MRC | Cognition and Brain Sciences Unit

Advanced Diffusion MRI

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Overview

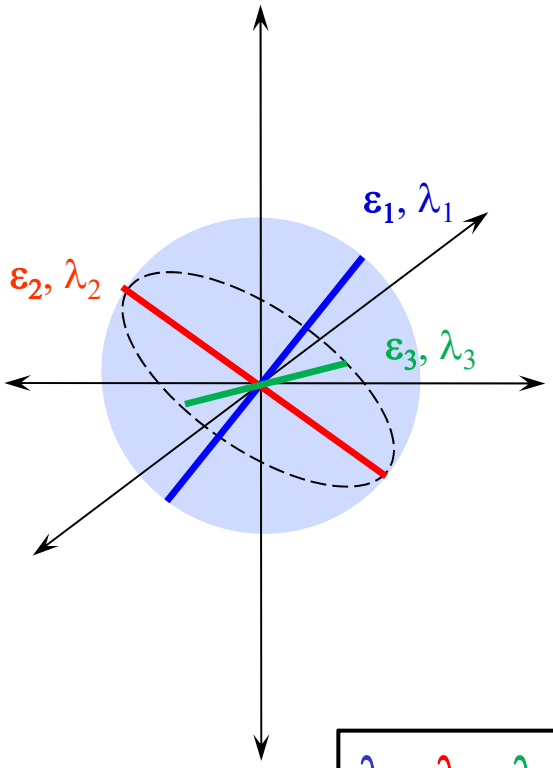
- Introduction to Tractography
- Advanced Modelling:
  - Probabilistic Modelling
  - Multiple-fibre models
  - Diffusion MRI and microstructure

- Hands on session

Introduction to Tractography

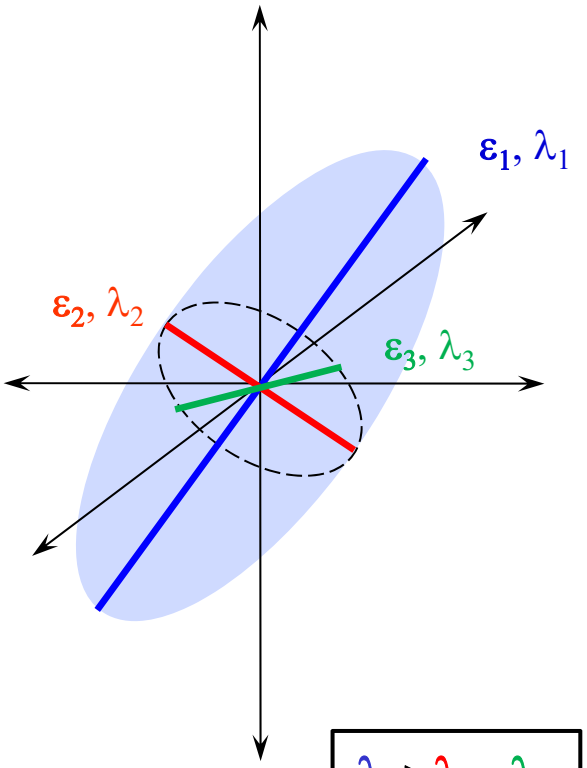
Diffusion ellipsoid: eigenvalues & eigenvectors

Isotropic Diffusion



$\lambda_1 = \lambda_2 = \lambda_3$

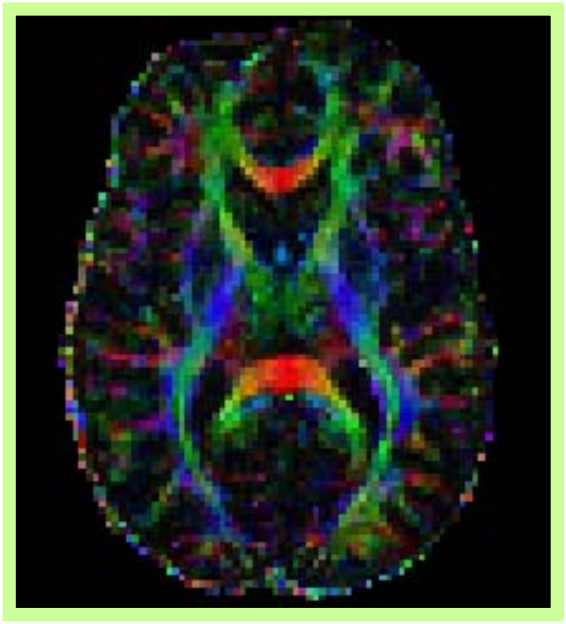
Anisotropic Diffusion



$\lambda_1 > \lambda_2 \sim \lambda_3$

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.

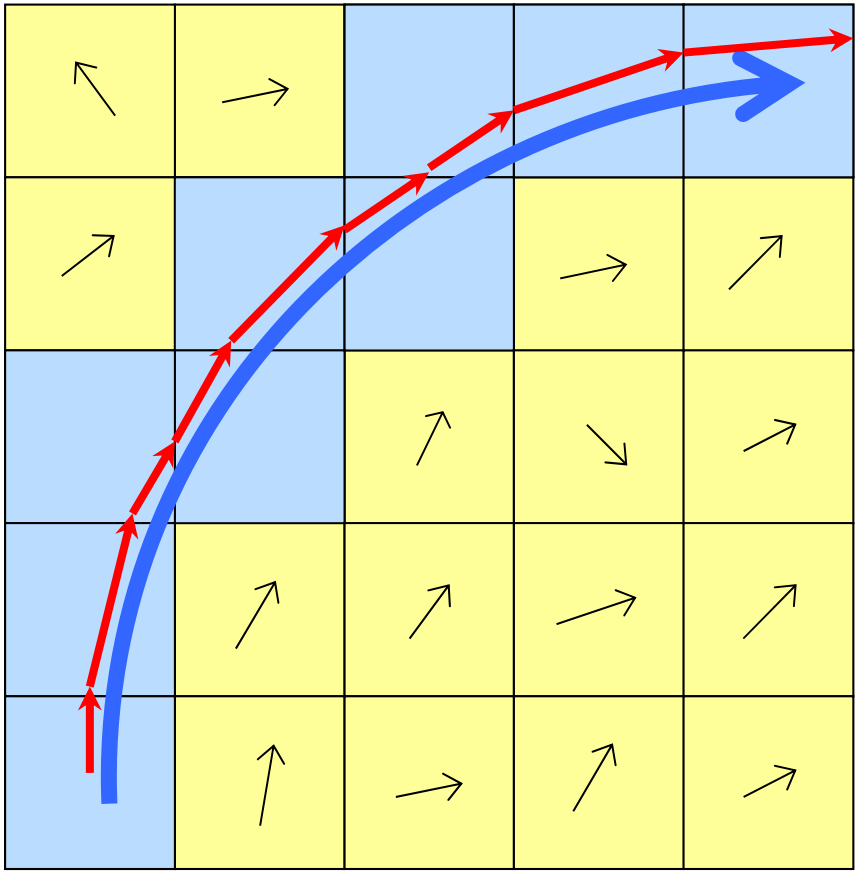
Green indicates directions in the *y* axis: front to back or back to front.

