MRC | Cognition and Brain Sciences Unit

Introduction to Diffusion MRI

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17th January 2018

Overview

- Basic concepts
- Diffusion and MRI
- Modelling of diffusion MRI signal
  - The difusion tensor
  - Scalar metrics
- Introduction to Tractography

- Advanced Modelling:
  - Probabilistic Modelling
  - Diffusion MRI and microstructure

- Common artefacts
- Quality Control

The basics

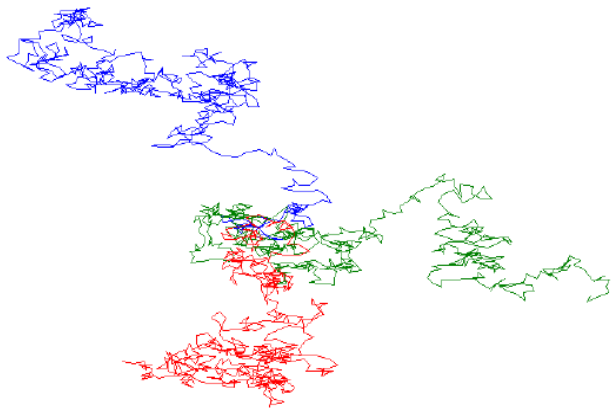
Concept of Molecular Diffusion

- Molecular diffusion refers to the random translational motion of molecules (also called Brownian motion) that results from the thermal energy carried by these molecules.

- In a free medium, molecular displacements obey a 3D Gaussian distribution.

- Molecules travel randomly in space over a distance that is statistically well described by a diffusion coefficient *D*.

- *D* depends only on the mass of the molecules, the temperature and viscosity of the medium.



Three random walks originating from a common starting point.

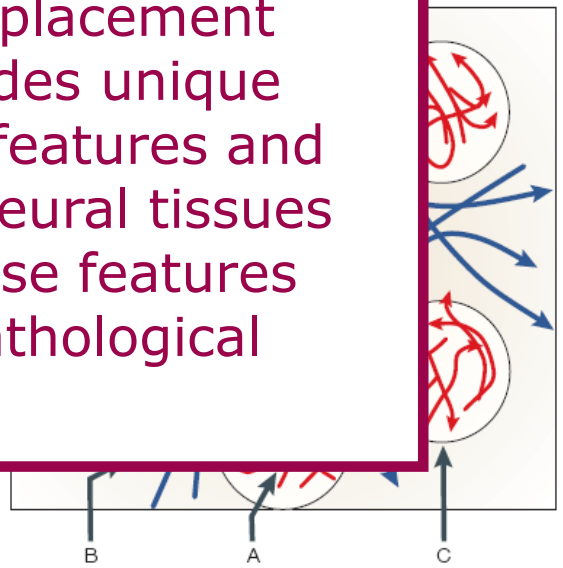
Diffusion in the Brain

- During their diffusion driven displacements, molecules probe tissue structure on a microscopic scale, well beyond the usual image resolution

- During d
move in b
crossing o
componer
fibres and

- The mov
by these d
displacement distribution is no longer Gaussian.

The non-invasive observation of the water diffusion-driven displacement distributions *in vivo* provides unique clues to the fine structural features and geometric organization of neural tissues and also to changes in these features with physiological and pathological states.



In biological tissues, obstacles modulate the free diffusion process.

Isotropic vs Anisotropic Diffusion

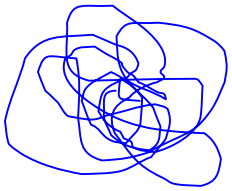
• Free diffusion (no obstacles) occurs equally in all directions. This is called **isotropic diffusion**.

• If the water diffuses in a medium having barriers, the diffusion will be uneven. Barriers can be many things (cell membranes, molecules, axons, etc), but in white matter the principal barrier is the myelin sheath of axons.

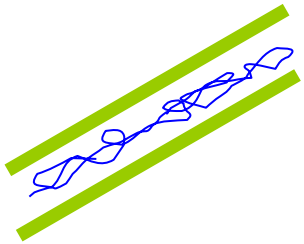
• Bundles of axons provide a barrier to perpendicular diffusion and a path for parallel diffusion along the orientation of the fibres. This is termed **anisotropic diffusion**.

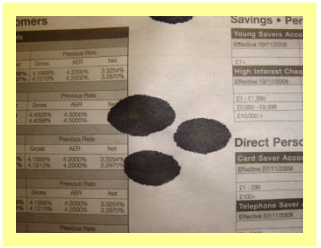
Diffusion trajectory

Isotropic
Diffusion (free water)



Anisotropic Diffusion
(coherent axonal bundle)

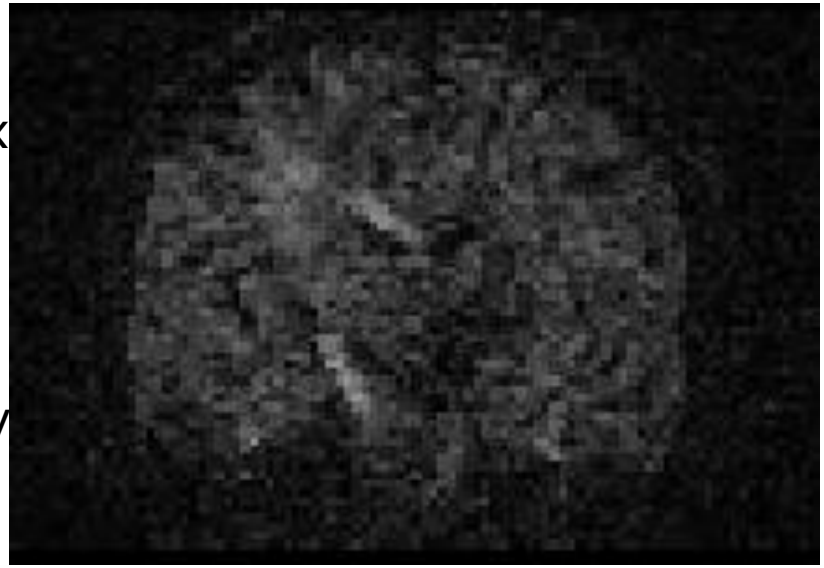




Diffusion and MRI

The diffusion MRI signal

- MRI signal profile as a function of the direction (θ,ϕ) of the DW gradients, S(θ,ϕ):
  - isotropic vox
  - anisotropic v



- Changing the gradient direction changes the amount of attenuation seen, depending on how much motion there is along that specific direction.

The diffusion weighting parameter (b-value)

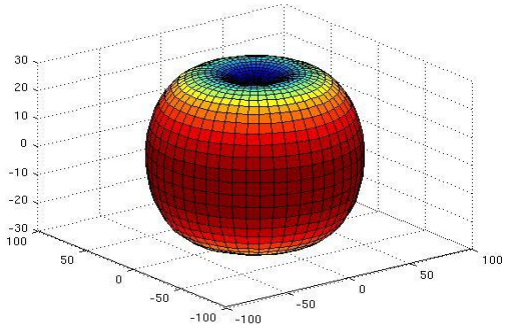
$$b = (\gamma G \delta)^2 (\Delta - \delta/3)$$

