



MRC Cognition
and Brain
Sciences Unit



UNIVERSITY OF
CAMBRIDGE

Introduction to Diffusion MRI – Part II

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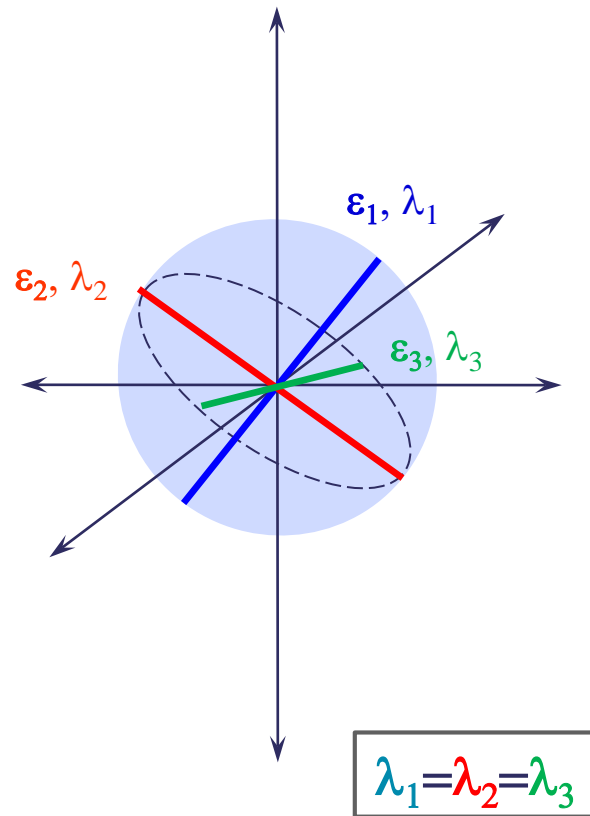
MRC Cognition and Brain Sciences Unit

Overview

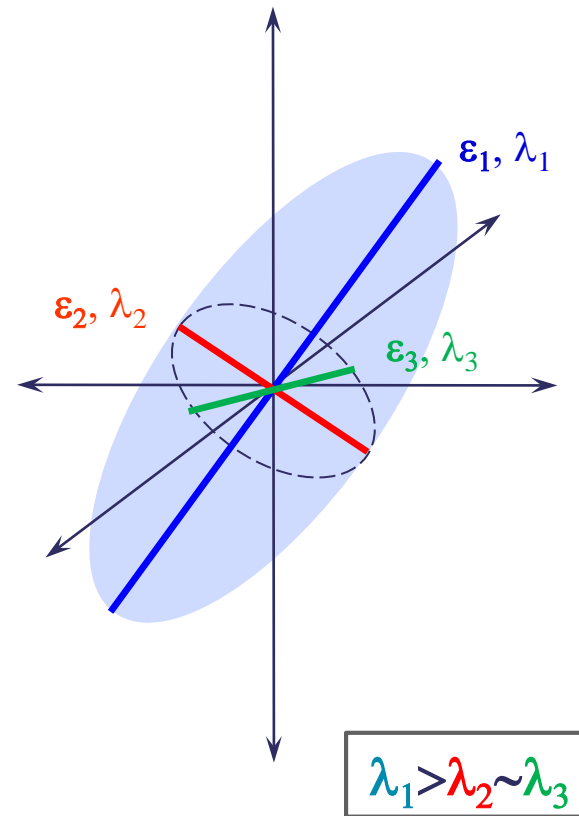
- Introduction to Tractography
- Advanced Modelling:
 - Probabilistic Modelling
 - Multiple-fibre models
 - Diffusion MRI and microstructure

Diffusion ellipsoid: Eigenvalues and eigenvectors

Isotropic Diffusion

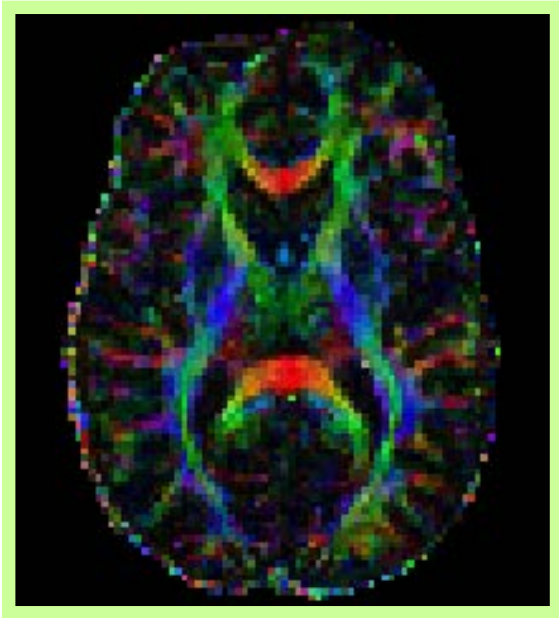


Anisotropic Diffusion



Colour coded FA maps

- Let ε_1 designate the longest axis of the diffusion ellipsoid.
- ε_1 can be identified with the main direction of diffusion.
- This directional information can be added to the FA map using a colour code:



Red indicates directions in the x axis: right to left or left to right.

Green indicates directions in the y axis: front to back or back to front.

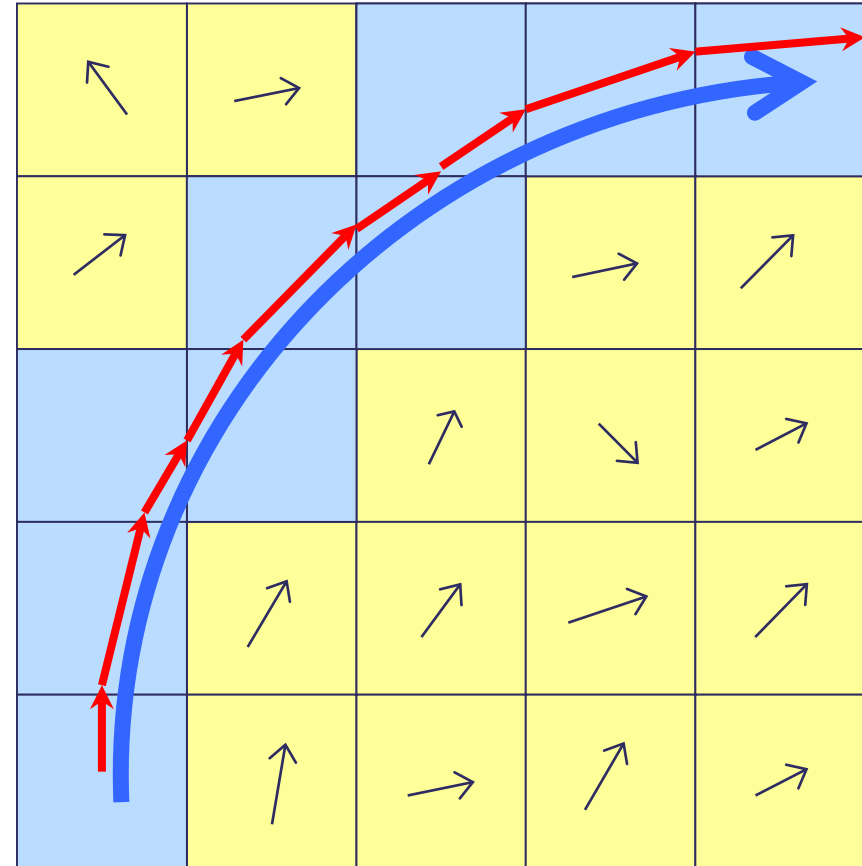
Blue indicates directions in the z axis: foot-to-head direction or vice versa.

Colour coded FA map.

