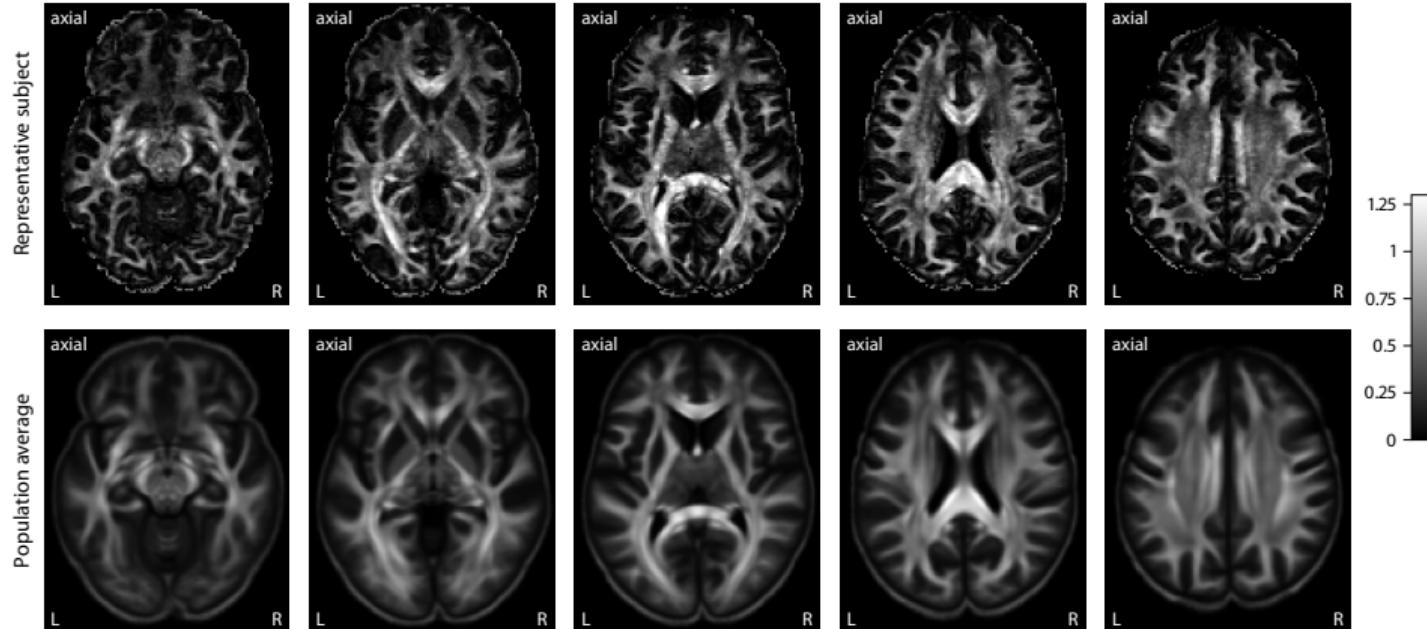
Estimation accuracy for 45 diffusion gradients evenly distributed over three b -shells, here 1000, 2000 and 3000 s/mm^2 (i.e. 16.7% of full HCP S500 data set).