DW gradient intensity

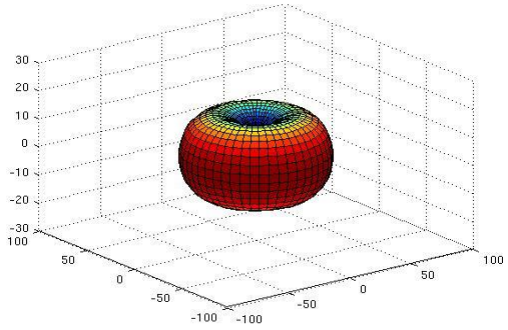
spacing between gradients

gradient duration

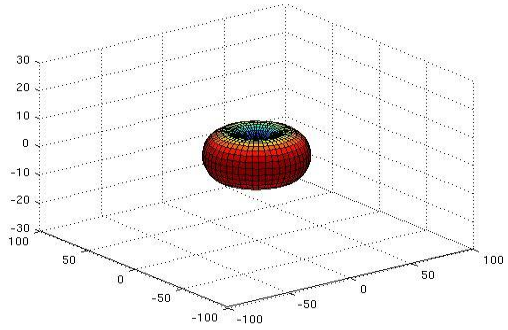
b = 1000 s/mm^2



b = 2000 s/mm^2

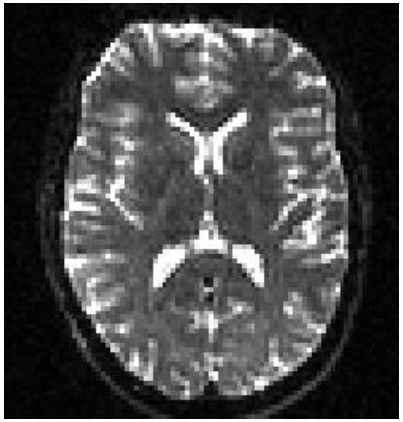


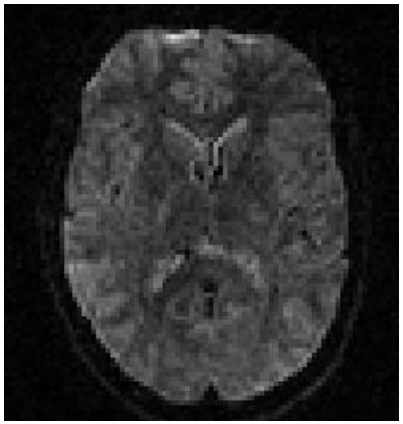
b = 3000 s/mm^2



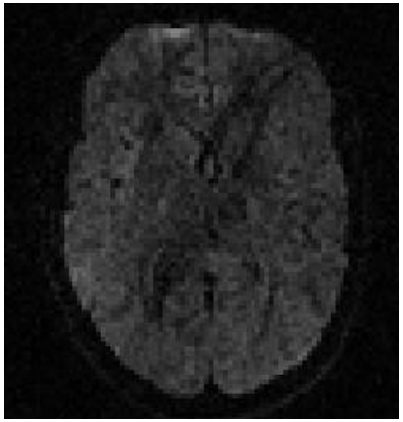
Changing the b-value in the Brain

$b = 0$ s/mm^2

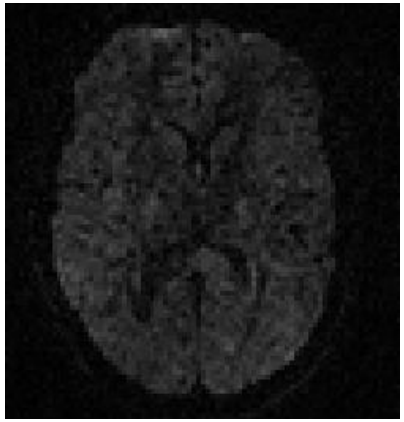




$b = 400$ s/mm^2



$b = 800$ s/mm^2



$b = 1200$ s/mm^2

Gaussian Modeling of the Diffusion Signal

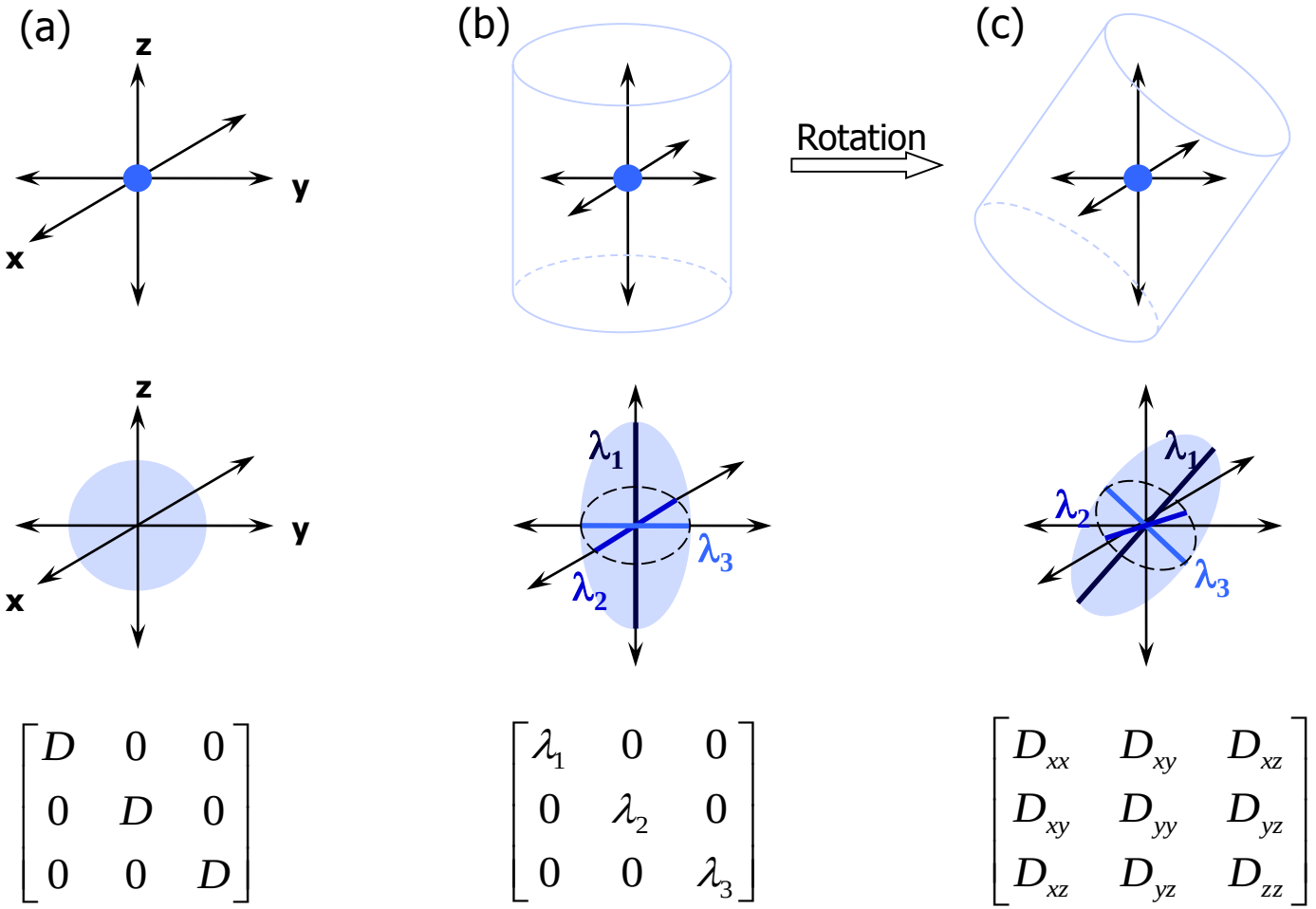
The Diffusion Tensor Model

- Diffusion is a 3D process and water molecules mobility in tissues is not necessarily the same in all directions.
- Organized fibrous tissues, such as muscle and cerebral white matter, demonstrate anisotropic diffusion.
- The simplest model that can characterise Gaussian diffusion in which the displacements pert unit time are not the same along all directions is the **diffusion tensor**.
- This is a 3x3 symmetric matrix:

$$\underline{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

- The diagonal elements correspond to diffusivities along the three orthogonal axes.

The Diffusion Ellipsoid



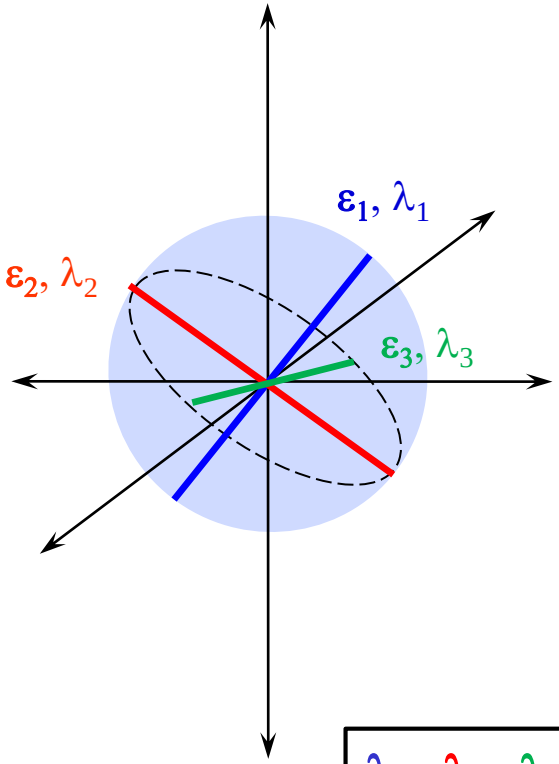
$$\begin{bmatrix} D & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & D \end{bmatrix}$$

$$\begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$$

$$\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

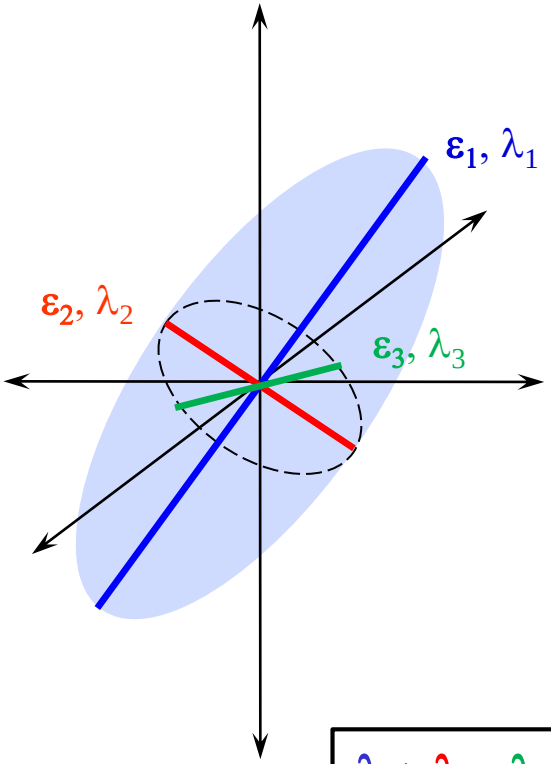
Eigenvalues and eigenvectors

Isotropic Diffusion



$\lambda_1=\lambda_2=\lambda_3$

Anisotropic Diffusion

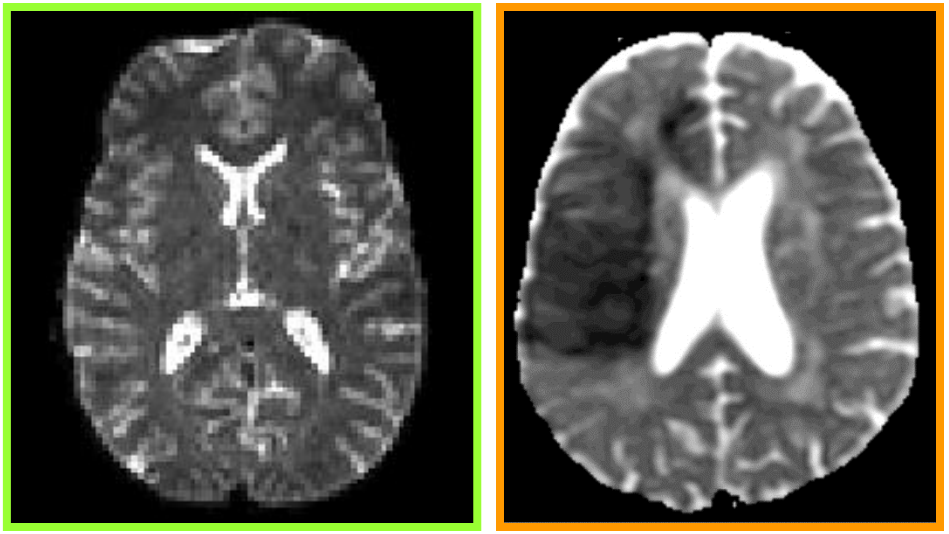


$\lambda_1>\lambda_2\sim\lambda_3$

Mean diffusivity (MD)

- Measurements of the DT and its components have been found to have several applications in the human brain.