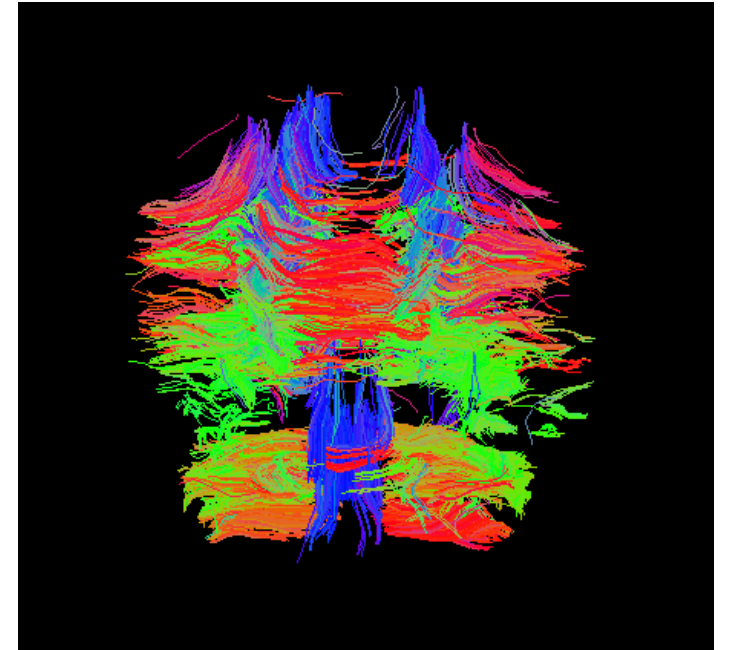
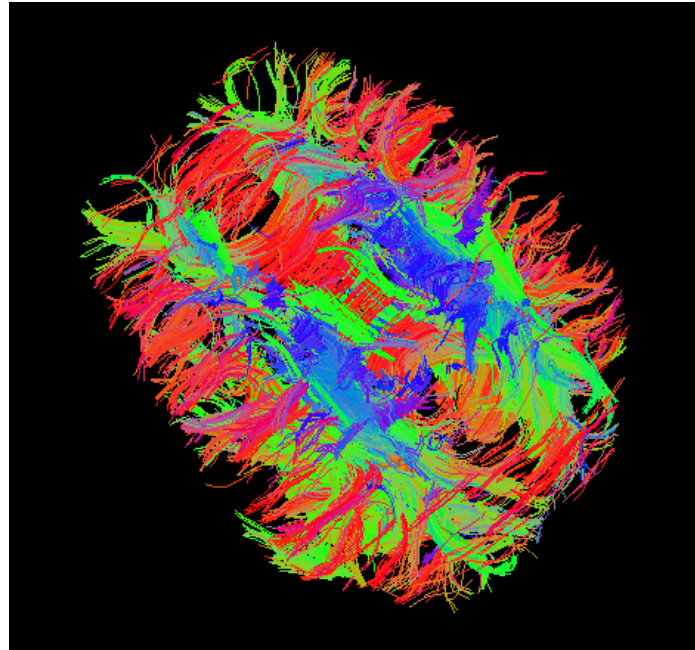
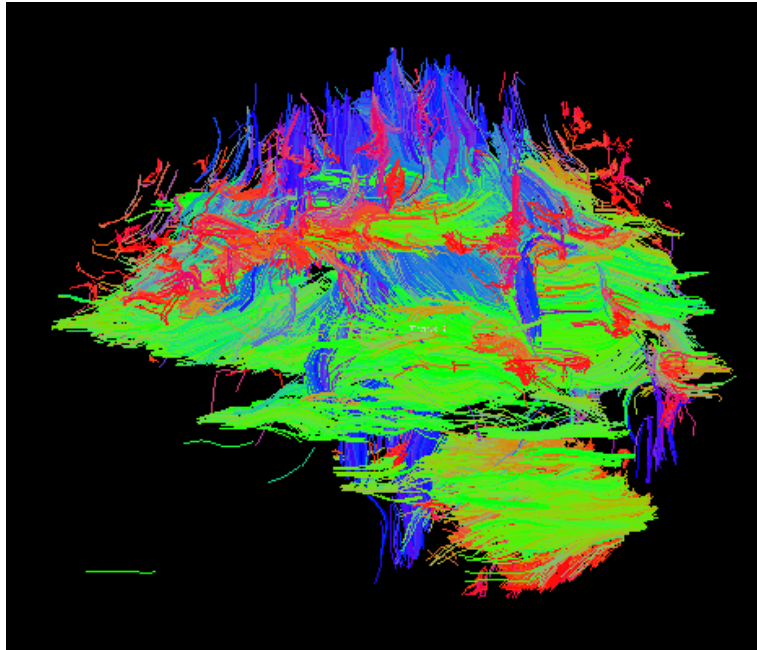
Introduction to Tractography

Tractography: basic principles

- After model fitting, the principal direction ϵ_1 can be calculated for all voxels.
- The trajectories of water molecules can be reconstructed using a method similar to the children's activity "connect the dots".
- We connect each voxel to the adjacent one toward which the fibre direction, ϵ_1 , is pointing.



Tractography in the Brain



Fibre tracks obtained for a dataset of a healthy volunteer using simple streamlining (FACT).

Probabilistic Modeling of Diffusion MRI Signal

Probabilistic Modelling

- The information provided by DTI can be very useful for the characterisation of brain white matter.
- However, the estimated tensor can be highly dependent on noise.
- Probabilistic modelling can be used to estimate a probability distribution function (PDF) for the DTI model parameters.
- The standard deviation (s.d.) of this PDF is a good marker for confidence in the results.

MCMC Methods

- Markov Chain Monte Carlo (MCMC) methods are based on Baye's Theorem:

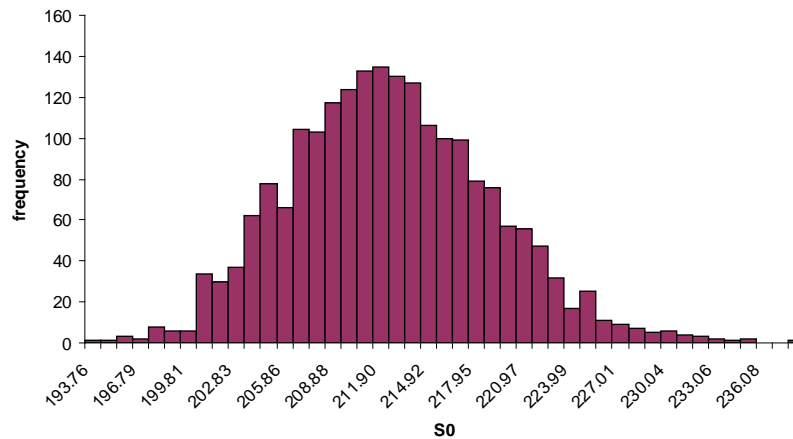
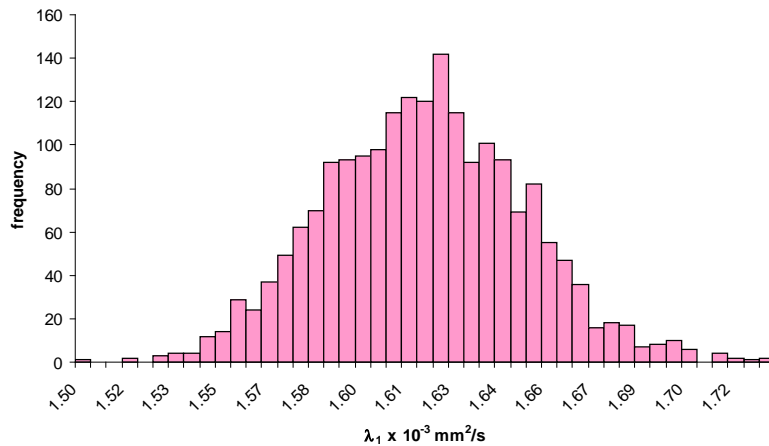
$$P(\omega | data) = \frac{P(data | \omega)P(\omega)}{P(data)}$$

where ω represents the vector of model parameters.

- The prior term $P(\omega)$ offers an opportunity for scientists to include knowledge they have about the expected values of the parameters.
- The term $P(data | \omega)$ gives the probability of observing the data given a sampled set of parameters, and it is dependent on the model used.

