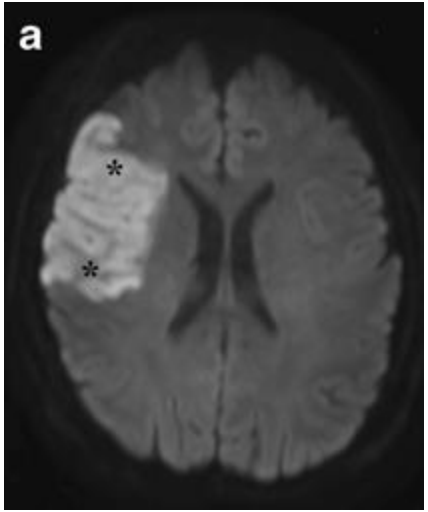
Analysis Techniques

Ellie Thompson and Anna Schroder

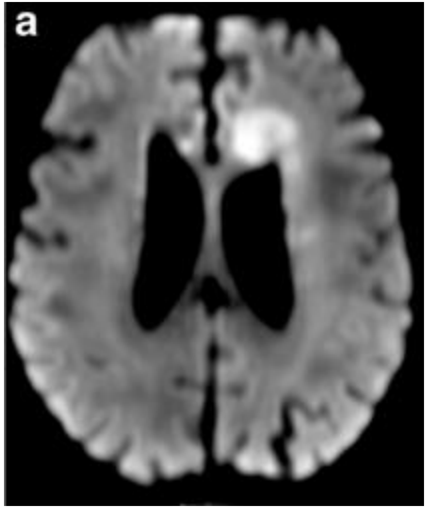
Overview

- Introduction: using analysis techniques to gain biomedical insights from diffusion MRI
- Practical 1: Diffusion tensor imaging
- Practical 2: Ball-and-stick model
- Practical 3: Constrained spherical deconvolution
- Summary

What can we do with diffusion MRI?



Acute stroke



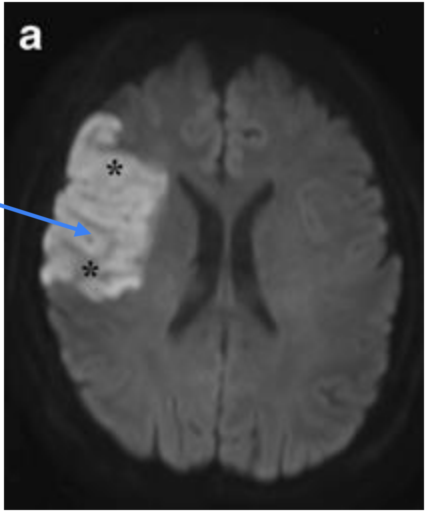
CNS lymphoma

Pre-processed scans provide some clinical insight, however they lack **quantitative biomarkers** or **complex microstructural** information

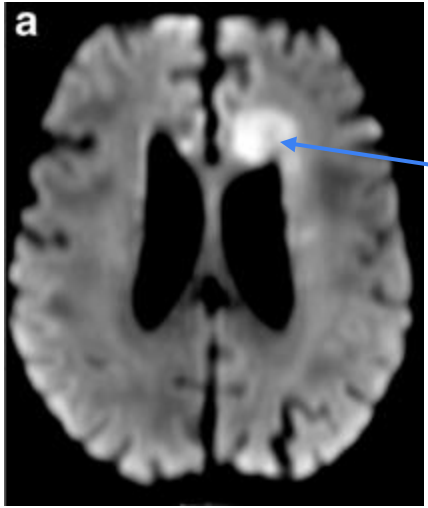
Drake-Pérez, M., Boto, J., Fitsiori, A. *et al*. Clinical applications of diffusion weighted imaging in neuroradiology. *Insights Imaging* 9, 535–547 (2018). https://doi.org/10.1007/s13244-018-0624-3

What can we do with diffusion MRI?