- **Mean diffusivity map:** MD is the average value of the rate of diffusion on each voxel. MD maps contain very useful information for detecting and evaluating brain ischemia and stroke.



$$MD = \frac{D_{xx} + D_{yy} + D_{zz}}{3} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

MD maps of a healthy brain (left) and a stroke patient (right).

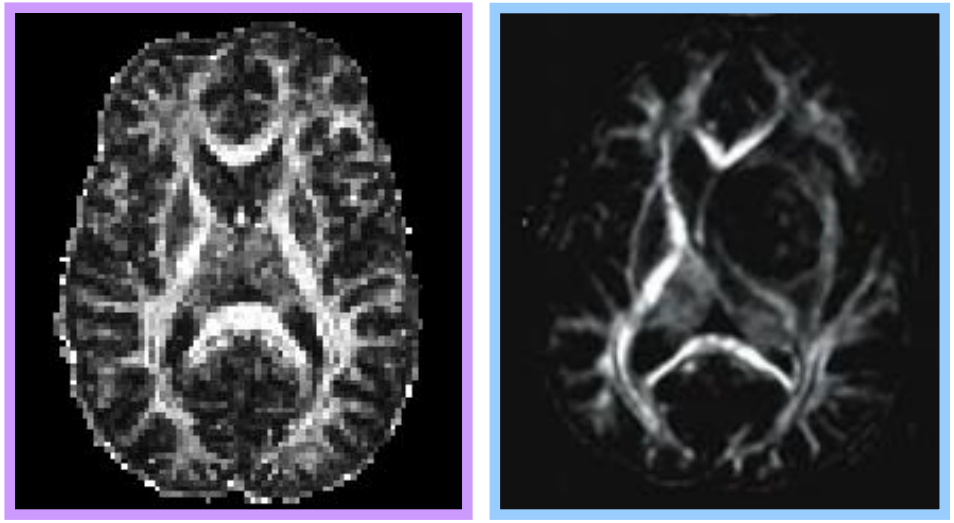
Fractional Anisotropy (FA)

- **Fractional Anisotropy map:** FA is a measure of the degree of diffusion anisotropy, and it is calculated from the diffusivity constants λ_1, λ_2, λ_3.

$$FA = \sqrt{\frac{3((\lambda_1 - <\lambda>)^2 + (\lambda_2 - <\lambda>)^2 + (\lambda_3 - <\lambda>)^2)}{2(\lambda_1^{\,2} + \lambda_2^{\,2} + \lambda_3^{\,2})}}$$

- FA produces high values for white matter (highly anisotropic) and low values for grey matter(isotropic).

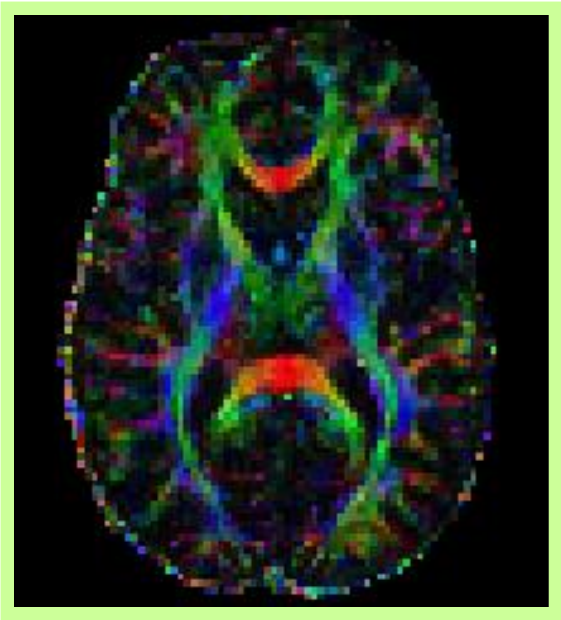
- It has been used to study white matter in terms of morphology, disease and trauma, brain development and neurosurgical planning.



FA maps of a healthy brain (left) and a brain tumour patient (right).

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.

Summary

- MRI can successfully encode the motion of spins due to molecular diffusion.

- In anisotropic tissue, such as cerebral white matter, the diffusion MRI measurements are highly dependent on the direction of the applied gradient.

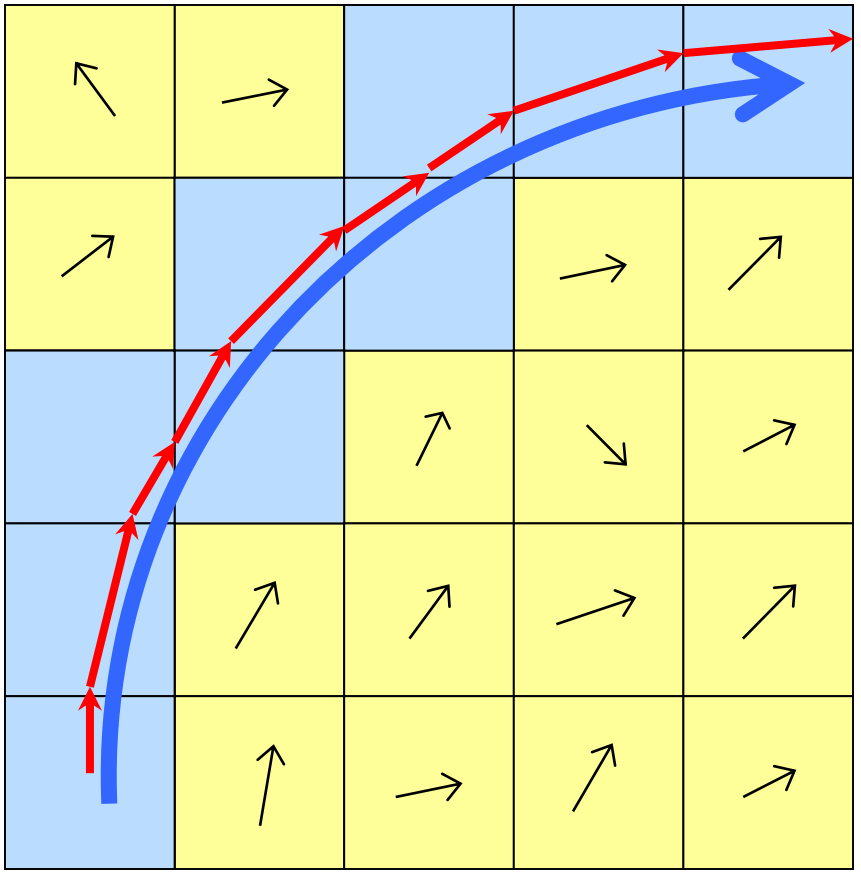
- Reliable inference of the tensor values in all structures requires sufficient sampling of non-collinear gradient directions and appropriate choice of b-values.

- There are many models available, suitable for different applications (more on this next week).

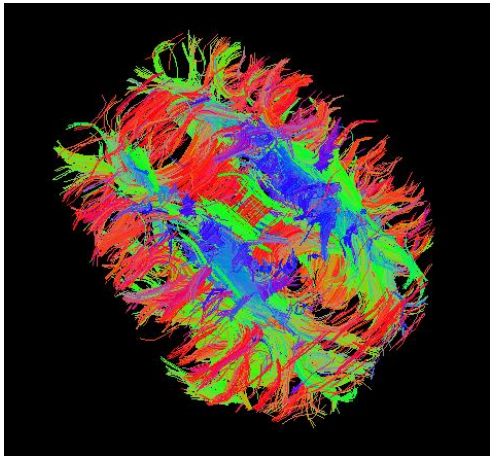
Tractography

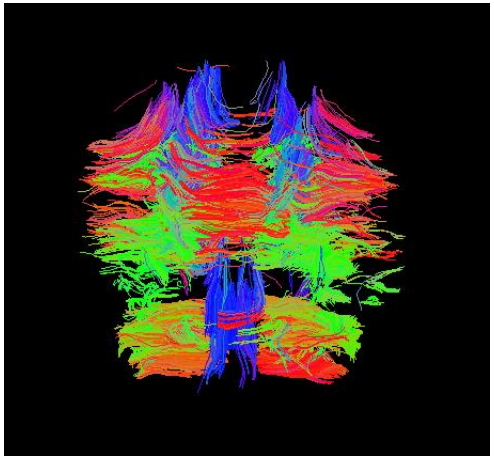
Tractography

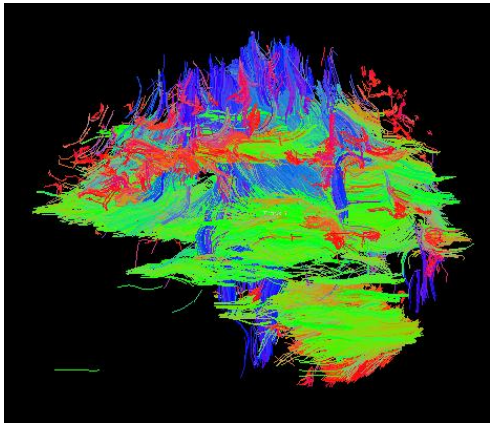
- Once direction ε_1 has been calculated for all voxels, the trajectories of water molecules can be reconstructed using a method similar to the children's activity "connect the dots": we connect each voxel to the adjacent one toward which the fibre direction, ε_1, is pointing.