MCMC Methods

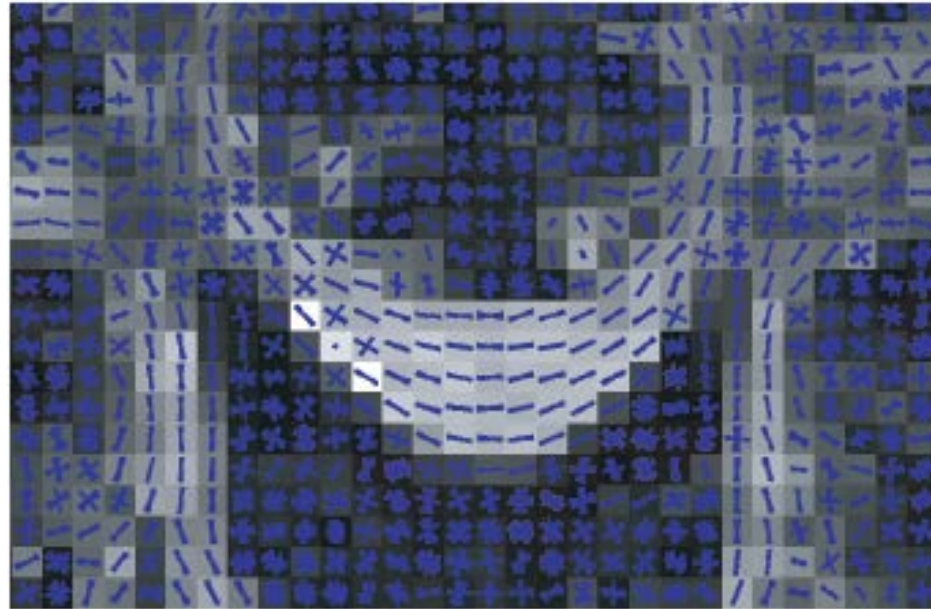
- Instead of producing a single set of parameters MCMC methods produce a PDF for each parameter.



- The standard deviation of these PDFs is a good marker for confidence in the results.
- **FA maps, MD maps**, etc., can be obtained by taking the average of each PDF as the most likely value of the model parameters.

PDF for fibre orientation

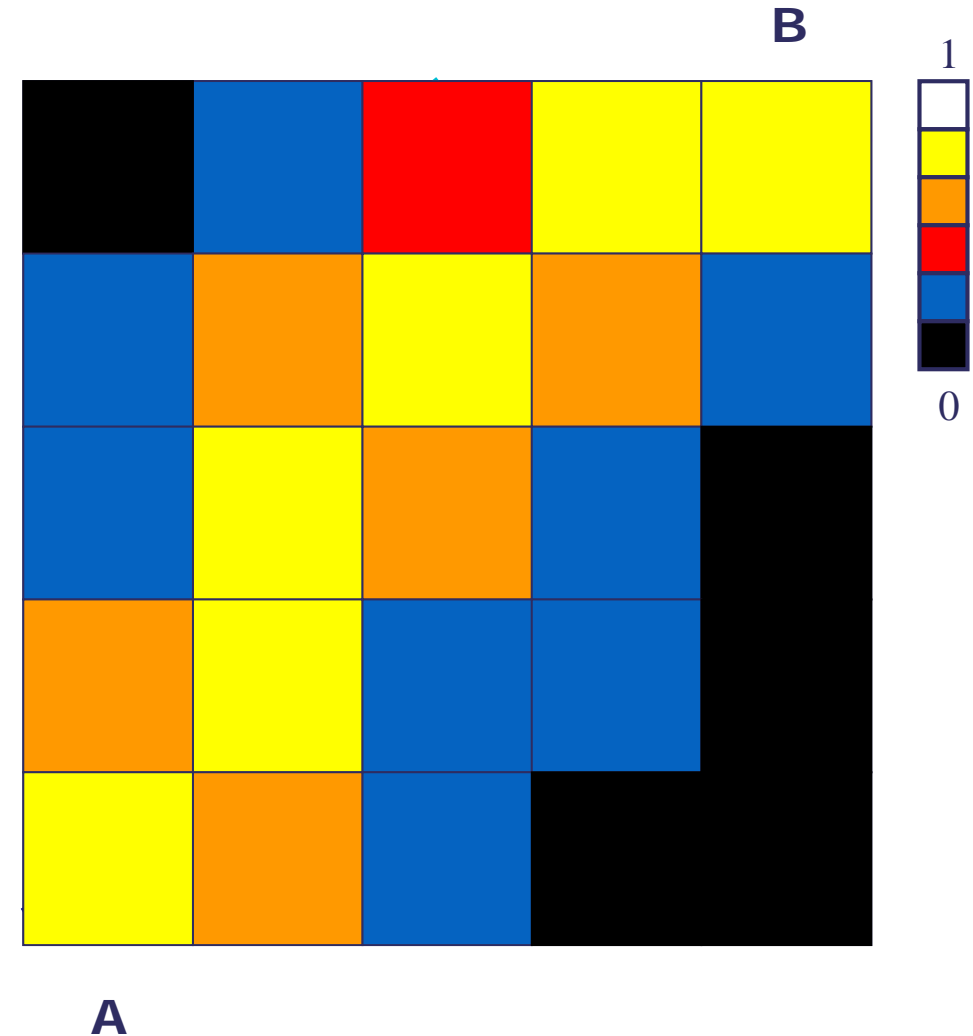
- For each voxel, we can obtain a PDF for the fibre orientation, by combining samples from the PDFs for θ and ϕ :



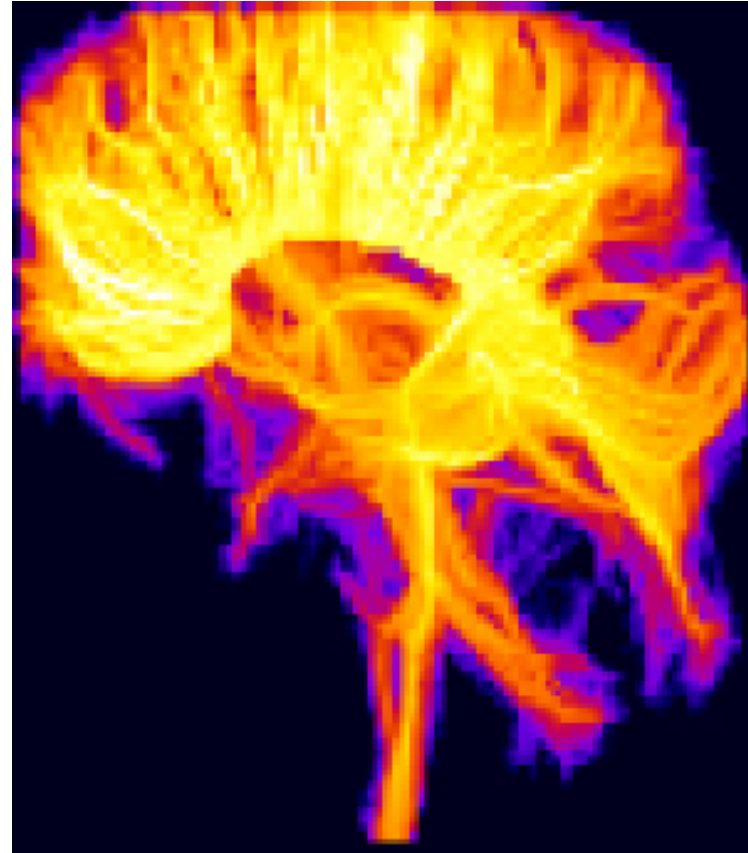
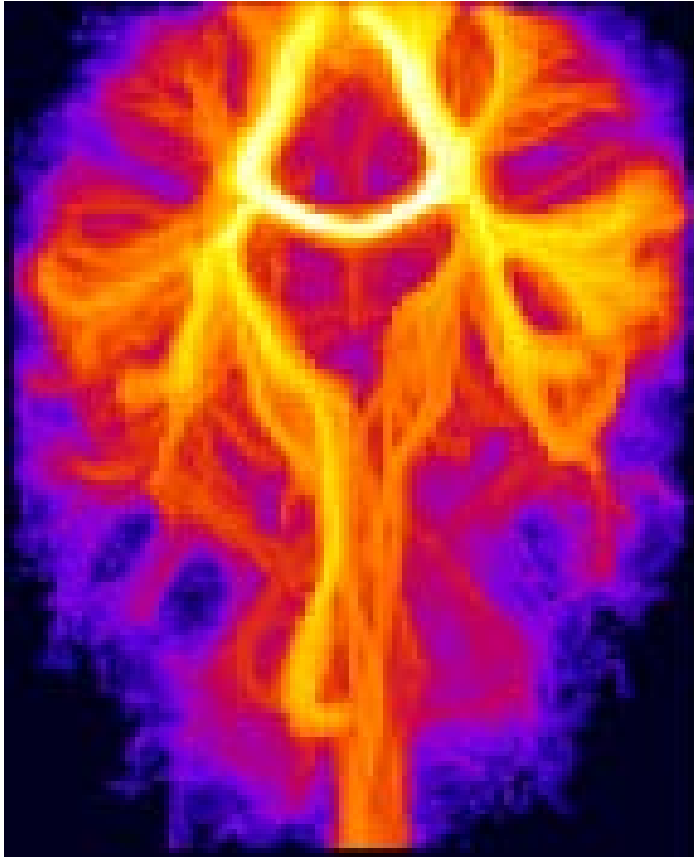
- Regions of one-fibre populations have very narrow distributions, while regions of crossing fibres show greater variability.