restricted diffusion



Acute stroke



restricted diffusion

CNS lymphoma

Pre-processed scans provide some clinical insight, however they lack **quantitative biomarkers** or **complex microstructural** information

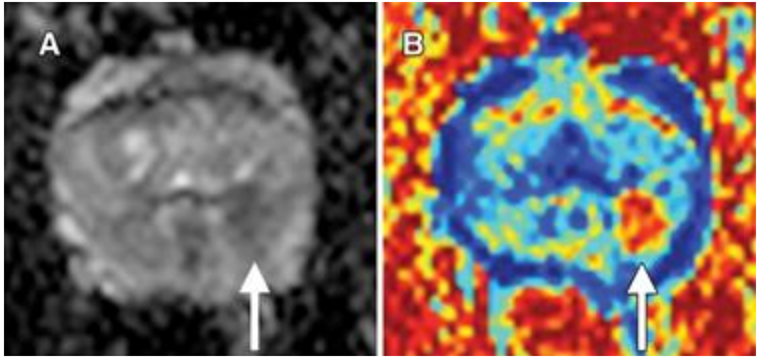
Drake-Pérez, M., Boto, J., Fitsiori, A. *et al*. Clinical applications of diffusion weighted imaging in neuroradiology. *Insights Imaging* 9, 535–547 (2018). https://doi.org/10.1007/s13244-018-0624-3

We can use analysis techniques to gain **biomedical insight** from dMRI

We can use analysis techniques to gain **biomedical insight** from dMRI

e.g. VERDICT-MRI: non-invasive histology for prostate cancer

Apparent diffusion coefficient (ADC) map



VERDICT intracellular volume fraction map

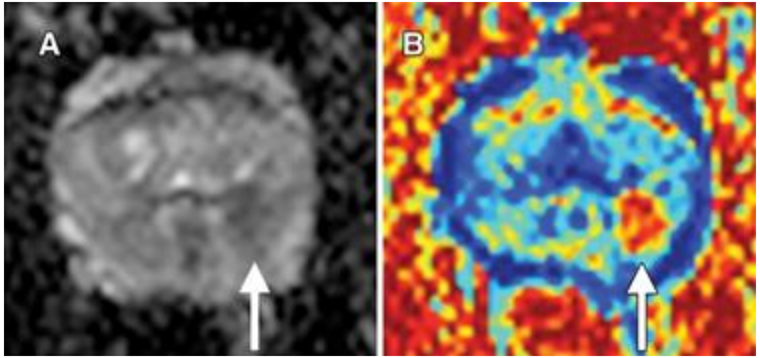
Images in a 57-year-old man with targeted biopsy–proven Gleason 3+4 prostate cancer.

Johnston EW, et al. VERDICT MRI for Prostate Cancer: Intracellular Volume Fraction versus Apparent Diffusion Coefficient. Radiology. 2019 May;291(2):391-397. doi: 10.1148/radiol.201918174