Orientation distribution recovery



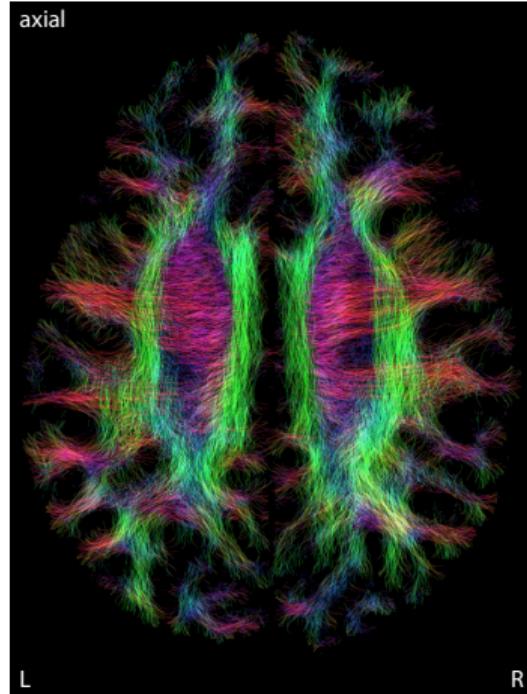
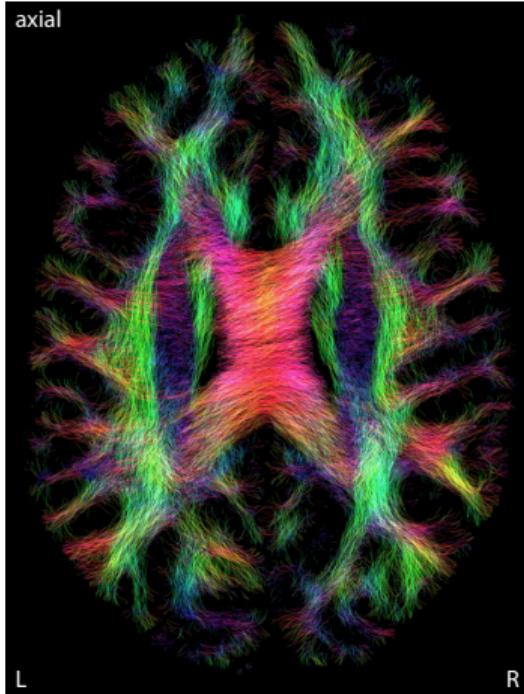
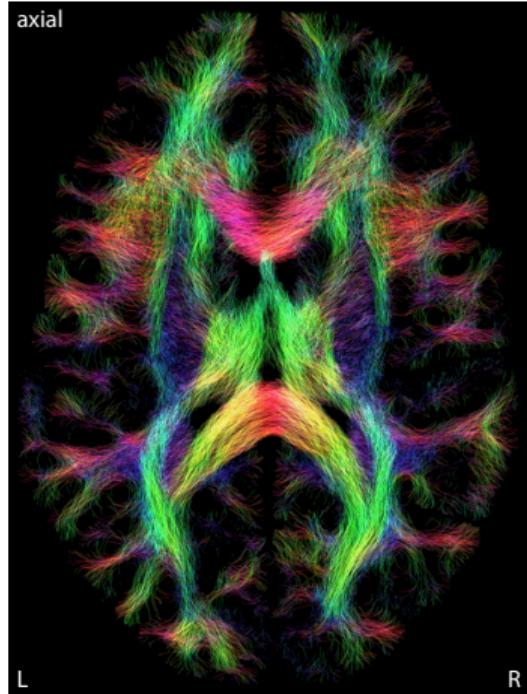
SMT enables the quantitative estimation of the neurite orientation distribution (Kaden *et al.*, *NeuroImage*, 2008) without any assumptions on *a priori* unknown diffusivities.

Orientation dispersion entropy



This summary statistic of directional heterogeneity takes the microdomain orientation distribution entirely (including fibre crossings and orientation dispersion) into account.

Fibre tractography and connectivity mapping



Created with MRtrix3

SMT allows us to track crossing fibre pathways and to quantify neural connectivity in the brain.

Clinically relevant animal model (Carson *et al.*, Ann. Clin. Transl. Neurol., 2015)

- ▶ Conditional knockouts (CKO) of *Rictor* and *Tsc2* in *Olig2-Cre* mice
- ▶ Both CKOs target the formation of oligodendrocyte precursors and oligodendrocyte differentiation, thus impacting CNS myelination.

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Ex-vivo study of P60 mouse brains

- ▶ 8 normal control mice
- ▶ 5 *Rictor*^{*Olig2-Cre*} CKO mice, with moderate adverse effects
- ▶ 5 *Tsc2*^{*Olig2-Cre*} CKO mice, with severe adverse effects