Probabilistic Tractography

- For each sample of the directional PDF we can produce a track (or streamline).
- Repeat this for a large number of samples.
- The probability of voxels A and B being connected can be calculated by dividing the number of streamlines that reach B, by the total number of streamlines generated from A.

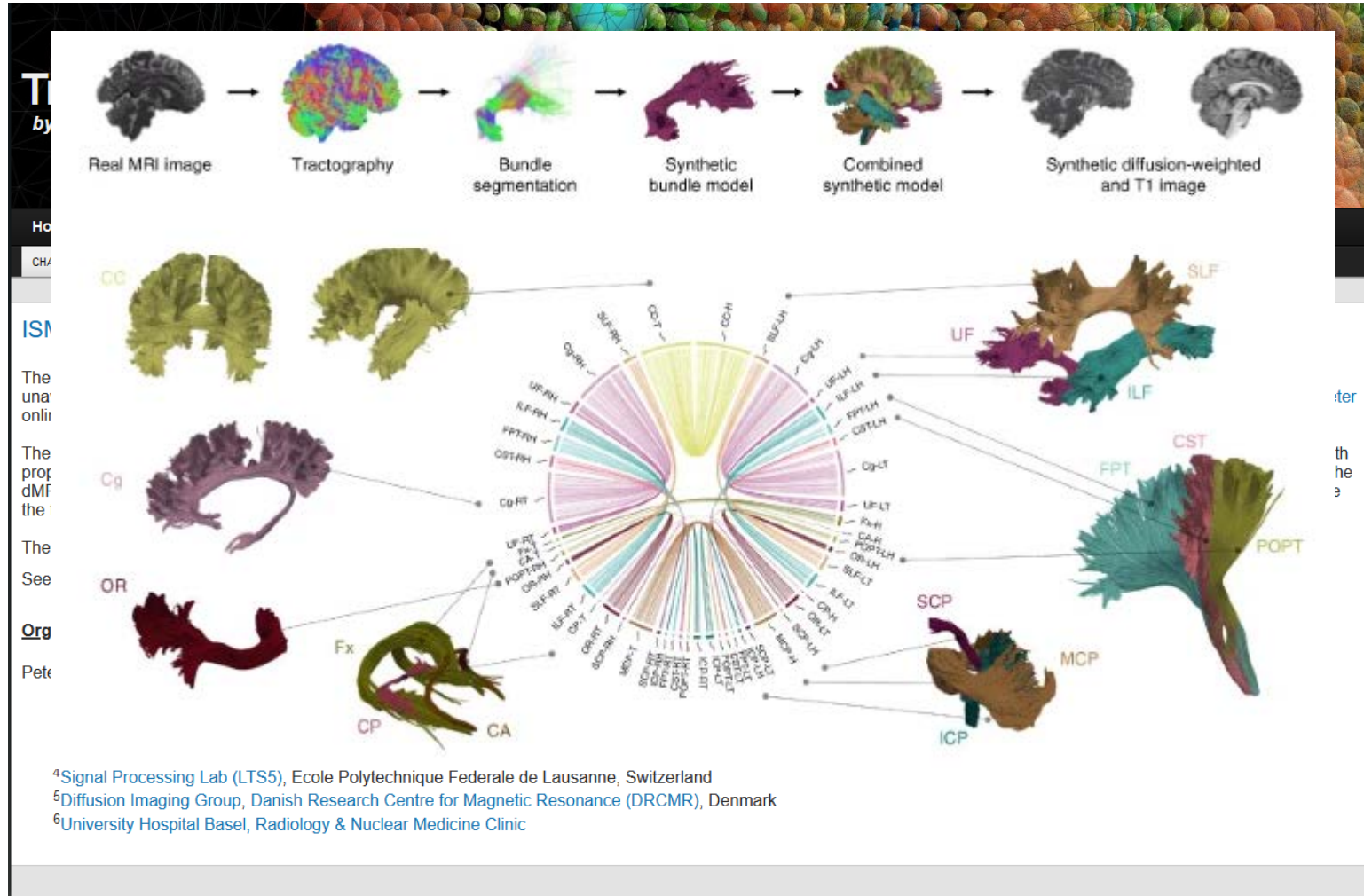


Probabilistic Tractography in the Brain



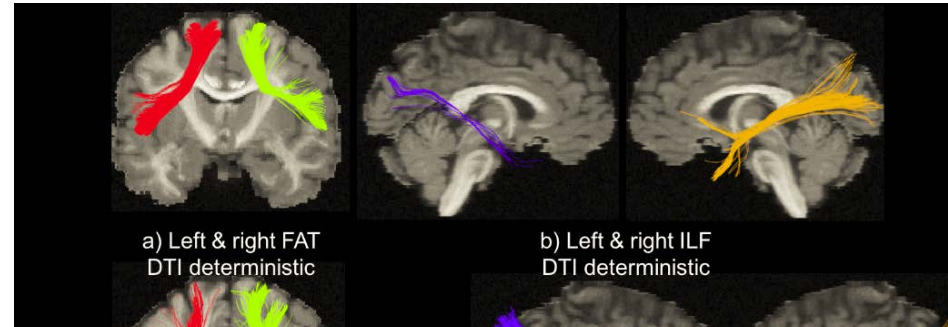
Probabilistic tractography dataset obtained for a healthy volunteer.