Tractography in the Brain







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

Advanced Modelling

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:

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

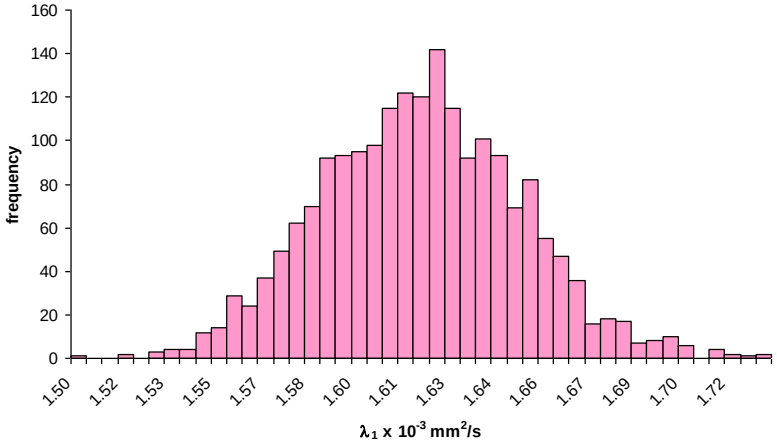
where ω represents the vector of model parameters.

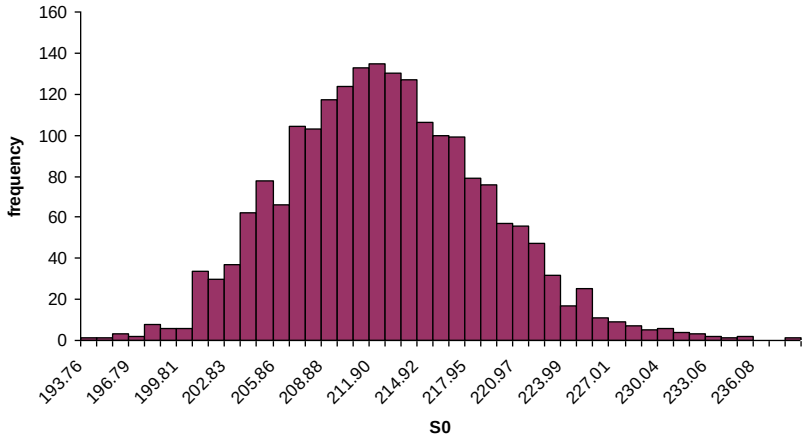
- The prior term $P(\omega)$ offers an opportunity for scientists to include knowledge they have about the expected values of the parameters.

- 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:



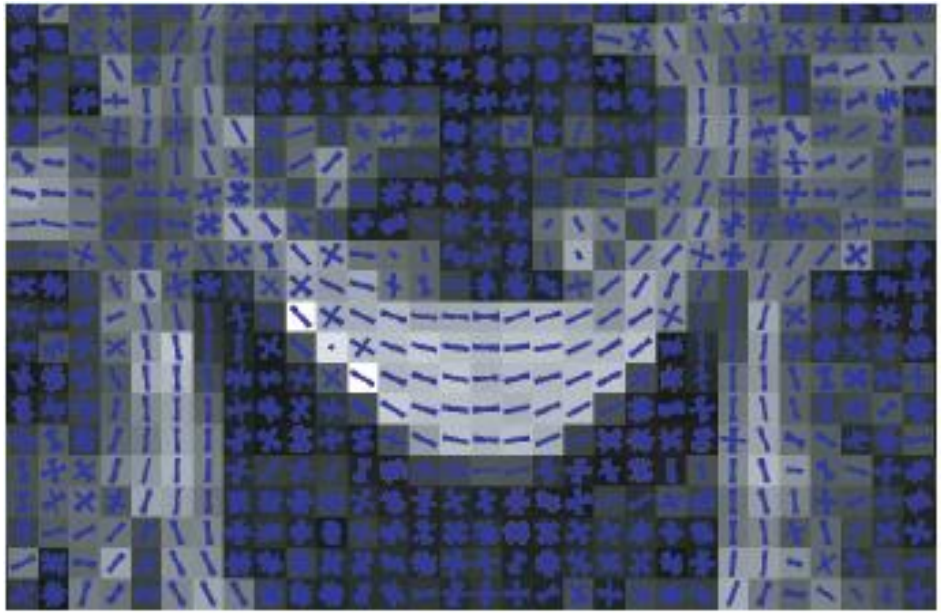


- The standard deviation of these PDFs is a good marker for confidence in the results.

- **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:

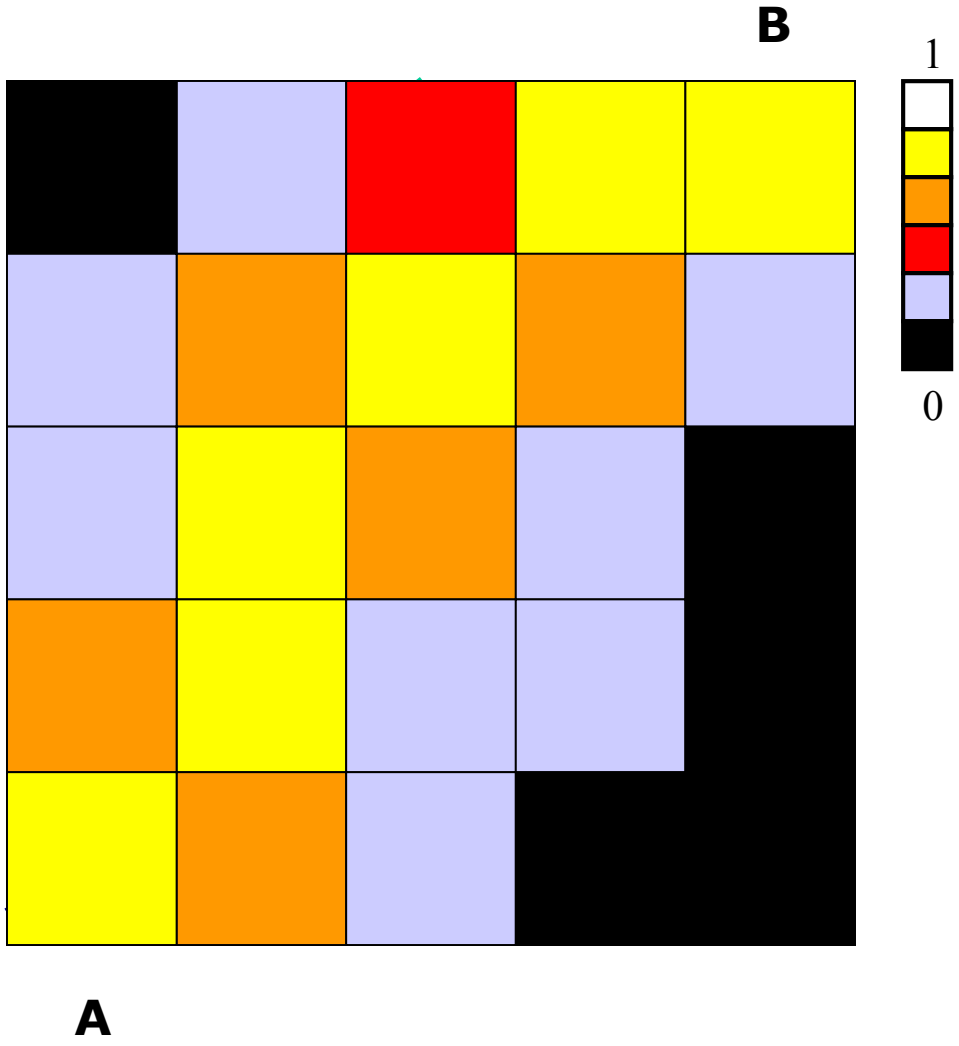


- Regions of one-fibre populations have very narrow distributions, while regions of crossing fibres show greater variability.