We can use analysis techniques to gain **biomedical insight** from dMRI

e.g. VERDICT-MRI: non-invasive histology for prostate cancer

Apparent diffusion coefficient (ADC) map



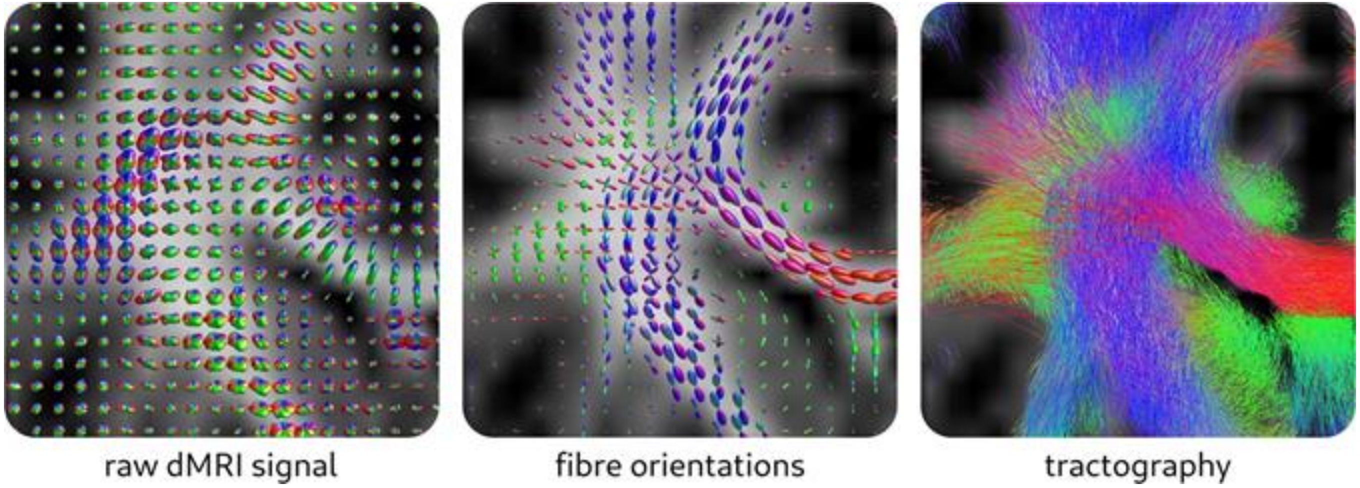
VERDICT intracellular volume fraction map

“New scanning technique reduces unnecessary biopsies by 90% meaning thousands of men could be spared pain and anxiety” - prostate cancer UK

Johnston EW, et al. VERDICT MRI for Prostate Cancer: Intracellular Volume Fraction versus Apparent Diffusion Coefficient. Radiology. 2019 May;291(2):391-397. doi: 10.1148/radiol.201918174