Tractography: A warning

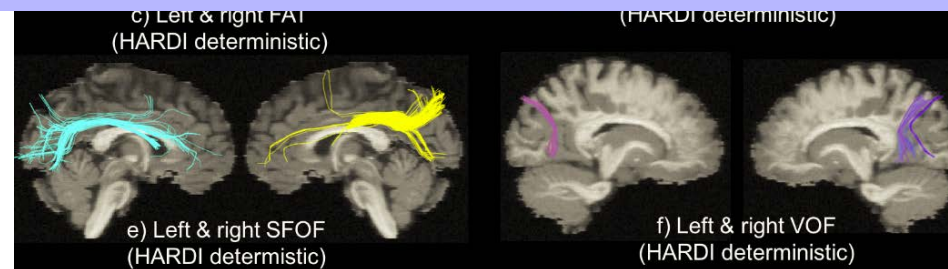


Tractography: A warning

- Examples of **invalid bundles**



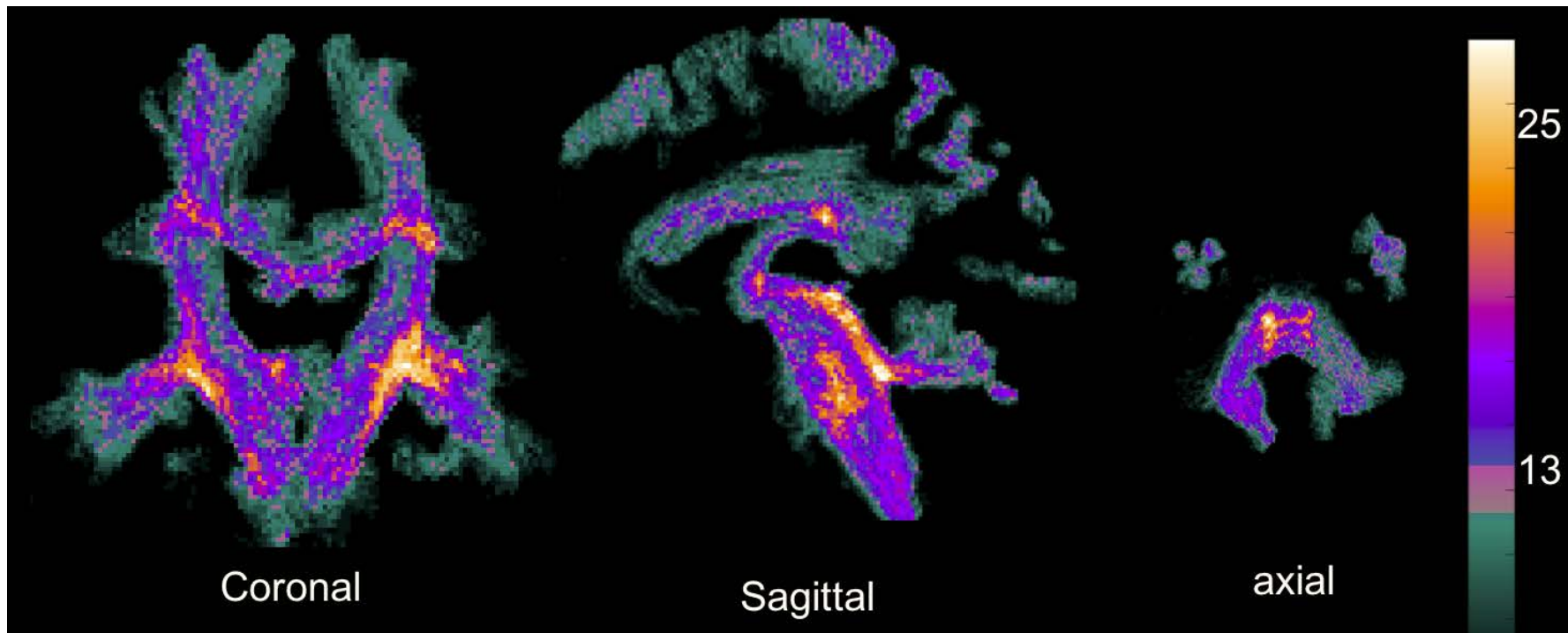
On average, for every correct bundle, **4 invalid bundles** were identified!!



Bundles	FAT	ILF	MLF	SFOF	VOF
Occurrence (%)	88%	85%	95%	81%	81%

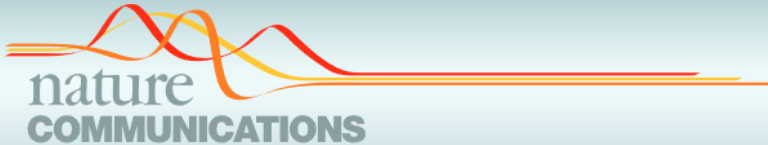
Tractography: A warning

- Most common occurring locations of intersecting **invalid bundles**



Tractography: A warning

http://tractometer.org/ismrm_2015_challenge/



Corrected: Author correction

ARTICLE

DOI: [10.1038/s41467-017-01285-x](https://doi.org/10.1038/s41467-017-01285-x)

OPEN

The challenge of mapping the human connectome based on diffusion tractography

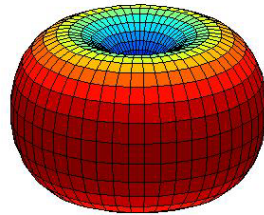
Klaus H. Maier-Hein

Multiple fibres

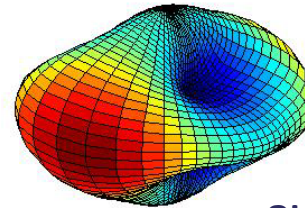
Beyond the Diffusion Tensor

Why the diffusion tensor is not the end of the story

- DTI has a key limitation: it assumes a single fibre per voxel, and it cannot be used to explain the signal profile obtained from multiple crossing fibres.



Signal profile from a single fibre



Signal profile from two crossing fibres

- This limitation results in artificially low FA values in regions of crossing fibres, and in greater variability of FA and MD estimates.
- It is also a major obstacle for tractography and connectivity mapping, since the model fails at fibre crossings.
- A variety of alternative models and algorithms aim to resolve the orientations of crossing fibres.

Multiple fibre approaches

Model-Based Approaches

- The multi-tensor model

Non-Parametric Approaches

- Diffusion Spectrum Imaging (DSI)
- Q-ball Imaging
- Constrained Spherical Deconvolution (CSD)
- Persistent Angular Structure (PAS)

Multiple fibre approaches

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The Multi-tensor Model

- The multi-tensor model is a simple generalisation of DTI.
- The signal in each voxel is modelled by a mixture of n Gaussian densities:

$$S(b, \vec{r}) = S_0 \sum_{i=1}^n f_i e^{-b \vec{r}^T \underline{D}_i \vec{r}}$$

where f_i represents the volume fraction of compartment i .

- This model assumes the number of distinct fibre populations, n , is known.
- The parameters $\underline{D}_1, \dots, \underline{D}_n$ cannot be expressed as a linear function of the signal, so non-linear optimisation is required.
- The principal eigenvector of each \underline{D}_i provides a separate fibre orientation estimate.

The Multi-tensor Model

- Practical considerations, such as the number of measurements and the noise level, limit the number of orientations the method can resolve reliably, and most studies use $n=2$.

Acquisition requirements

- A minimum of $n \times 7$ unique gradient directions are required to estimate the model parameters.
- In 2005 Alexander and Barker recommended using b in the range 2200-2800 s/mm².

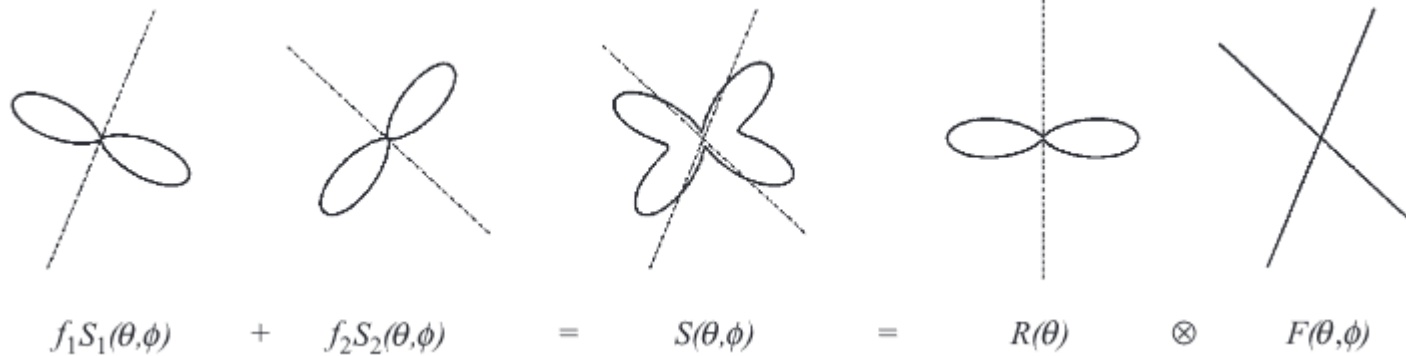
Limitations

- Increased acquisition time and lower SNR.
- Using 64 directions the 2-tensor model can resolve 60 degree crossings, but does not consistently resolve 30 degree crossings.