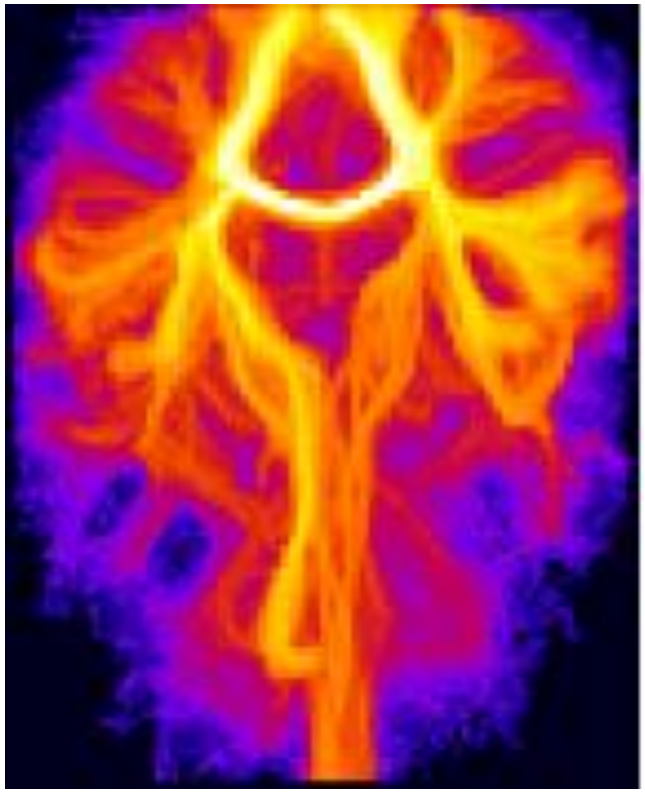
Probabilistic Tractography

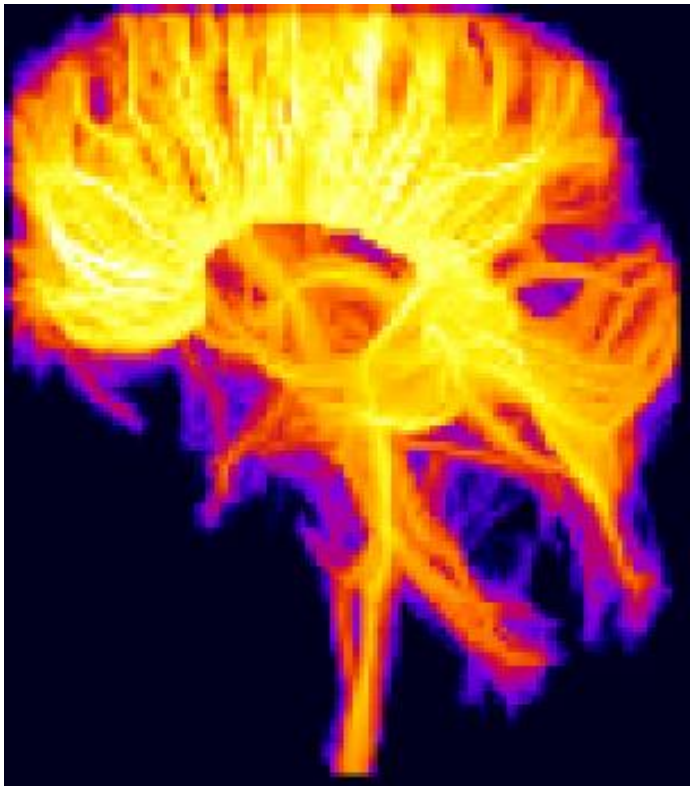
- For each sample of the directional PDF we can produce a track (or streamline).

- 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

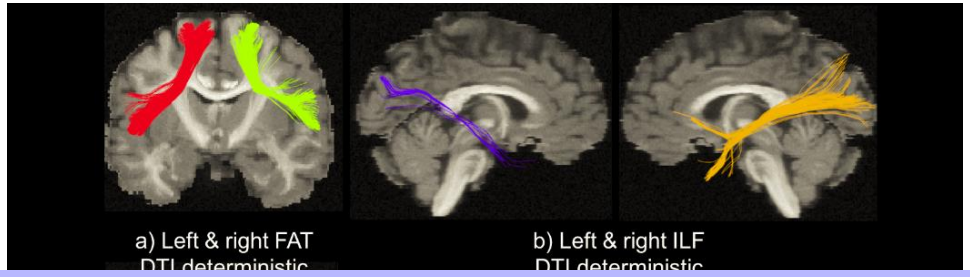




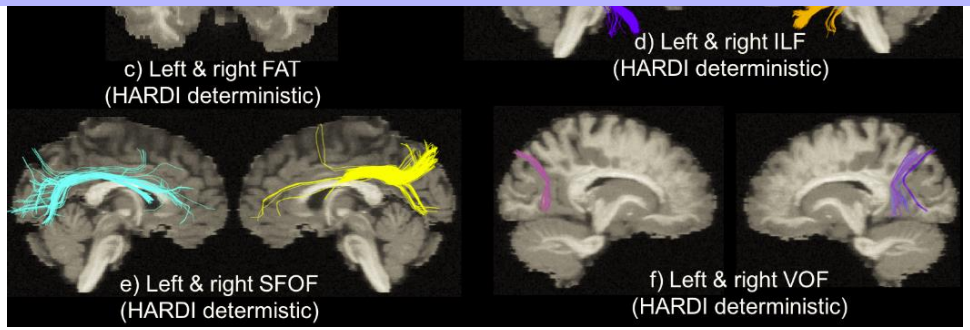
Probabilistic tractography dataset obtained for a healthy volunteer.

Tractography: A warning

- Examples of **invalid bundles**



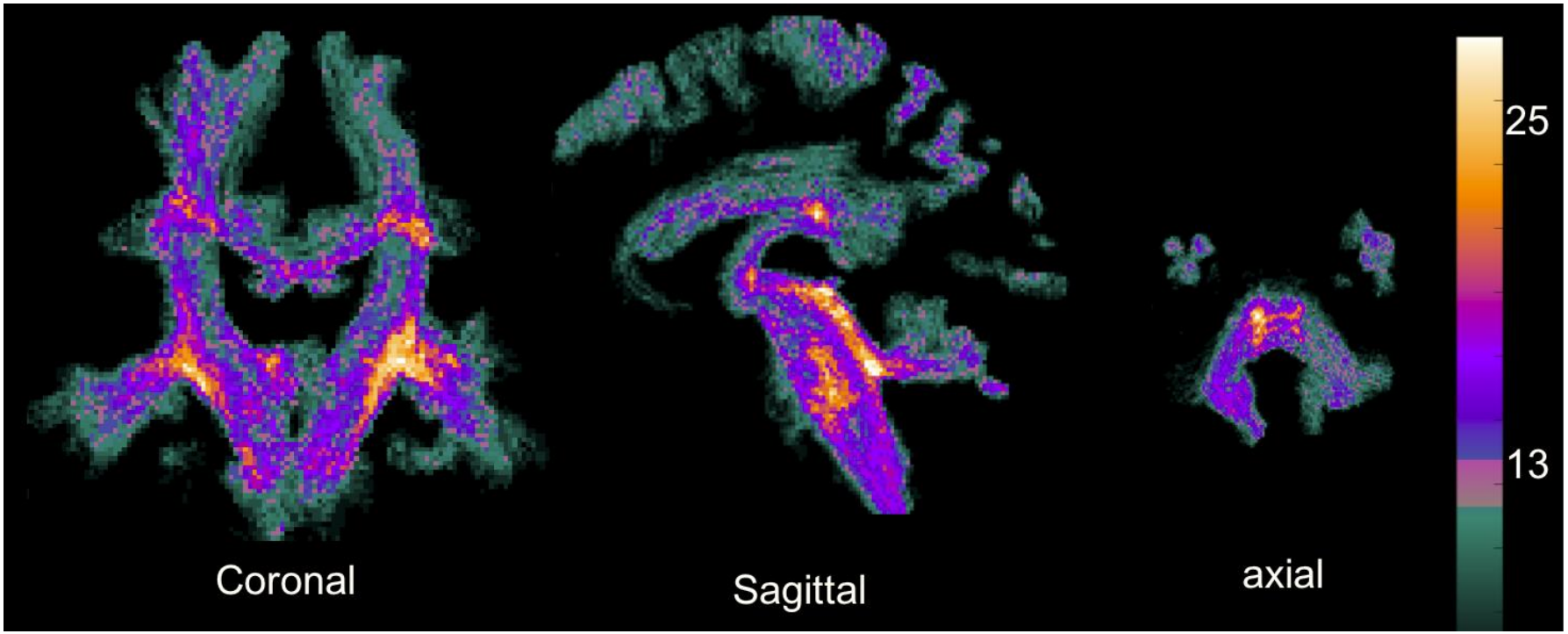
On average, for every correct bundle, **4 invalid bundles** were identified!!