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

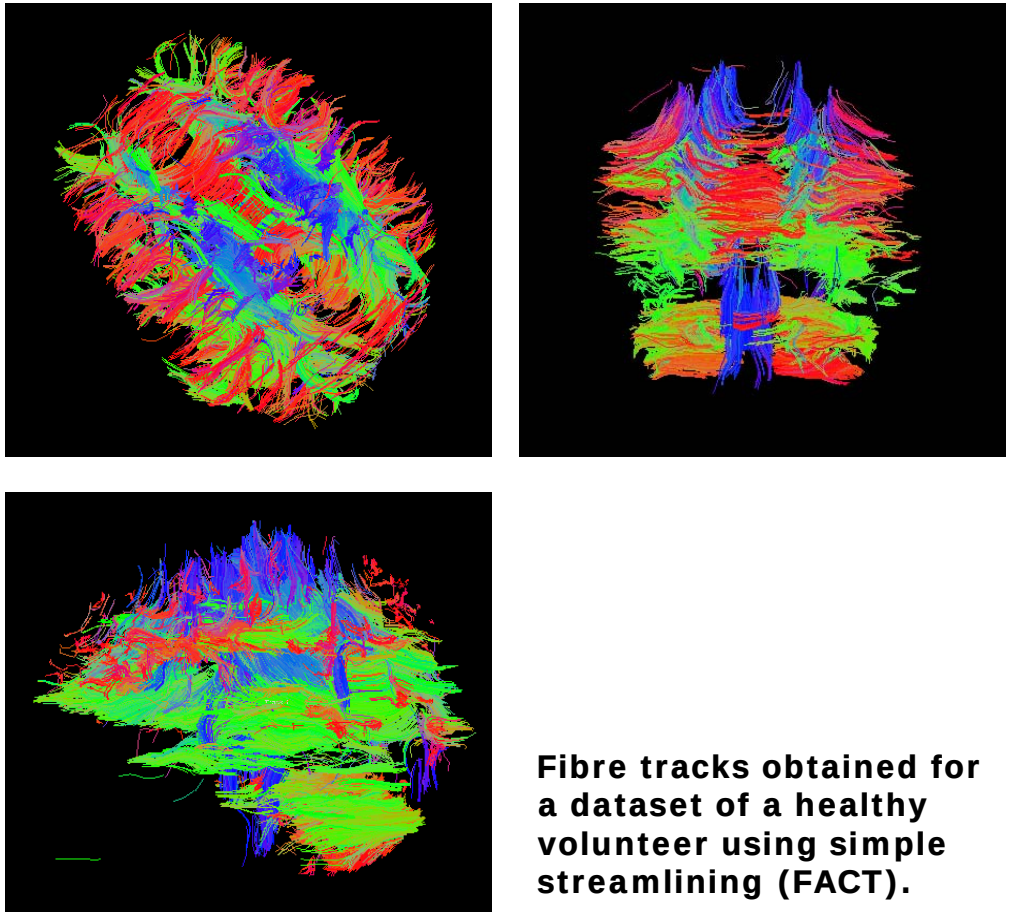
Colour coded FA map.

Tractography

- Once direction ε_1 has been 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 (1)

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

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

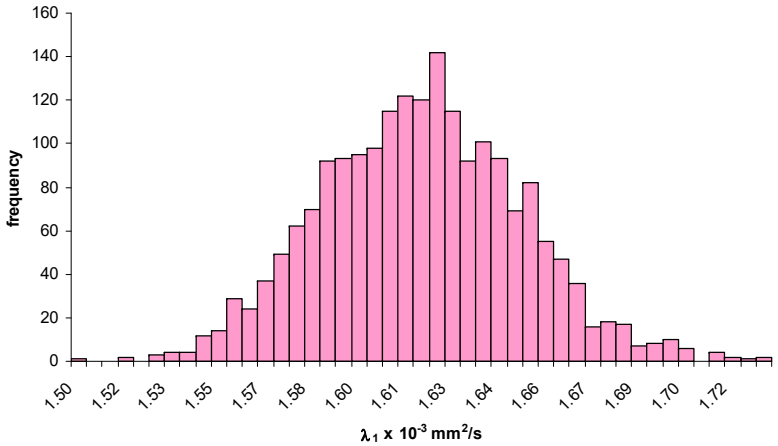
where ω represents the vector of model parameters.

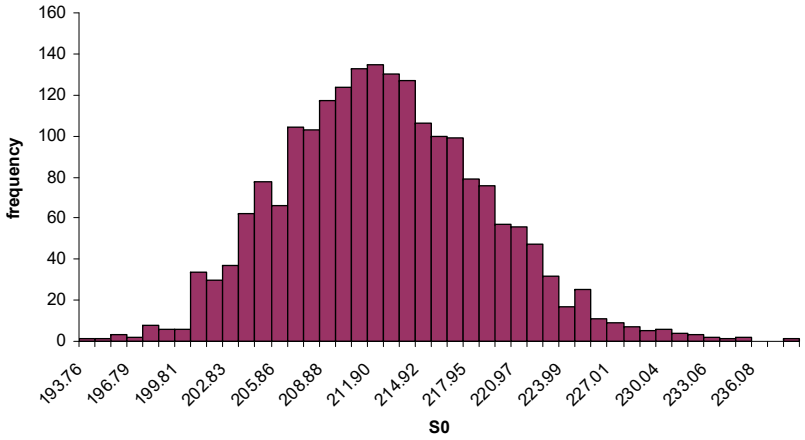
- The prior term $P(\omega)$ offers an opportunity for scientists to include knowledge they have about the expected values of the parameters.