We can use analysis techniques to gain **biomedical insight** from dMRI

e.g. modelling fibre orientations for tractography

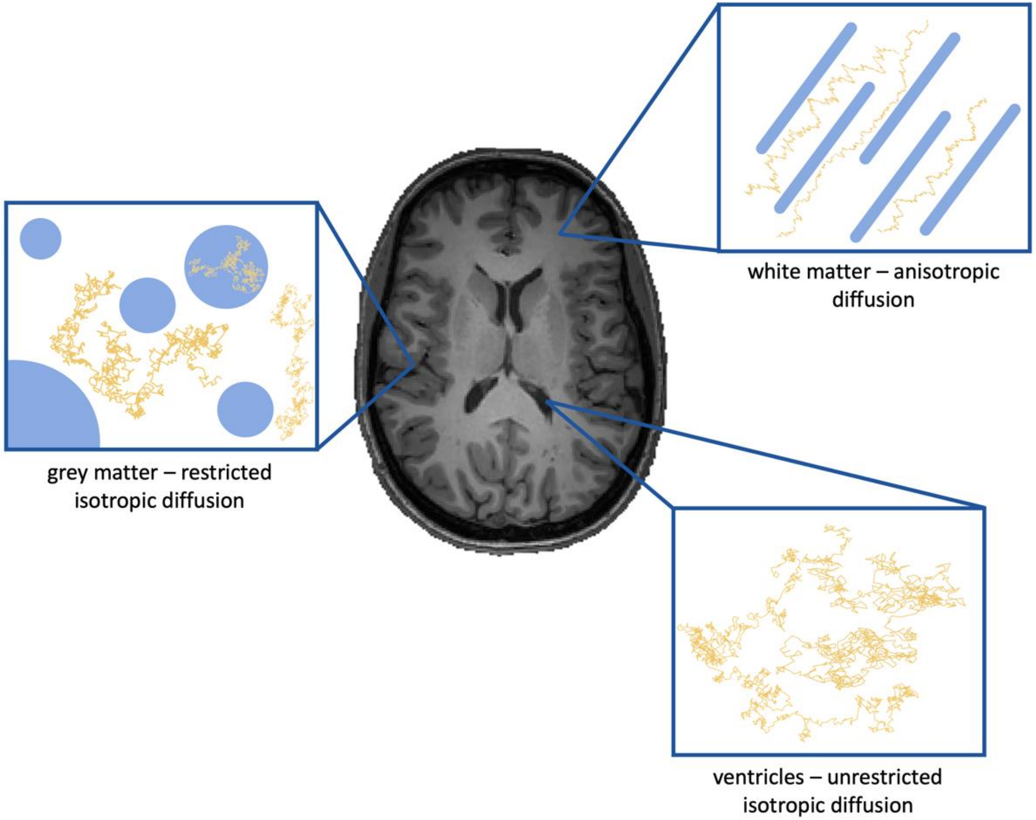


J-D Tournier, Diffusion MRI in the brain – Theory and concepts,Progress in Nuclear Magnetic Resonance Spectroscopy,112–113, 2019,Pages 1-16,

Why does the diffusion MRI signal reflect tissue structure?

- The diffusion of water molecules depends on the local tissue environment

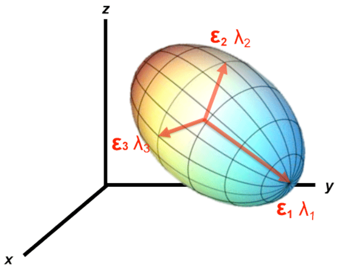
- We can infer properties of the underlying tissue by fitting models to the diffusion-weighted signal



Signal representations vs models

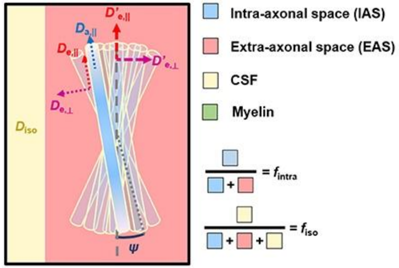
Signal representations describe the signal through mathematical formulae (basis functions)

- General and have few assumptions – independent of a theory
- Coefficients of the basis may be sensitive to pathological changes
- e.g Diffusion tensor, diffusion kurtosis



Biophysical models are based on theories that relate the signal to biological properties of the tissue

- provide key insight how biophysical parameters will affect the signal
- difficult to validate



Novikov, D. S., Kiselev, V. G., & Jespersen, S. N. (2018). On modeling. Magnetic resonance in medicine, 79(6), 3172–3193. https://doi.org/10.1002/mrm.27101
Jelescu, I. O., & Budde, M. D. (2017). Design and validation of diffusion MRI models of white matter. Frontiers in physics, 28, 61. https://doi.org/10.3389/fphy.2017.00061

Estimating diffusivity

- We can relate the diffusion MRI signal to the diffusivity within a voxel using a simple exponential model
- Single measure of diffusivity within a voxel