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

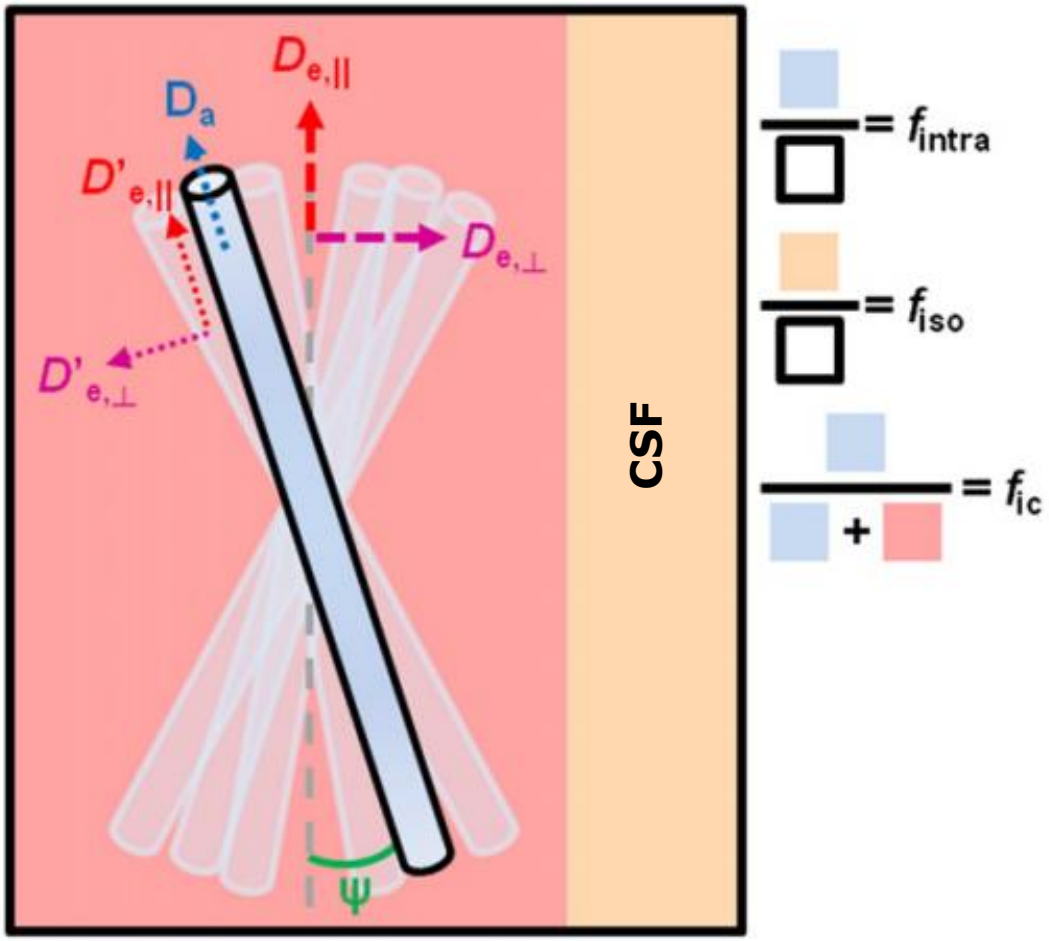
Tractography: A warning

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



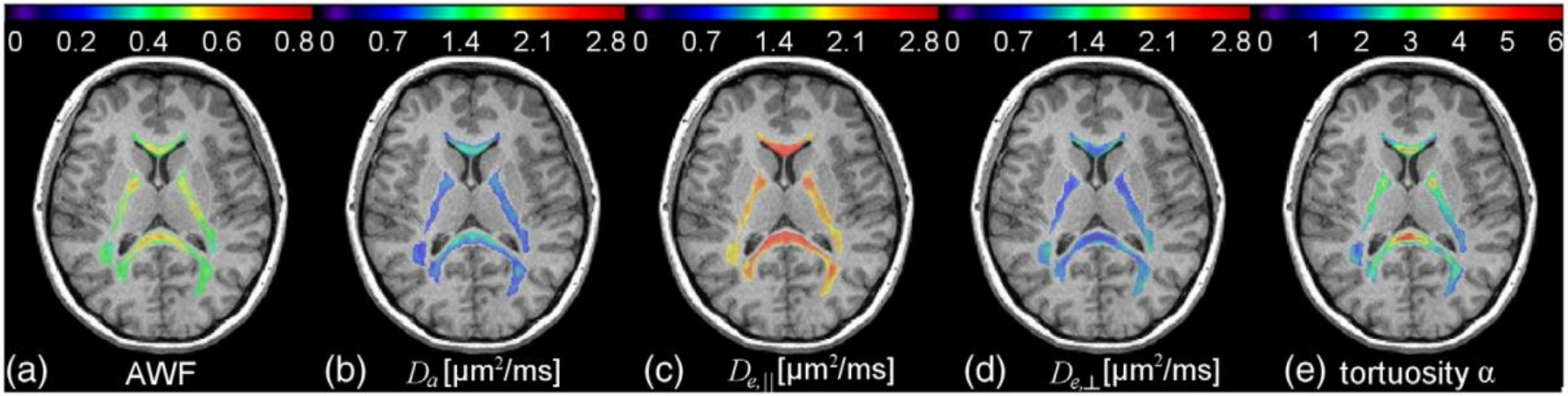
Diffusion MRI and Microstructure

Modelling multiple diffusion compartments



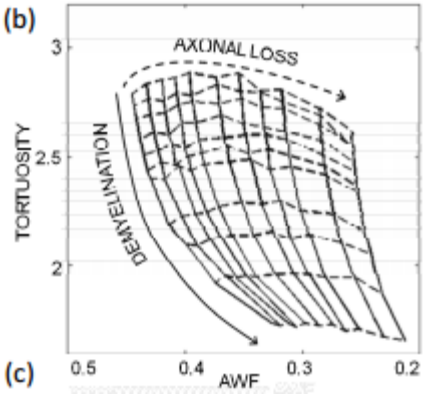
White Matter Tract Integrity (WMTI)

- Introduced by Fieremans et al. (2011).



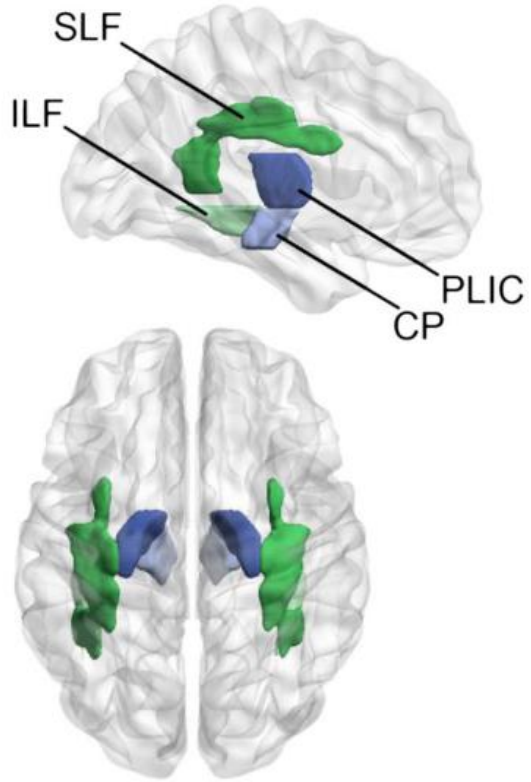
- AWF and tortuosity differentiate between axonal loos and demylination (Fieremans et al. 2012).

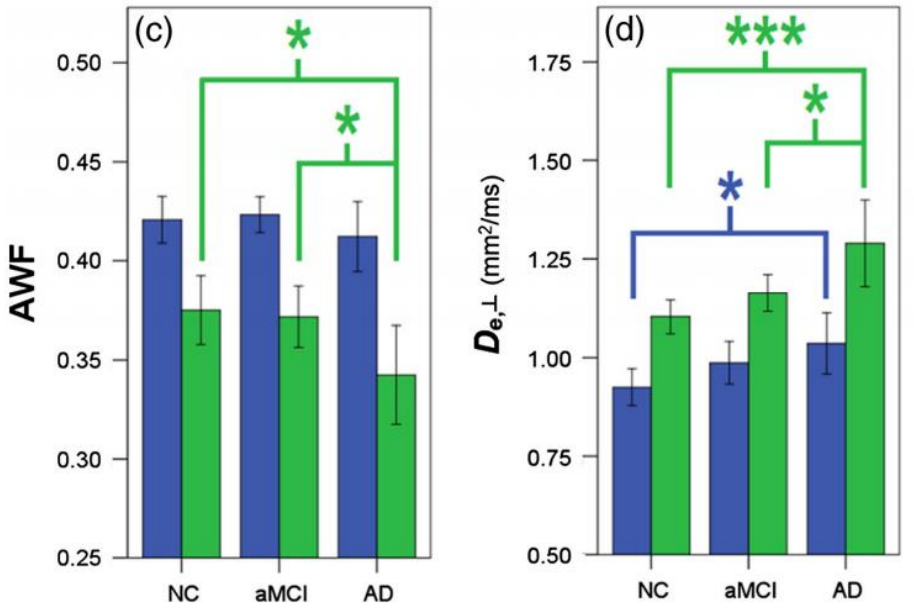
- Typical acquisition time: 10-15minutes (usually two b-values in the range 1000-2500 s/mm^2 x 30-60 directions).



White Matter Tract Integrity (WMTI)

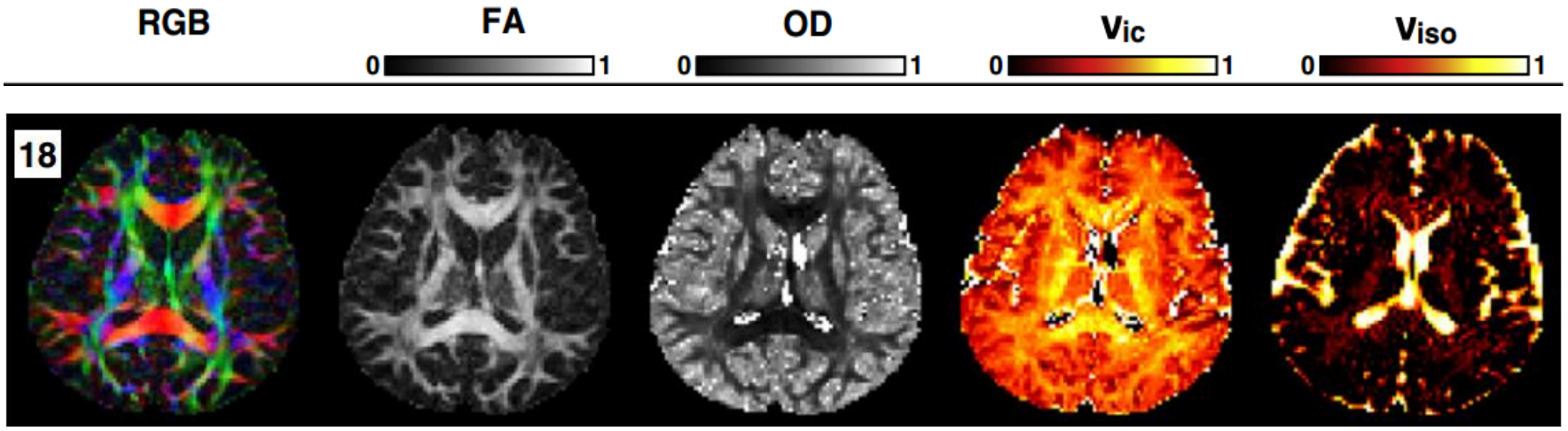
- WMTI metrics reflect differences between MCI and Alzheimer's disease (Benitez et al. 2014).