- The term $P(data \mid \omega)$ gives the probability of observing the data given a sampled set of parameters, and it is dependent on the model used.

MCMC Methods (2)

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



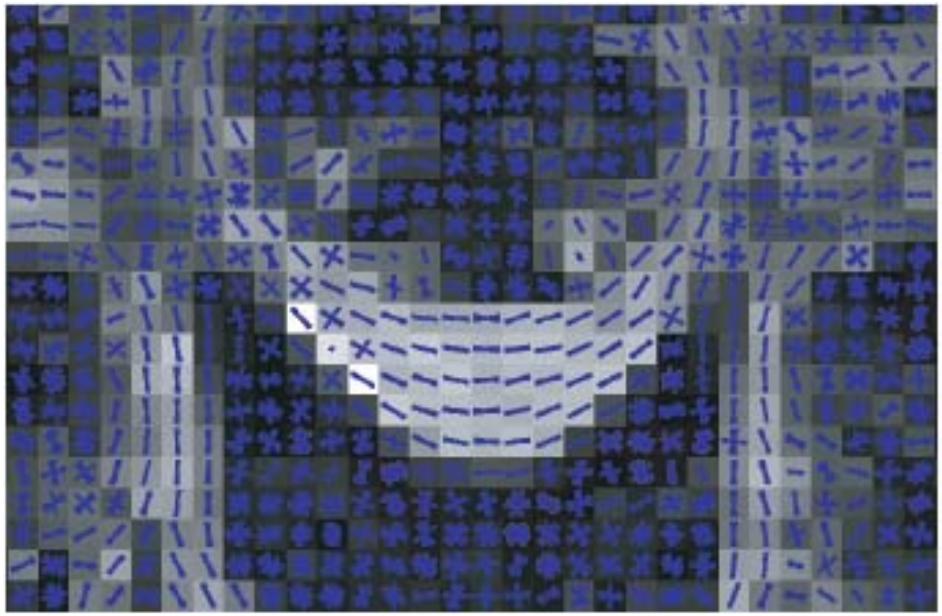


- The standard deviation of these PDFs is a good marker for confidence in the results.

- **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:

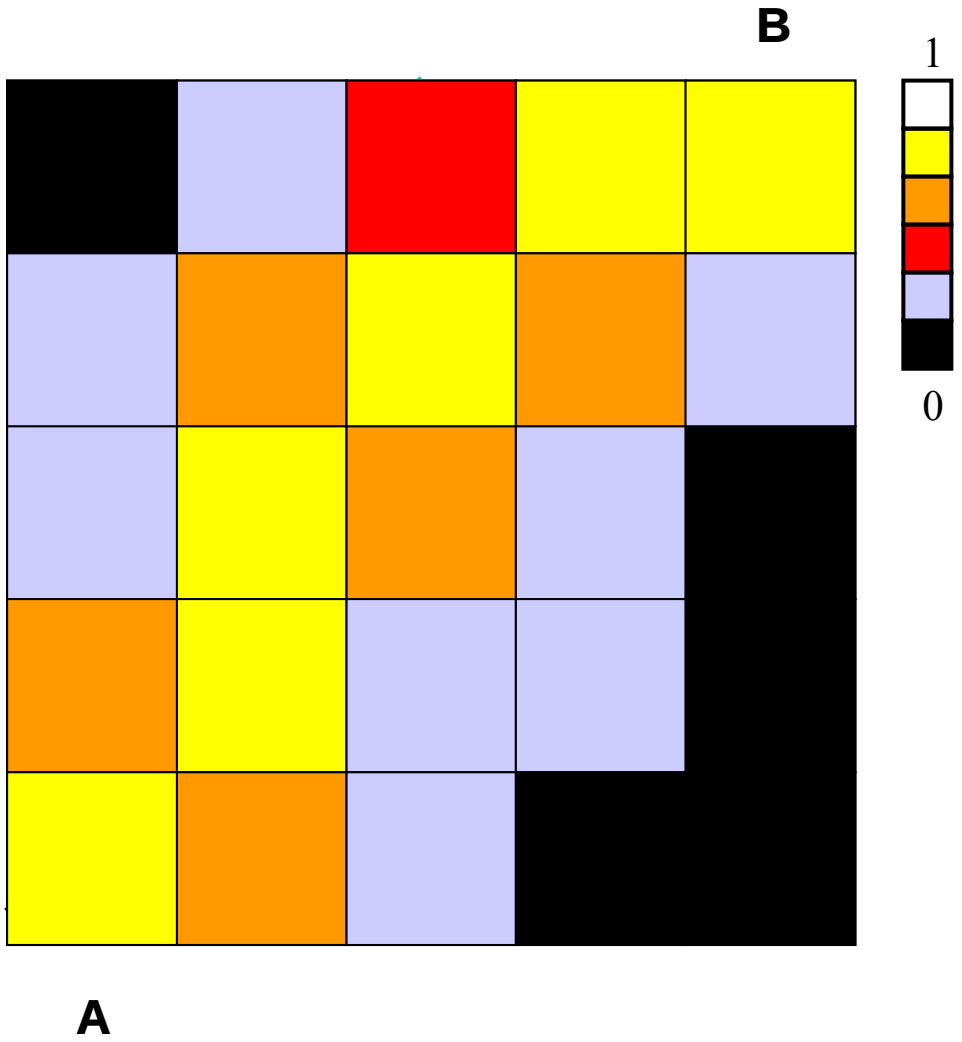


• Regions of one-fibre populations have very narrow distributions, while regions of crossing fibres show greater variability.