Constrained Spherical Deconvolution (CSD)

- CSD is able to estimate the distribution of fibre orientations within a voxel without making assumptions about the number of fibres present.
- The original method (Tournier et al. 2007) requires a single-shell high angular resolution diffusion data (>60 directions).
- Ideally, the b -value used should be in the region of 2,500 – 3,000 s/mm² (for *in vivo* human brains).
- Multi-shell multi-tissue CSD (MSMT-CSD) was introduced by Jeurissen et al. in 2014.
- MSMT-CSD requires multi-shell high angular resolution diffusion data, containing multiple b -values.
- To resolve WM, GM & CSF the acquisition should contain at least 2 shells plus the $b=0$ volumes (i.e. 3 unique b -values).

Constrained Spherical Deconvolution (CSD)



Tournier et al. 2007

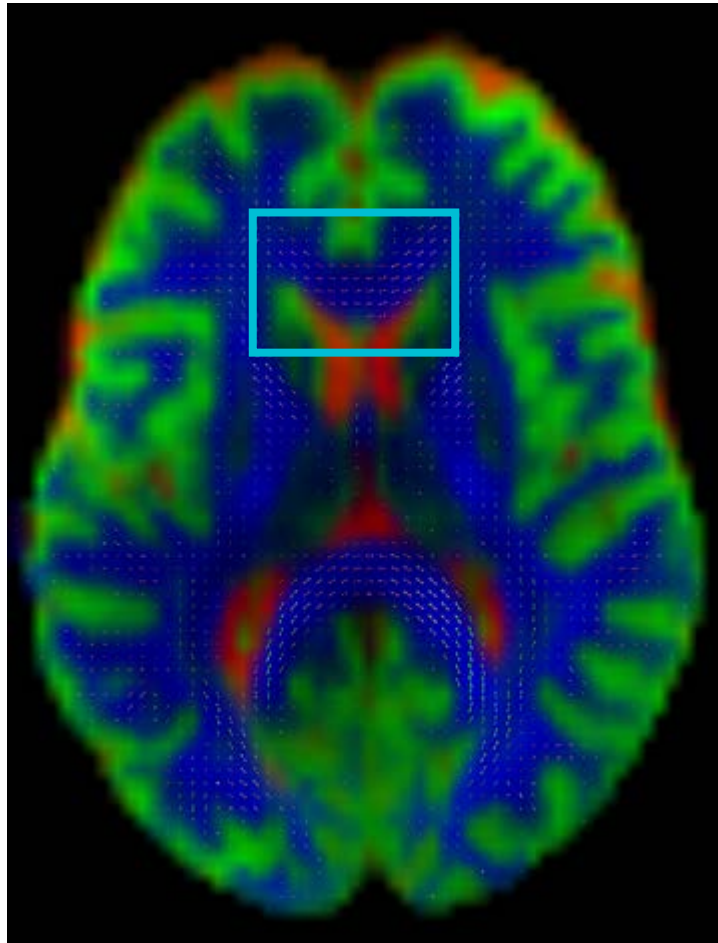
- Two distinct fibre orientations
- $S_1(\theta, \phi), S_2(\theta, \phi)$ – diffusion weighted signal attenuation
- f_1, f_2 – volume fractions

- Overall diffusion weighted signal attenuation

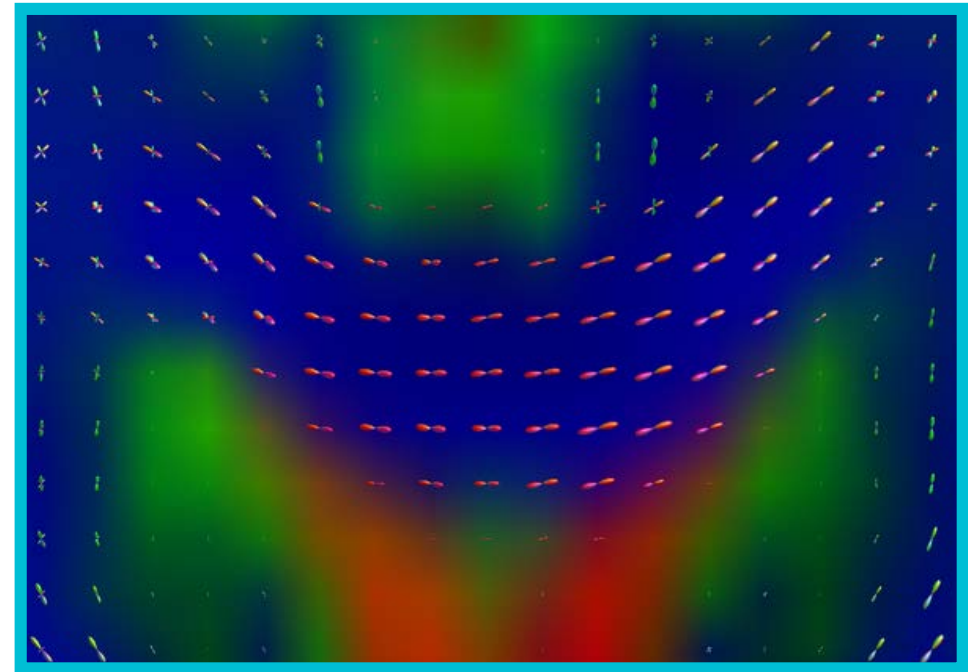
- Axially symmetric response function describing the signal attenuation measured for a single fibre population.

- Fibre orientation density function describing the fibre orientations present in the voxel

Constrained Spherical Deconvolution (CSD)



White matter
Grey matter
CSF



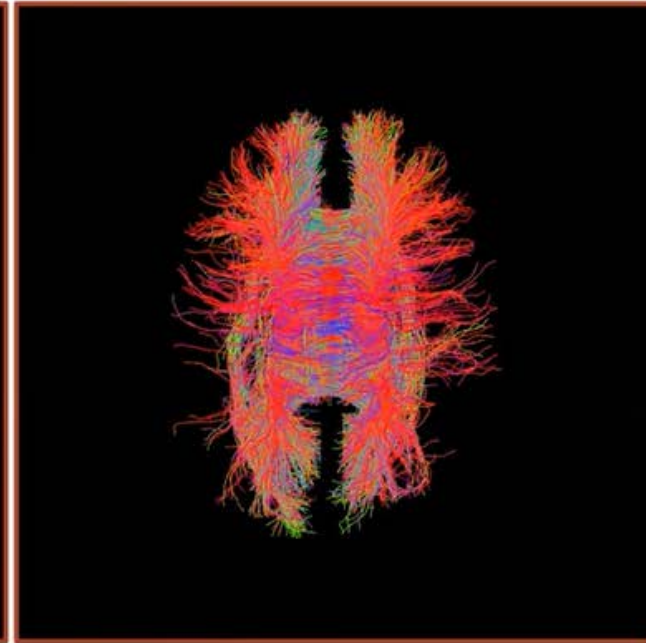
Constrained Spherical Deconvolution (CSD)