Measured
Imaging parameters
To be estimated

B-value for gradient k

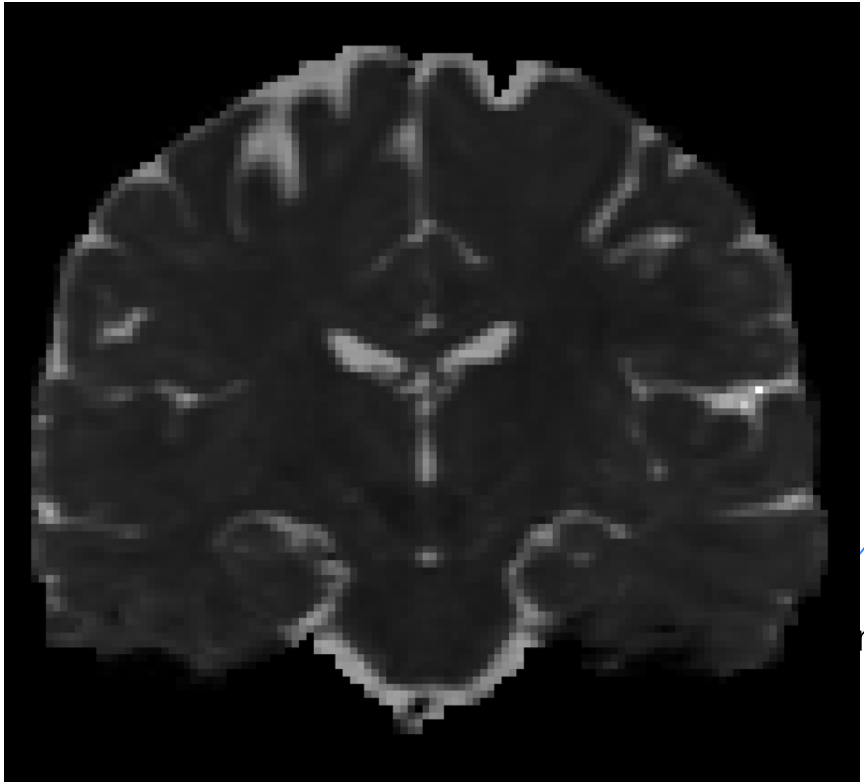
$$S_k = S_0 \exp(-b_k d)$$

Signal after applying a diffusion-weighted gradient k in direction q_k with b-value b_k

Signal with no diffusion-weighted gradient applied

Diffusivity within a voxel

Estimating diffusivity



Measured
Imaging parameters
To be estimated

B-value for gradient k

$$S_k = S_0 \exp(-b_k d)$$

ng a gradient k b-value b_k

Signal with no diffusion-weighted gradient applied

Diffusivity within a voxel

The Diffusion Tensor

- The diffusion tensor enables us to characterise Gaussian diffusion in 3D in each voxel

B-value for gradient k

Unit vector of the direction of gradient k

Measured
Imaging parameters
To be estimated

$$S_k = S_0 \exp(-b_k \hat{\mathbf{g}}_k^T \mathbf{D} \hat{\mathbf{g}}_k)$$

The diffusion tensor

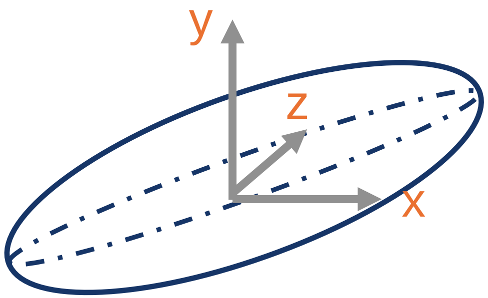
Signal after applying a diffusion-weighted gradient k in direction q_k with b-value b_k

Signal with no diffusion-weighted gradient applied

What is the diffusion tensor?

- 3x3 positive-definite symmetric matrix characterising displacement/diffusion in 3D

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

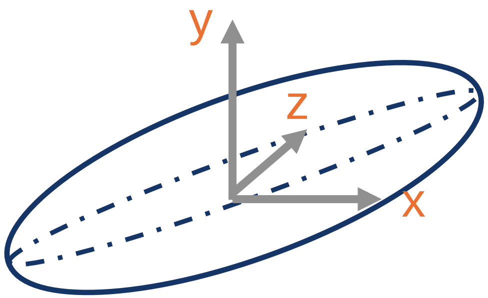


- D_{xx}, D_{yy}, D_{zz} : diffusion along 3 orthogonal axis (always positive)
- D_{xy}, D_{xz}, D_{yz}: correlation between displacements along these orthogonal axis (positive or negative)

What is the diffusion tensor?