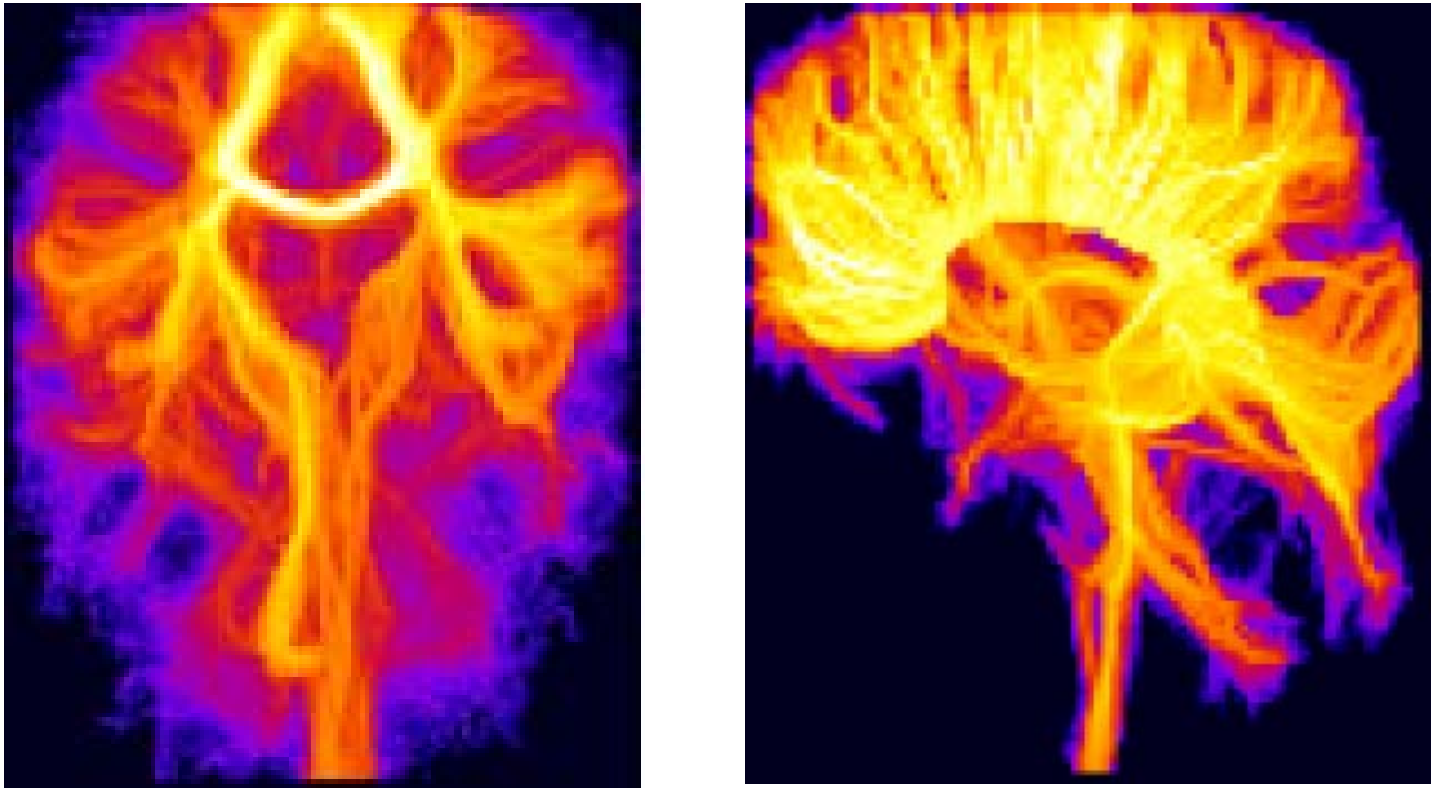
Probabilistic Tractography

- For each sample of the directional PDF we can produce a track (or streamline).

- If we 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.



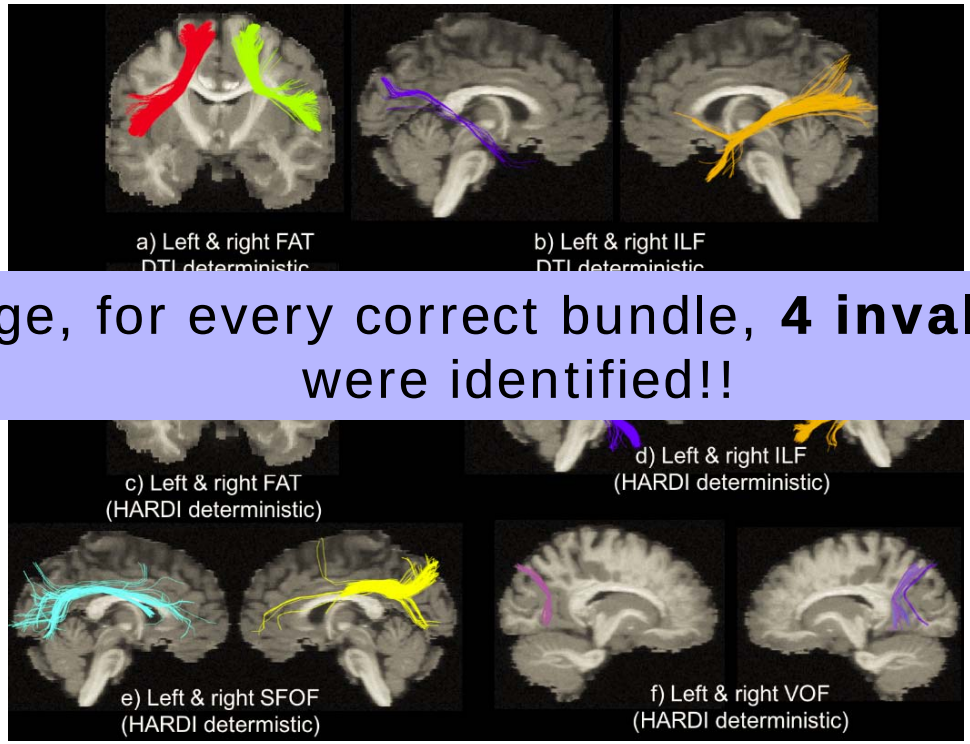
Probabilistic Tractography in the Brain



Probabilistic tractography dataset obtained for a healthy volunteer.