Neurite Orientation Dispersion and Density Imaging (NODDI)

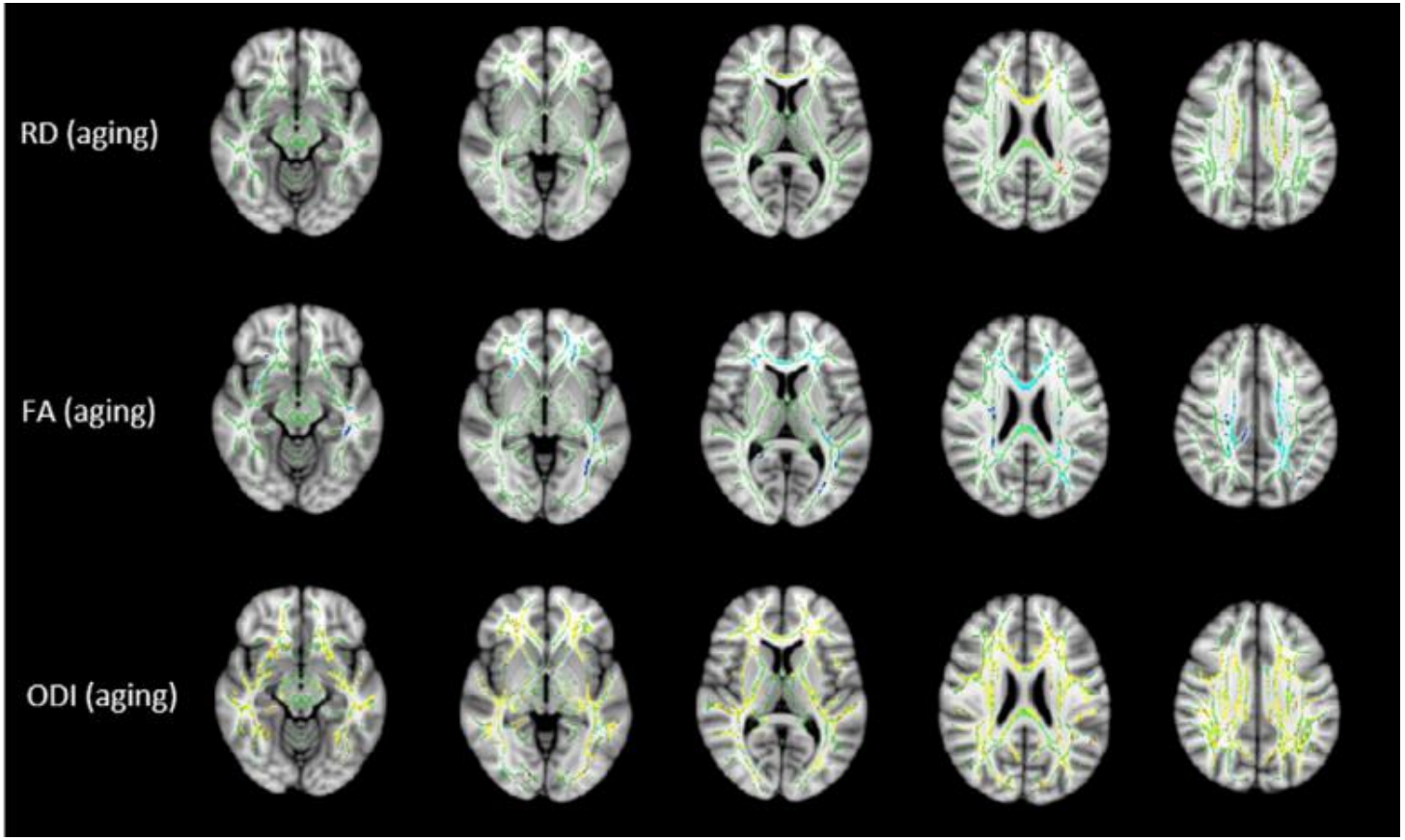
- Introduced by Zhang et al. (2012).



- 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.

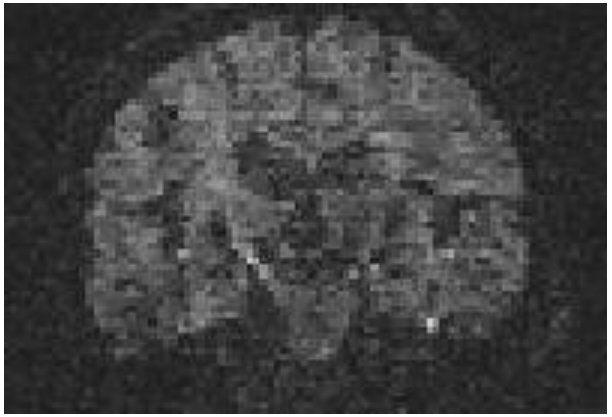
- Advanced diffusion MRI acquisitions and modelling allows us to model multiple fibre orientations and multiple tissues types.

- 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.

Common Artefacts and Quality Control

Common artefacts

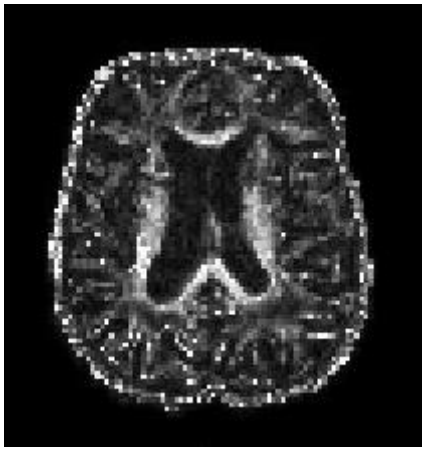
- **Motion artefacts**
  - Stripping and signal voids



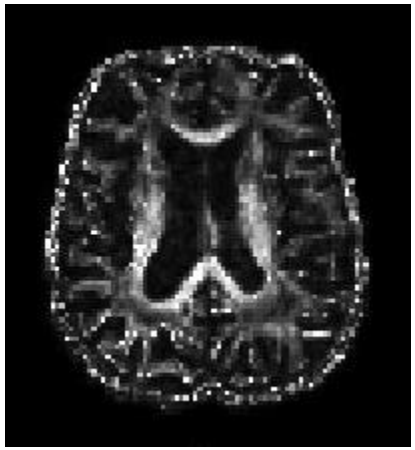
  - Mismatch of voxels across volumes -> poor modelling

Motion artefacts

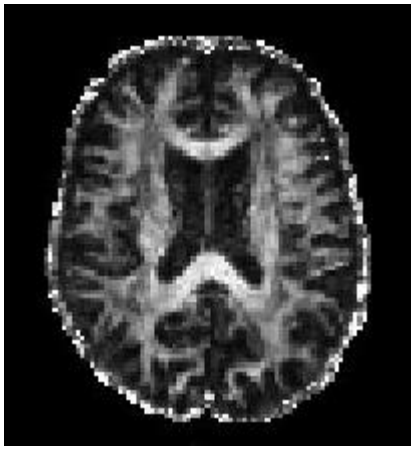
- Can it be corrected?
- Effect on FA maps