**DTI
Tractography**



**CSD Deterministic
Tractography**

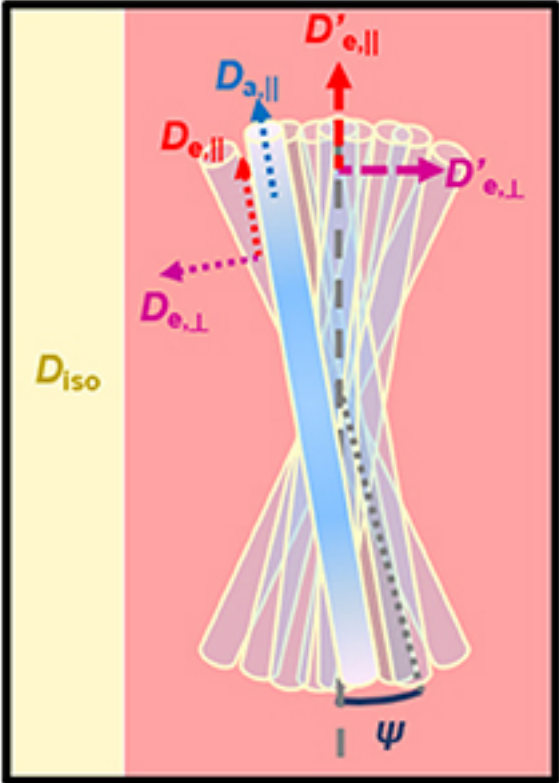


**CSD Probabilistic
Tractography**

From Gabriel Girard, DIPY tutorial 2021

Diffusion MRI and Microstructure

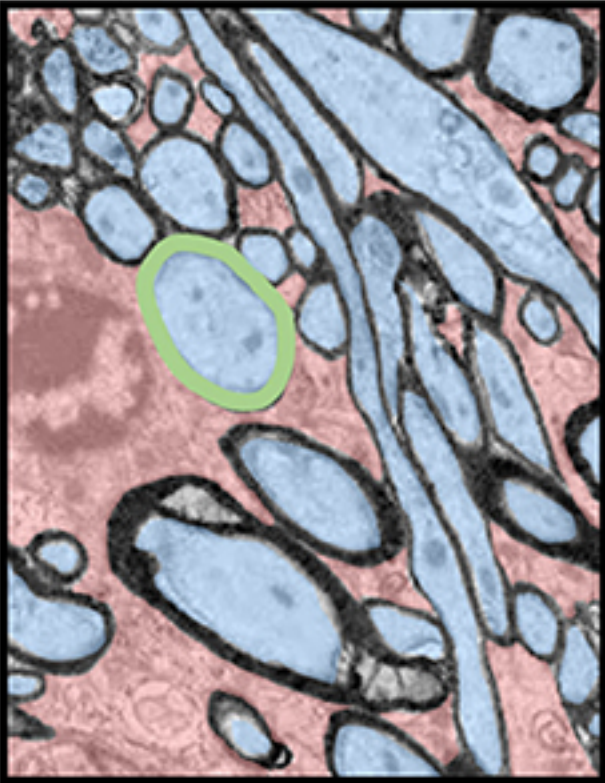
Modelling multiple diffusion compartments



- Intra-axonal space (IAS)
- Extra-axonal space (EAS)
- CSF
- Myelin

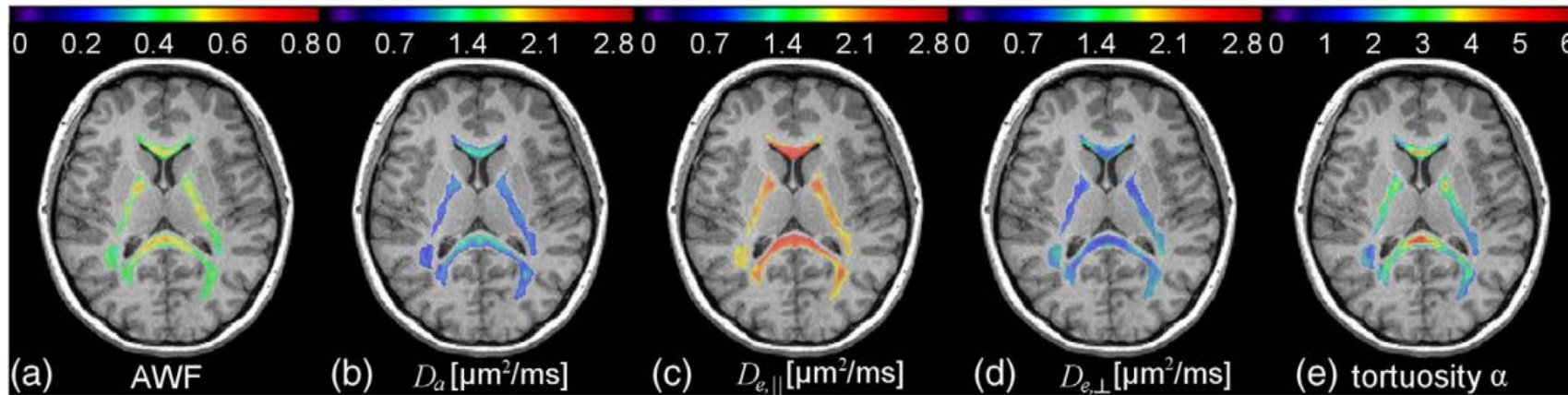
$$\frac{\text{lightblue square}}{\text{lightblue square} + \text{lightcoral square}} = f_{\text{intra}}$$

$$\frac{\text{yellow square}}{\text{lightblue square} + \text{lightcoral square} + \text{yellow square}} = f_{\text{iso}}$$

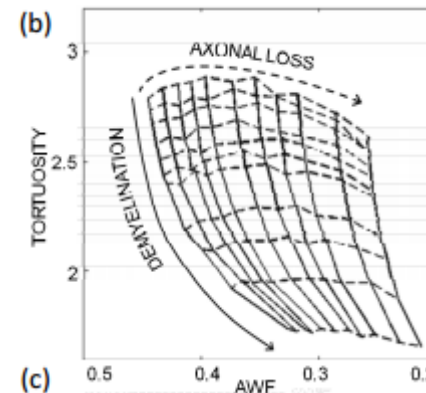


White Matter Tract Integrity (WMTI)

- Introduced by Fieremans et al. (2011).

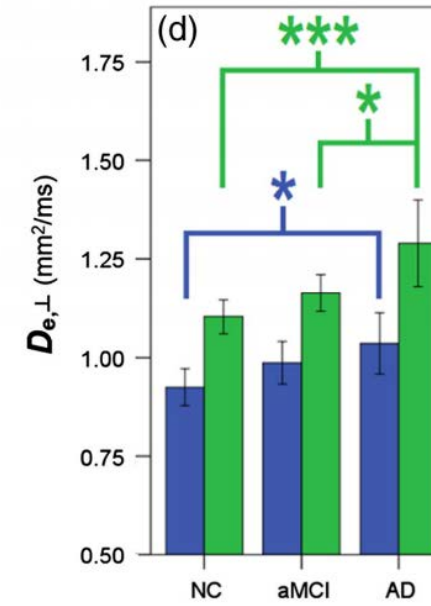
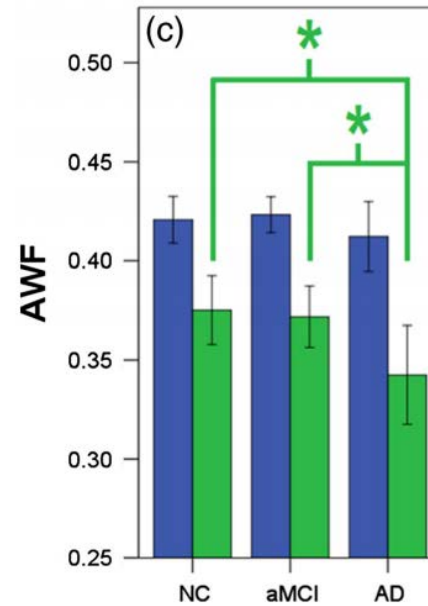
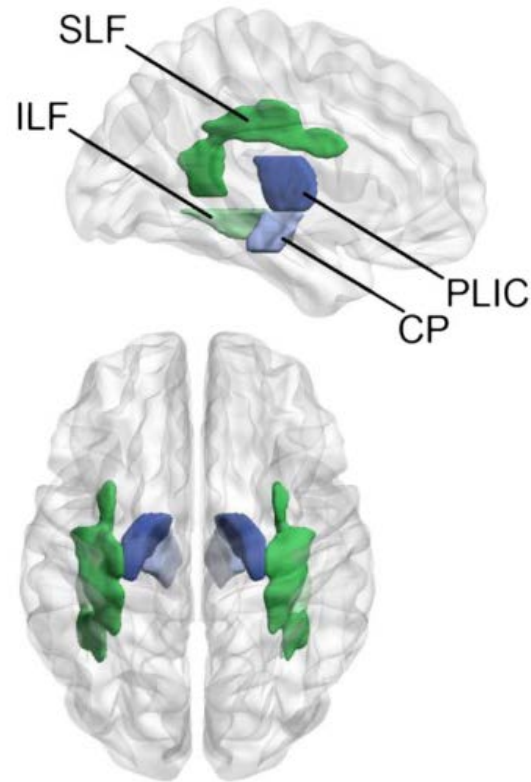


- AWF and tortuosity differentiate between axonal loss and demyelination (Fieremans et al. 2012).
- Typical acquisition time: 10-15minutes (usually two b-values in the range 1000-2500 s/mm^2 x 30-60 directions).