Tractography: A warning

- Examples of **invalid bundles**

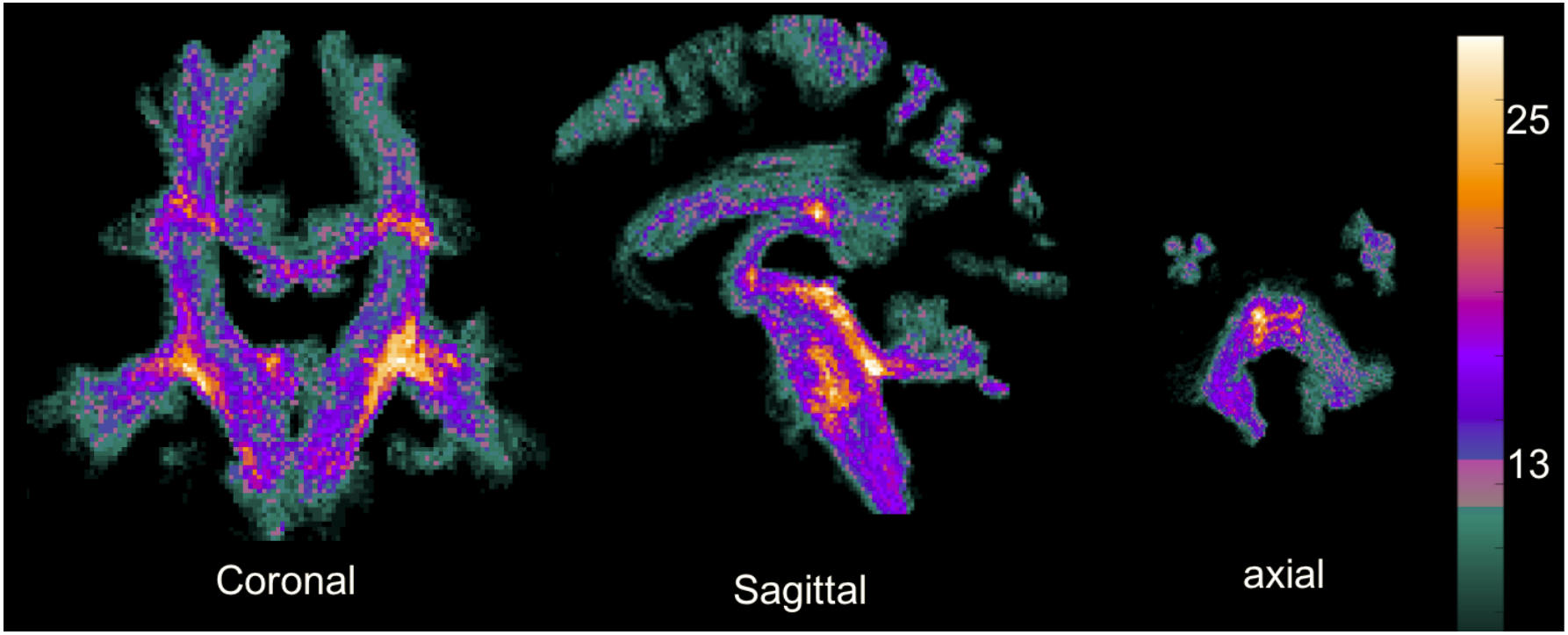


On average, for every correct bundle, **4 invalid bundles** were identified!!

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

Tractography: A warning

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

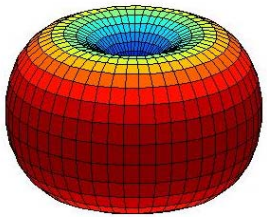


Multiple fibres

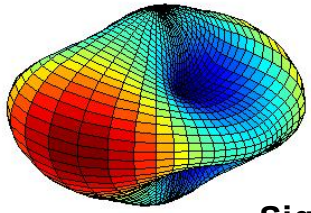
Beyond the Diffusion Tensor

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)

The Multi-tensor Model (1)

• The multi-tensor model is a simple generalisation of DTI, which replaces the single Gaussian model by a misture 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.

• Unlike the DTI model, the parameters $\underline{D}_1$, …, $\underline{D}_n$ cannot be expressed as a linear function of the measurements, so the model fitting requires non-linear optimisation.

The Multi-tensor Model (2)

- Once fitted, the principal eigenvector of each $\underline{D}_i$ provides a separate fibre orientation estimate.

- 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 $n\times7$ unique gradient directions are required to estimate the model parameters.

- In 2005 Alexander and Barker recommended using b in the range 2200-2800 s/mm^2.

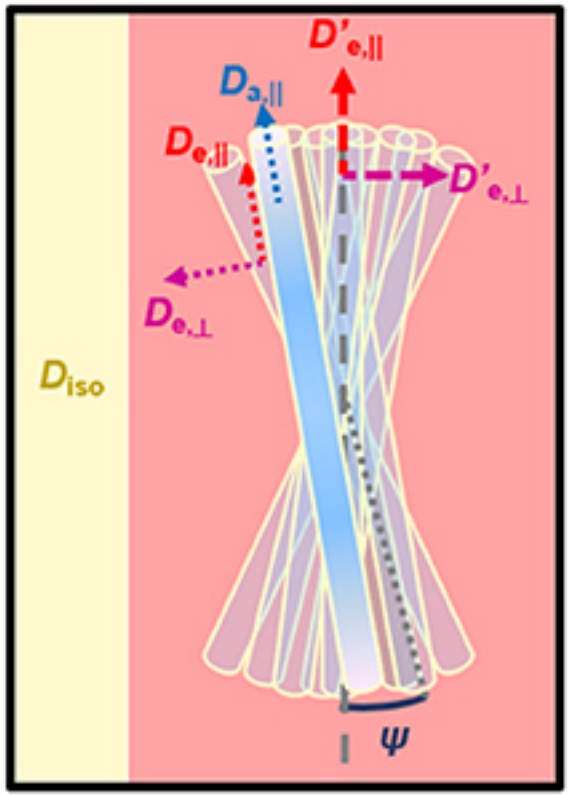
Limitations

- 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.