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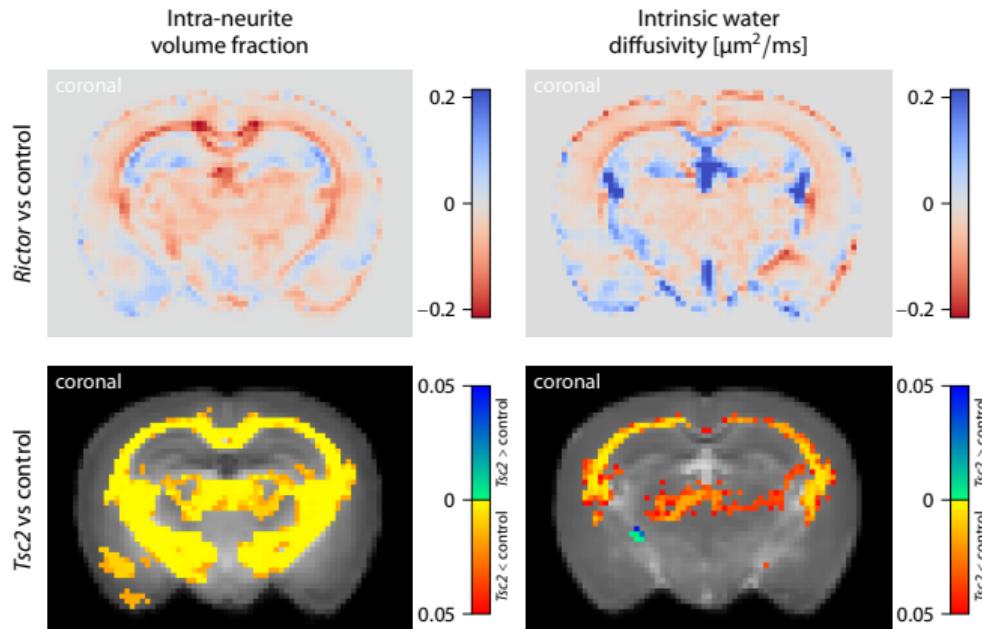
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Diffusion MRI scan (Kelm *et al.*, NeuroImage, 2016)

- ▶ 15.2 T Bruker Biospec scanner
- ▶ 3D fast spin-echo sequence with TR = 200 ms, TE = 19 ms and 150 µm isotropic resolution
- ▶ Minimal diffusion protocol: 60 gradient directions evenly distributed over two *b*-shells of {3000, 6000} s/mm² with fixed timing δ = 5 ms and Δ = 12 ms

Voxel-wise group analysis



SMT uncovers white matter abnormalities in both CKO models, demonstrating the translational potential of the technique for the evaluation of neuropathology.

NODDI (Zhang *et al.*, NeuroImage, 2012)

✗ Single Watson/Bingham distribution

Multi-compartment SMT

- ✓ Arbitrary orientation distributions, including fibre crossings and orientation dispersion
- ✓ No additional acquisition costs



Parametric spherical deconvolution: Inferring anatomical connectivity using diffusion MR imaging

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The human brain forms a complex neural network with a connectional architecture that is still far from being known in full detail, even at the macroscopic level. The advent of diffusion MR imaging has enabled the exploration of the structural properties of white matter *in vivo*. In this article we propose a new forward model that maps the microscopic

grouped into fiber bundles. However, detailed knowledge about the connectional architecture of white matter is still rather limited even at the macroscopic level, not least due to the anatomical variability between subjects. With the advent of diffusion magnetic resonance

Multiple Bingham distributions for the accurate representation of fibre crossings and orientation dispersion (Kaden *et al.*, NeuroImage, 2007).

structural organization of the cerebral cortex. Moreover, we will demonstrate the proposed approach with diffusion-weighted data sets featuring high angular resolution.

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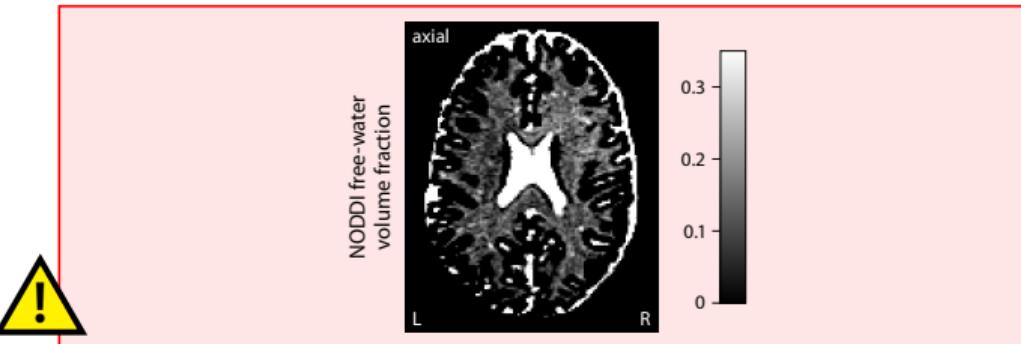
Keywords: Parametric spherical deconvolution; Finite mixture of Bingham distributions; Anatomical connectivity; Bayesian statistics; Diffusion MR imaging

for the reconstruction of fiber pathways.