FA map
before correction



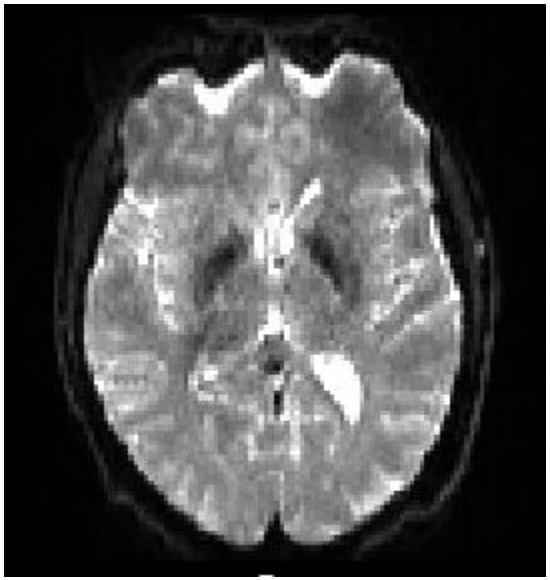
FA map
after correction



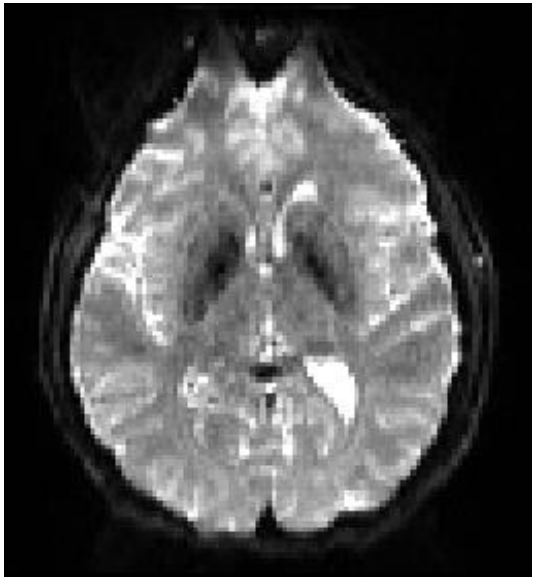
'Good' FA map

Common artefacts

- **EPI distortion**
  - Brain distortion in areas of high susceptibility



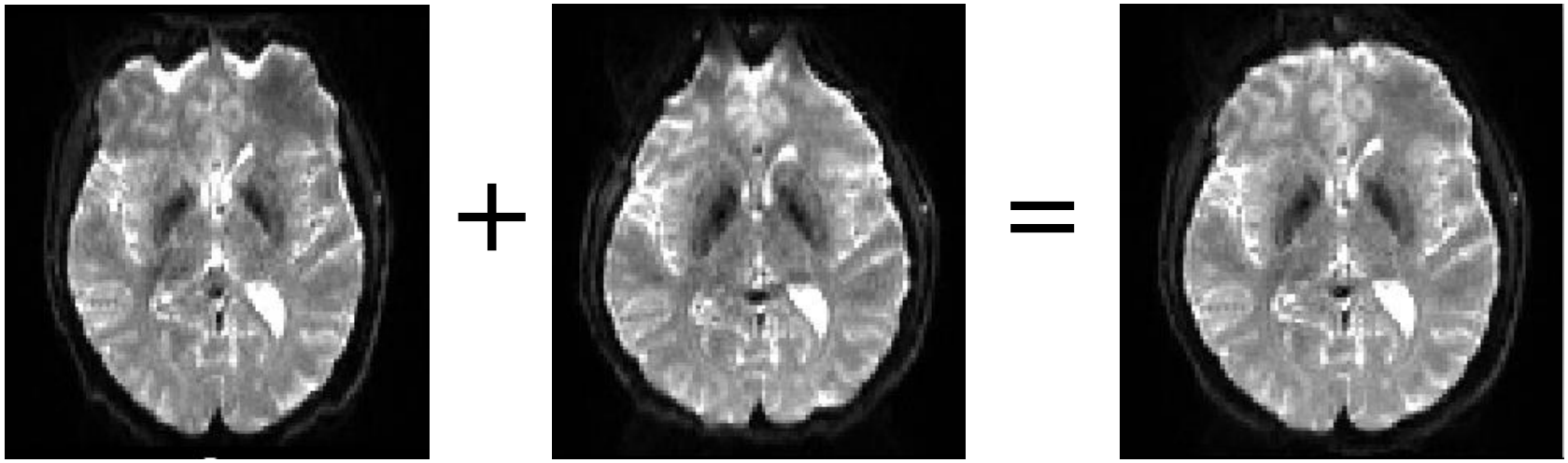
A>>P



P>>A

Common artefacts

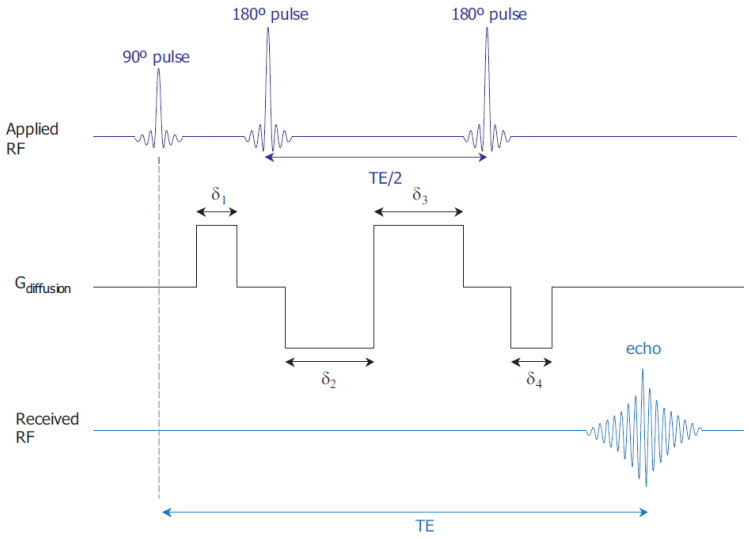
- **EPI distortion**
  - Can it be corrected?



A>>P P>>A

Common artefacts

- **Eddy currents**
- Can it be corrected?
  - Acquisition: Twice refocused SE sequence

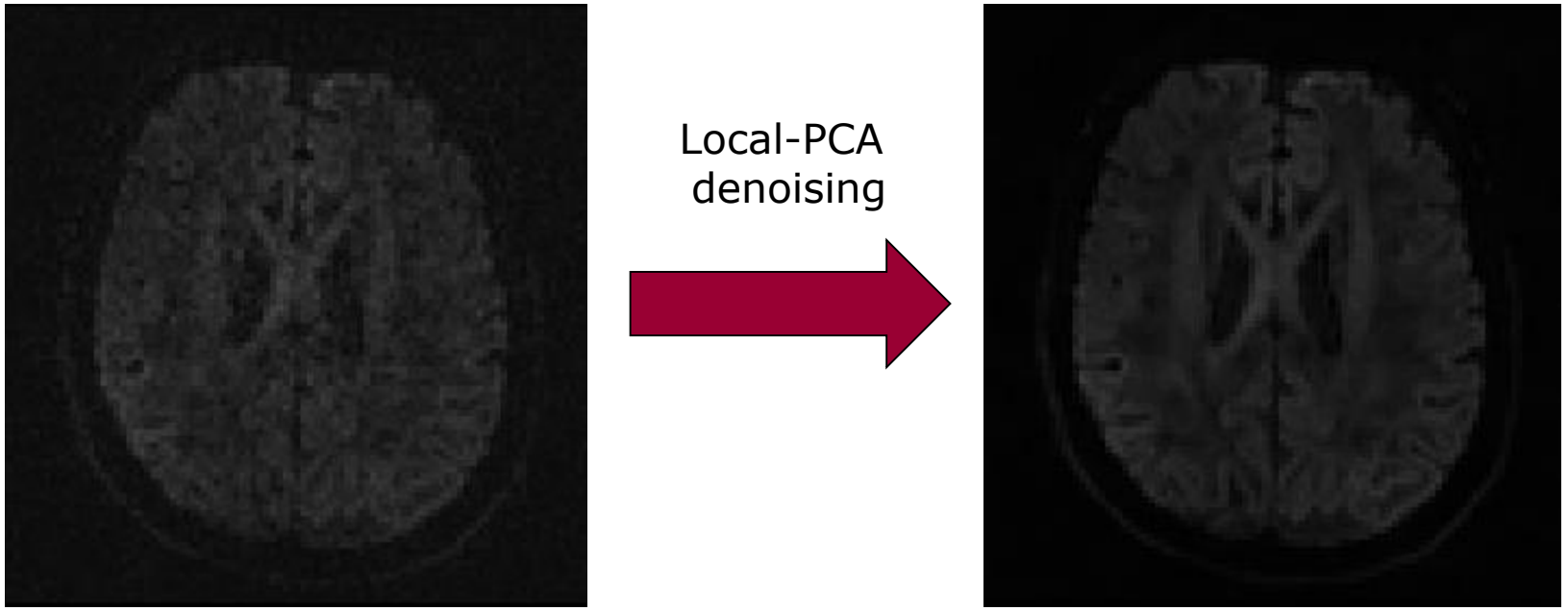


Common artefacts

- **Eddy currents**
- Can it be corrected?
  - Acquisition + modelling: topup + eddy (fsl)
    - A->P and P->A acquisitions
    - Mapping and correction of distortions
    - Slightly increased scanning time
  - Realignment of volumes using 6/12 parameter registration (eddy_correct, fsl)

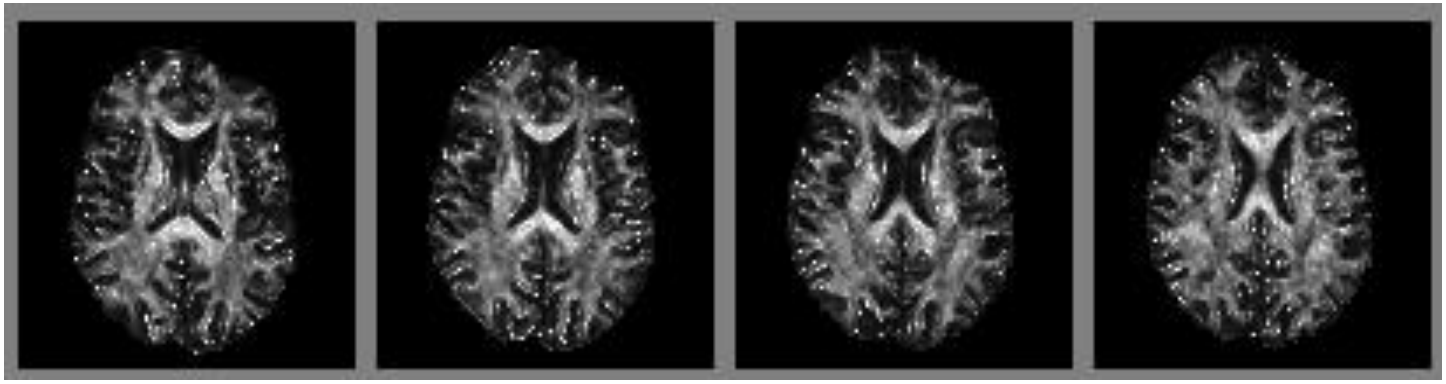
Common artefacts

- **Poor SNR**
  - Can it be corrected?



Common artefacts

- **FA > 1 (or speckled images)**



- Can it be corrected?
  - Apply smoothing or other de-noising methods (e.g. local PCA)
  - Consider acquiring more than one b-value (with corresponding increase in acquisition time)

Quality control

- Check that you have the expected number of volumes:

$$N_{total} = N_0 + N_b \times N_d$$

- Check you b-values are as expected
- Visually inspect all your data and reject any datasets with extreme artefacts (e.g. stripping)
  - Consider an automatic stripping detection algorithm
- Check motion parameters after motion correction and reject any outliers
- Check the model fit residuals and reject any outliers
- If running a multi-centre study, check also basic imaging parameters, especially TE.