Diffusion MRI and Microstructure

Modelling multiple diffusion compartments



Intra-axonal space (IAS)

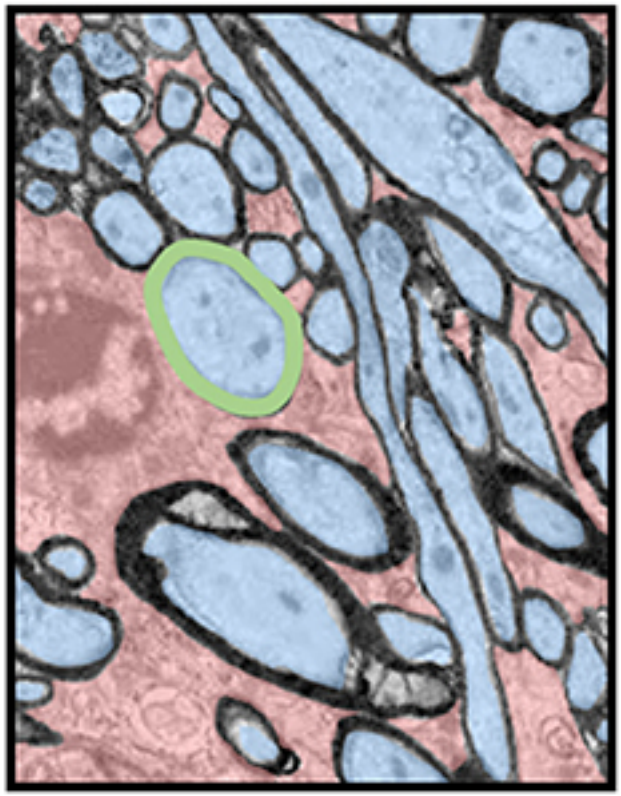
Extra-axonal space (EAS)

CSF

Myelin

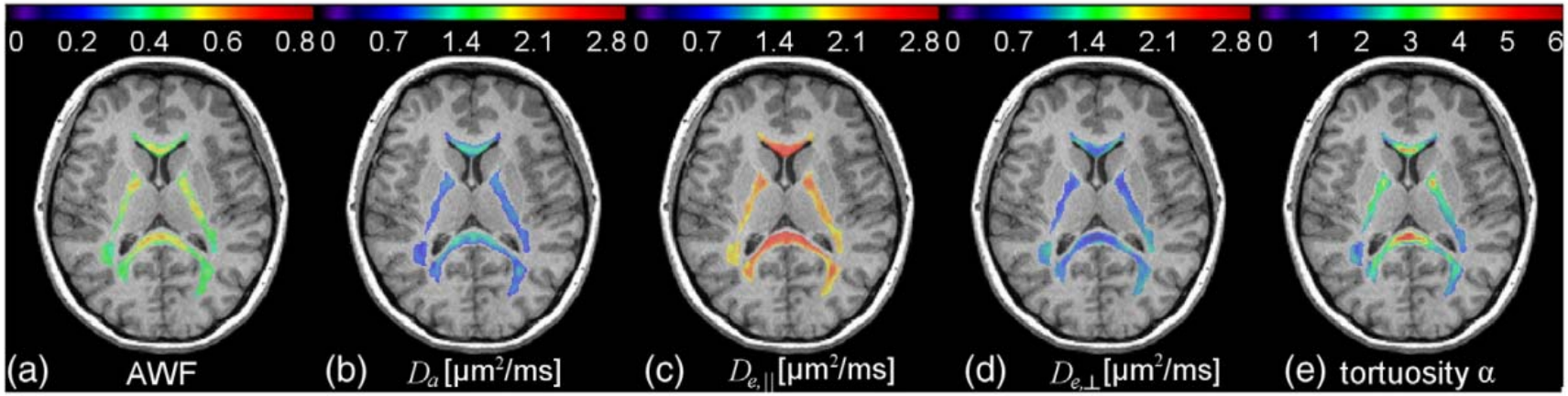
$$\frac{\square}{\square + \square} = f_{intra}$$

$$\frac{\square}{\square + \square + \square} = f_{iso}$$

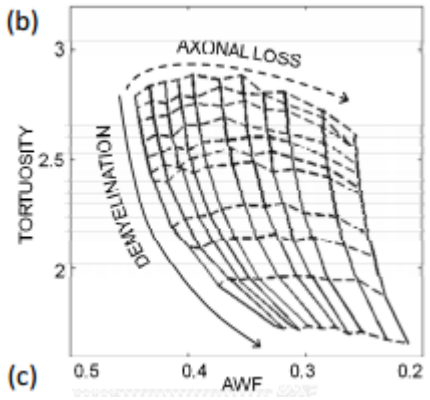


White Matter Tract Integrity (WMTI)

- Introduced by Fieremans et al. (2011).



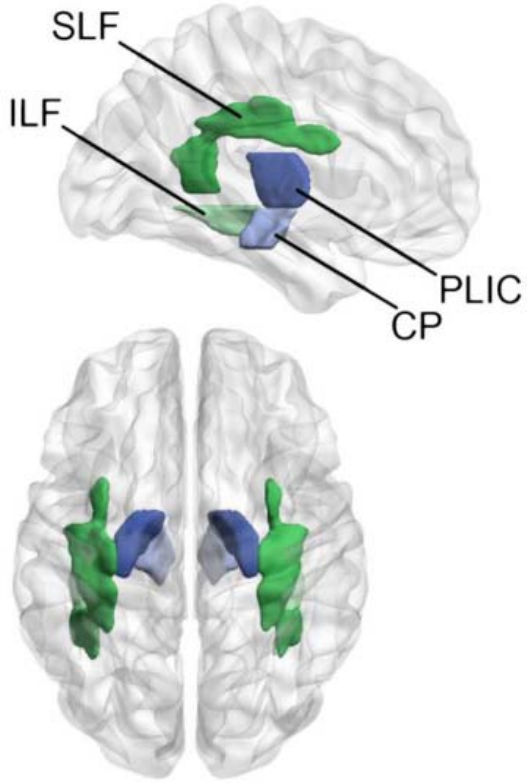
- AWF and tortuosity differentiate between axonal loss and demylination (Fieremans et al. 2012).