To obtain information on the course of fiber tracts and the degree of the connectedness of distant brain areas, we need to construct a forward model that maps the microgeometry of nervous tissue onto the diffusion process and further onto the measured MR signals. Since the architecture of neural cells is highly complex, there is no doubt about the necessity to make assumptions and simplifications. Also, the number of diffusion encoding gradients is limited and we typically measure no more than one b -value in addition to $b=0$, which is required by the normalization of the T_2^* -relaxation. Usually, fiber bundles are mapped onto diffusion-weighted MR signals by the diffusion tensor model proposed by Basser *et al.* (1994). This approach proved inadequate for describing crossings and branchings of nerve fiber tracts, but it is fairly straightforward to represent several fiber bundles by a sum of multiple diffusion tensors weighted by their respective volume fractions (Tuch *et al.*, 2002; Parker and Alexander, 2003; Horsley *et al.*,

Introduction

It is widely accepted that specialization is a fundamental property of brain organization, involving the segregation and integration of neural populations (Zeki and Shipp, 1988). These discrete cortical areas are connected by long-range nerve fibers



NODDI (Zhang *et al.*, *NeuroImage*, 2012)

- ✗ Fixed intrinsic diffusivity (in human *in-vivo* studies $1.7 \mu\text{m}^2/\text{ms}$)
- ✗ Adverse effects on the recovery of the orientation dispersion and neurite density index
- ✗ **Systematic overestimation of free-water content in the cerebral white matter**

Multi-compartment SMT

- ✓ The intrinsic water diffusivity is estimated from the data.



$$\frac{1}{n} \sum_{i=1}^n \exp(-bg^t D_i^{\text{ext}} g) = \left(\prod_{i=1}^n \exp(-bg^t D_i^{\text{ext}} g) \right)^{1/n}$$

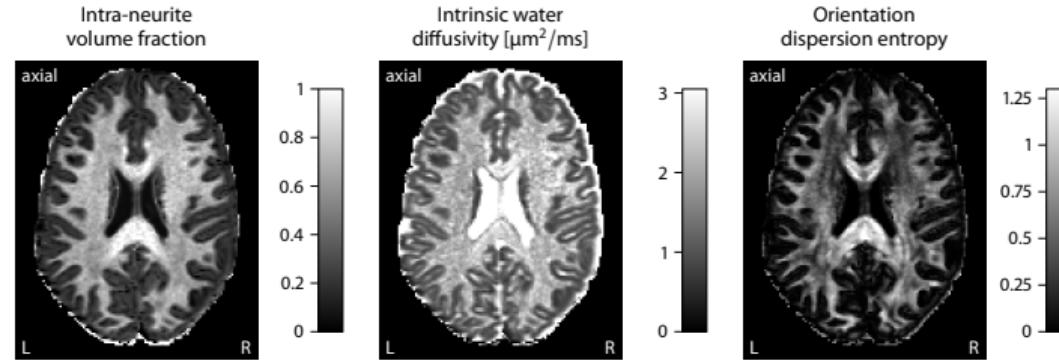
NODDI (Zhang *et al.*, NeuroImage, 2012)

- ✗ This method averages the extra-neurite microscopic diffusion tensor over the neurite orientation distribution, which leads to contradictory results.

Multi-compartment SMT

- ✓ The developed technique overcomes these logical inconsistencies.

Conclusions



- ▶ SMT is able to disentangle microscopic diffusion anisotropy from fibre crossings and orientation dispersion.
- ▶ The technique uses off-the-shelf diffusion sequences with two or more b -shells, which can be easily adopted in the clinical domain.
- ▶ SMT provides promising MRI biomarkers that offer *direct* sensitivity to microstructural tissue abnormalities.



Pioneering research
and skills



- ▶ This work was funded by UK EPSRC (EP/G007748/1, EP/M020533/1, EP/N018702/1), EU Horizon 2020 (634541-2) and US NIH (R01 EB001744, 5K08 NS050484, T32 EB014841, S10 RR029523).
- ▶ Data were provided in part by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.



GitHub



- ▶ We are very excited to announce the launch of SMT at <https://ekaden.github.io>.
- ▶ The software is fully compatible with SPM, FSL and MRtrix3.