- 3x3 positive-definite symmetric matrix characterising displacement/diffusion in 3D

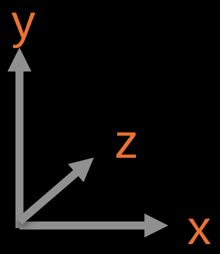
$$\boldsymbol{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}$$

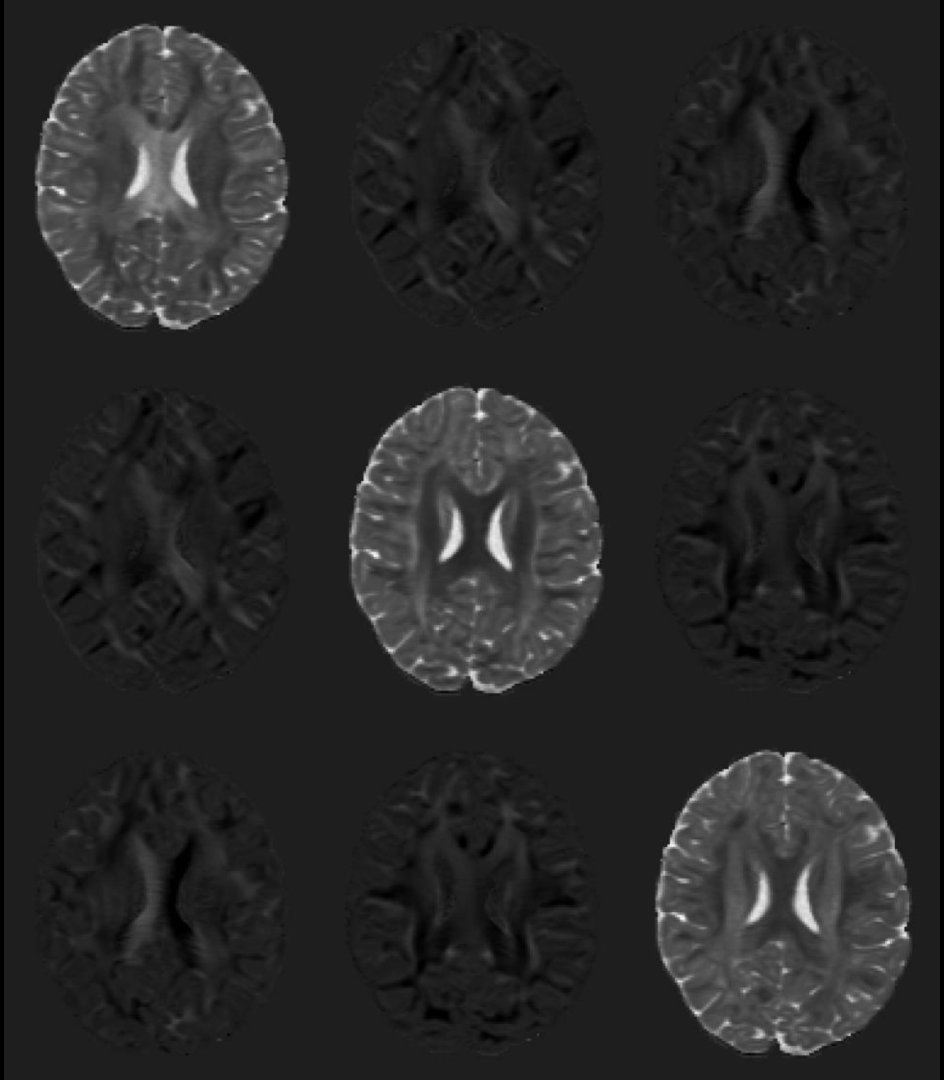


- D_{xx}, D_{yy}, D_{zz} : diffusion along 3 orthogonal axis (always positive)
- D_{xy}, D_{xz}, D_{yz}: correlation between displacements along these orthogonal axis (positive or negative)