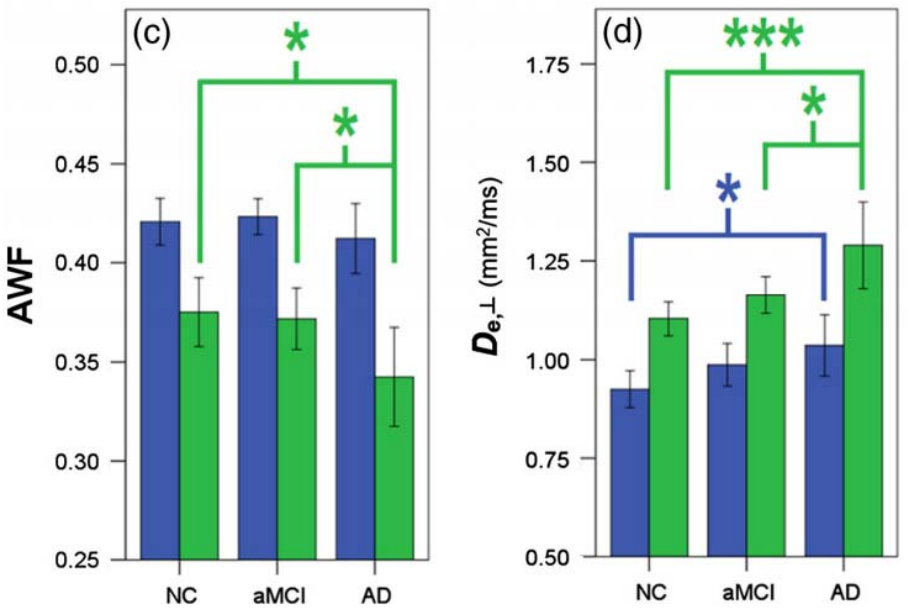


- Typical acquisition time: 10-15minutes (usually two b-values in the range 1000-2500 s/mm^2 x 30-60 directions).

White Matter Tract Integrity (WMTI)

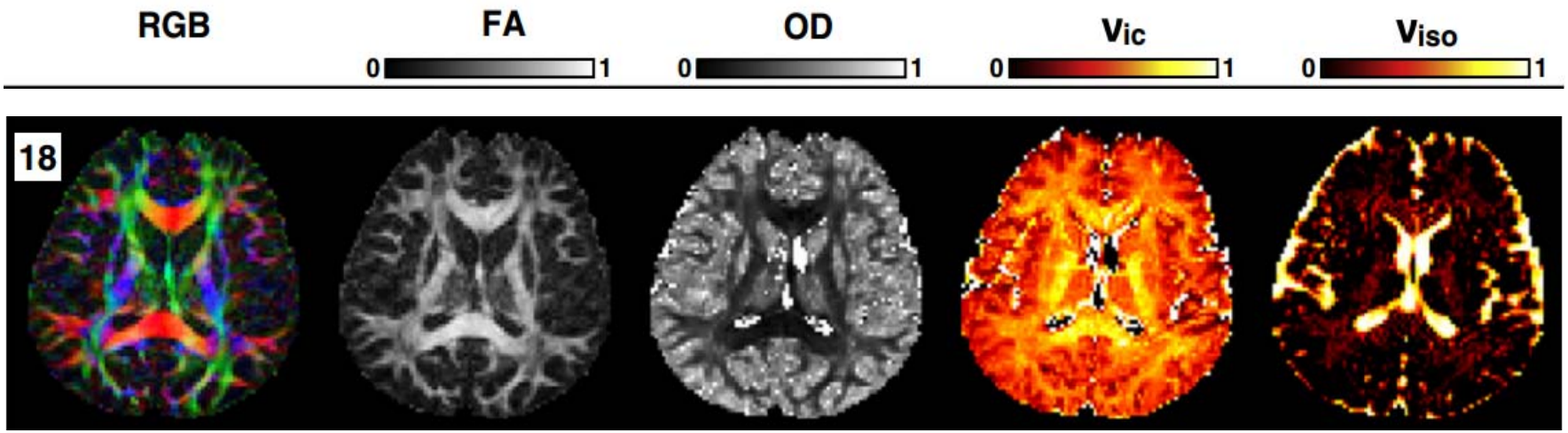
- WMTI metrics reflect differences between MCI and Alzheimer's disease (Benitez et al. 2014).





Neurite Orientation Dispersion and Density Imaging (NODDI)