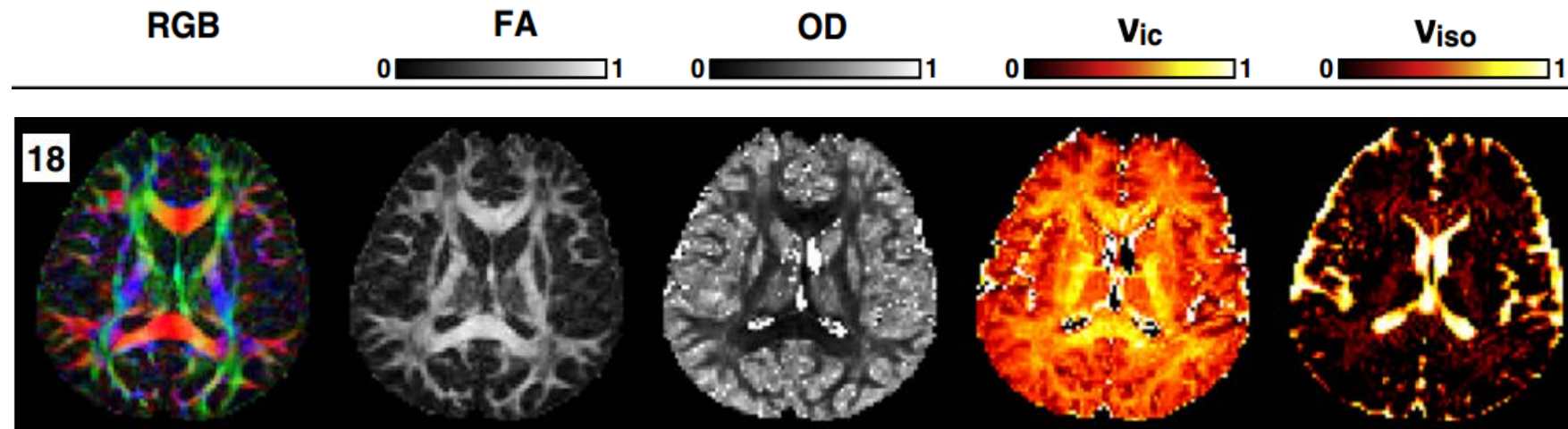
White Matter Tract Integrity (WMTI)

- WMTI metrics reflect differences between MCI and Alzheimer's disease (Benitez et al. 2014).



Neurite Orientation Dispersion and Density Imaging (NODDI)

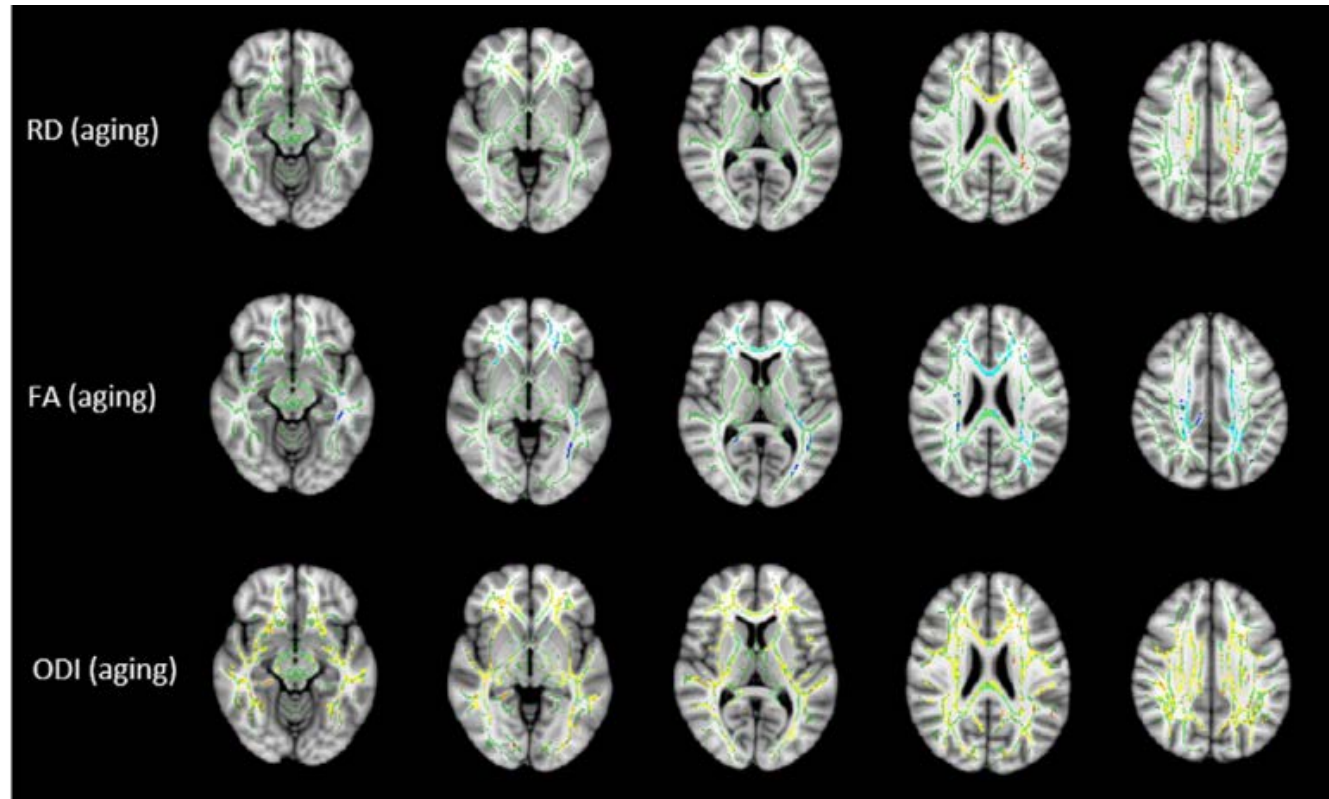
- Introduced by Zhang et al. (2012).



- Typical acquisition time: **30 minutes** ($b=711\text{s/mm}^2 \times 30 \text{ dir}$, $b=1000 \text{ s/mm}^2 \times 30 \text{ dir}$, $b=2000\text{s/mm}^2 \times 60 \text{ dir}$, and $b=2855 \text{ s/mm}^2 \times 60 \text{ dir}$).

Neurite Orientation Dispersion and Density Imaging (NODDI)

- NODDI in young to middle-aged adults (Kodiweera et al. 2016).



Summary

- Tractography is a popular method used to reconstruct white matter fibre pathways.
- Easy to run, with multiple methods and software packages to choose from.
- HOWEVER, this technique is severely affected by false positives and spurious findings, and results should be interpreted with scepticism.
- Advanced diffusion MRI acquisitions and modelling beyond DTI allows us to model multiple fibre orientations and multiple tissues types.



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Thank you