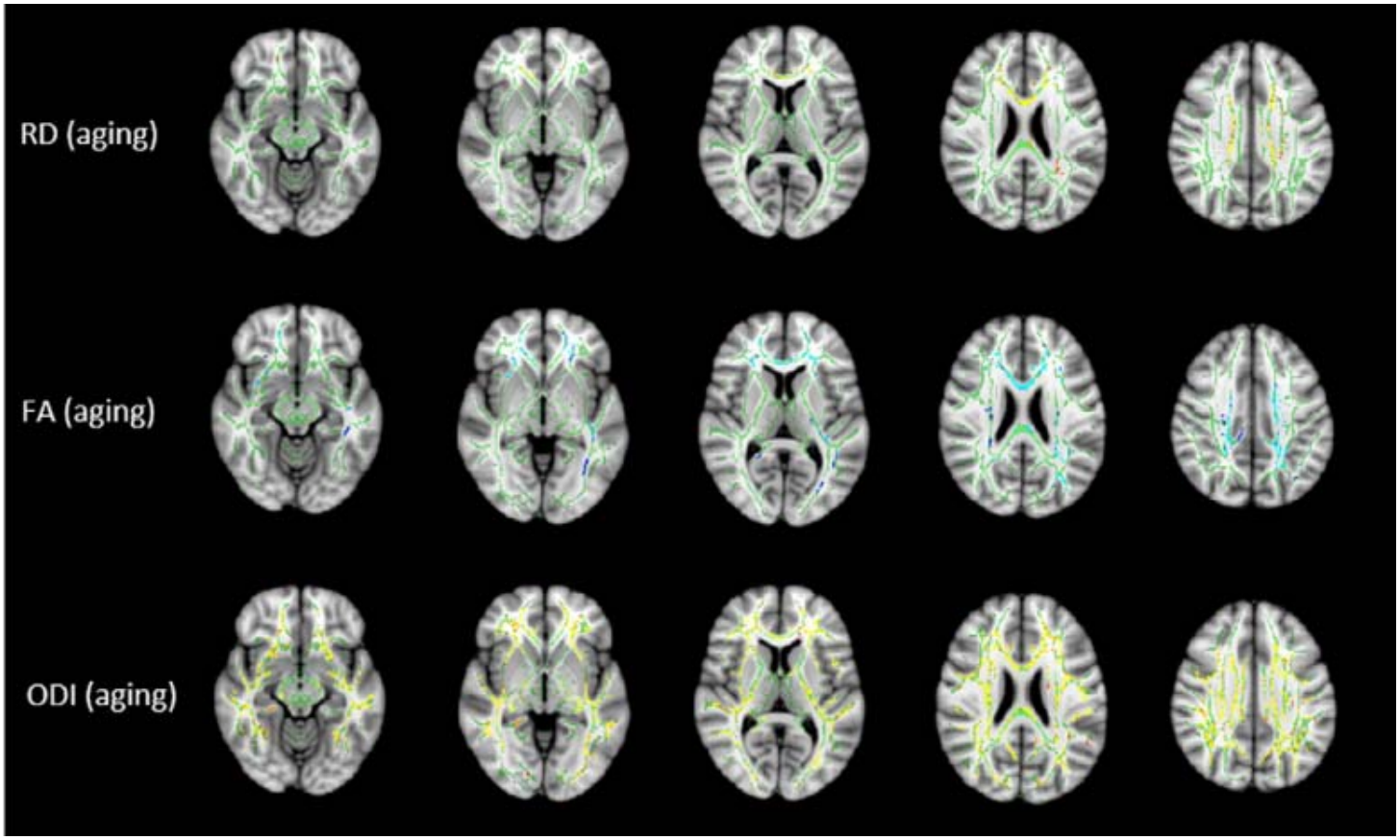
- Introduced by Zhang et al. (2012).



- Typical acquisition time: **30 minutes** (b=711s/mm^2 x 30 dir, b= 1000 s/mm^2 x 30 dir, b=2000s/mm^2 x 60 dir, and b=2855 s/mm^2 x 60 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, whit 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.

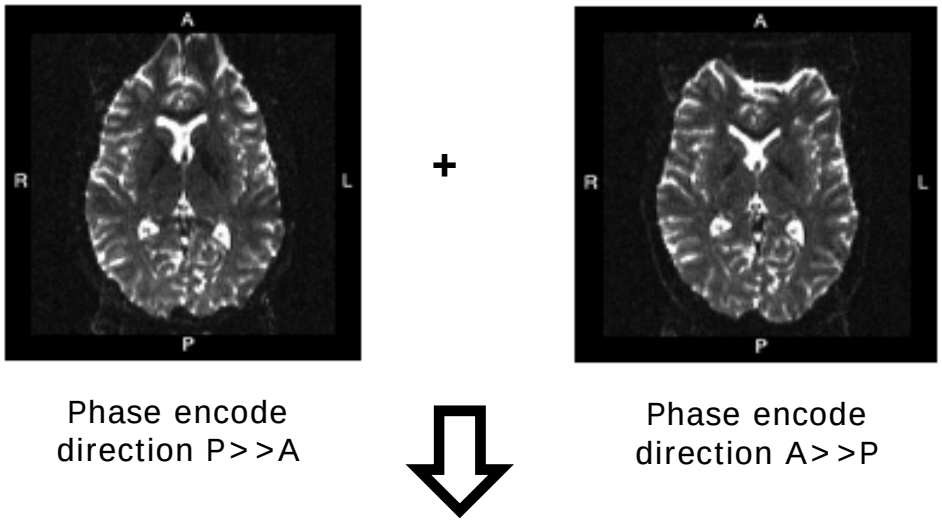
- Advanced diffusion MRI acquisitions and modelling allows us to model multiple fibre orientations and multiple tissues types.

- There are many models to choose from with specific data acquisition requirements, so talk to your local MRI physicist if you are planning a diffusion experiment.

Hands on session

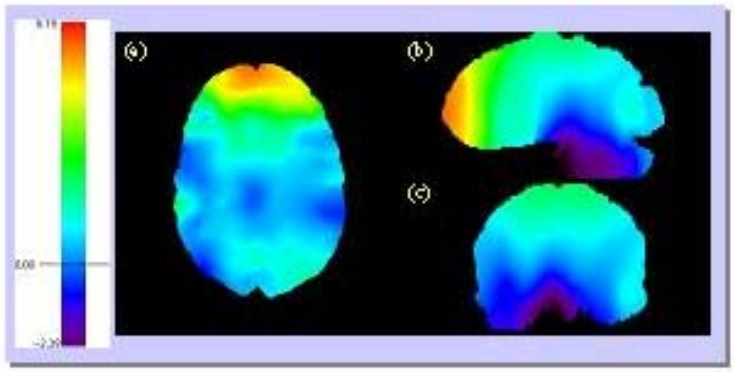
Hands on Session

- **EPI distortion correction - TOPUP**



Phase encode direction P>>A

Phase encode direction A>>P



EPI distortion map. The colour coding shows the amount of displacement in pixel units.

Hands on Session

- **Group level analysis**
  - VBM style analysis
  - Tract based spatial statistics (tbss)
    - Pre-processing
    - Model fitting
    - Choose target + normalisation
    - Generate a white matter skeleton
    - Define design matrix and contrasts
    - Perform inference