The elements of diffusion tensor in the brain

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

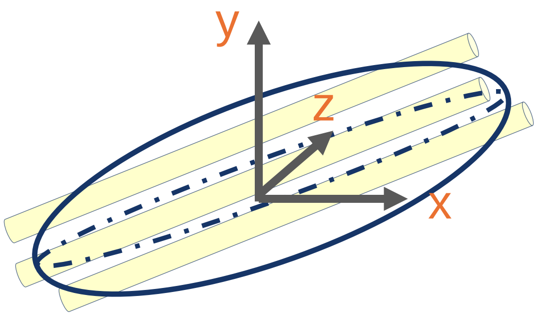


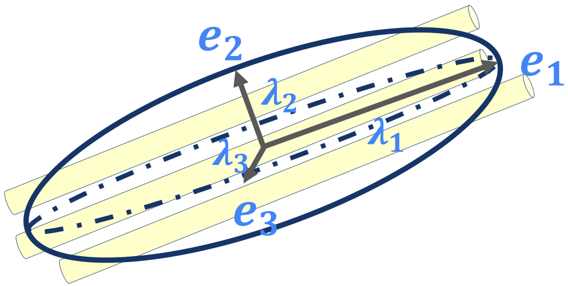


Ellipsoid from DT

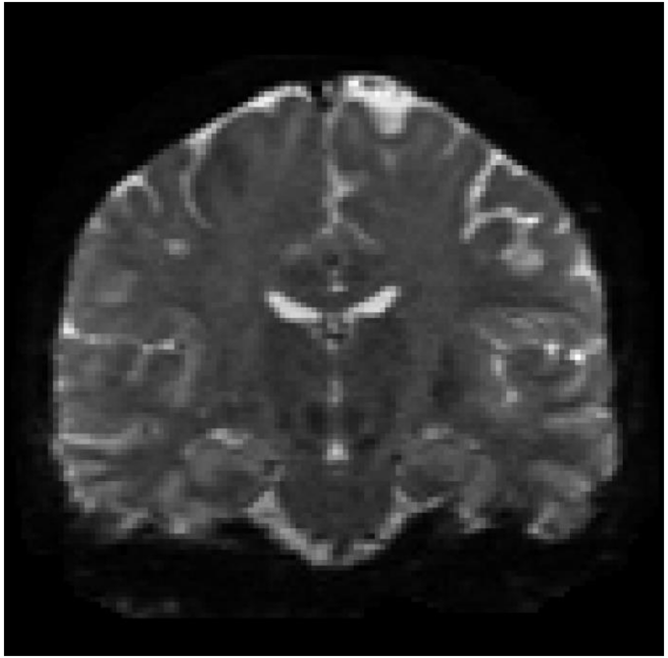
- We can decompose the Diffusion tensor into eigen-values and eigen-vectors

$$\boldsymbol{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix} = [e_1 \quad e_2 \quad e_3] \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \begin{bmatrix} e_1 \\ e_2 \\ e_3 \end{bmatrix}$$

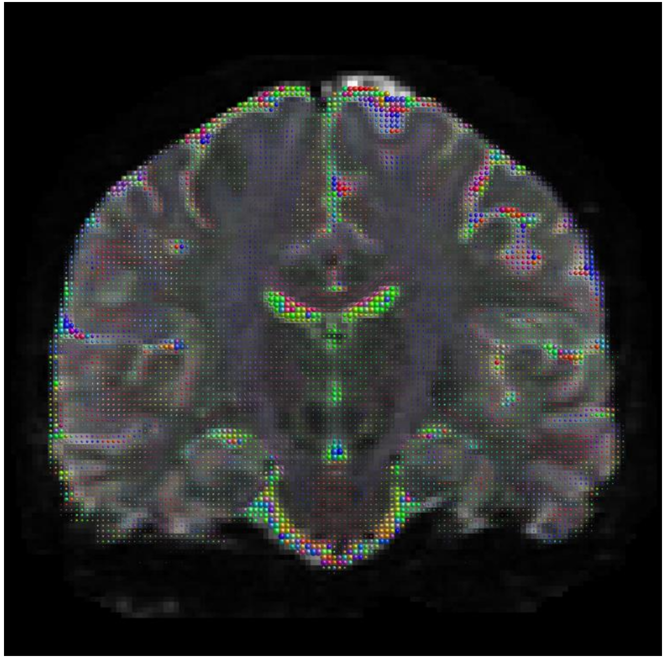




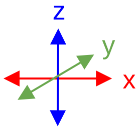
Diffusion Tensor in real data



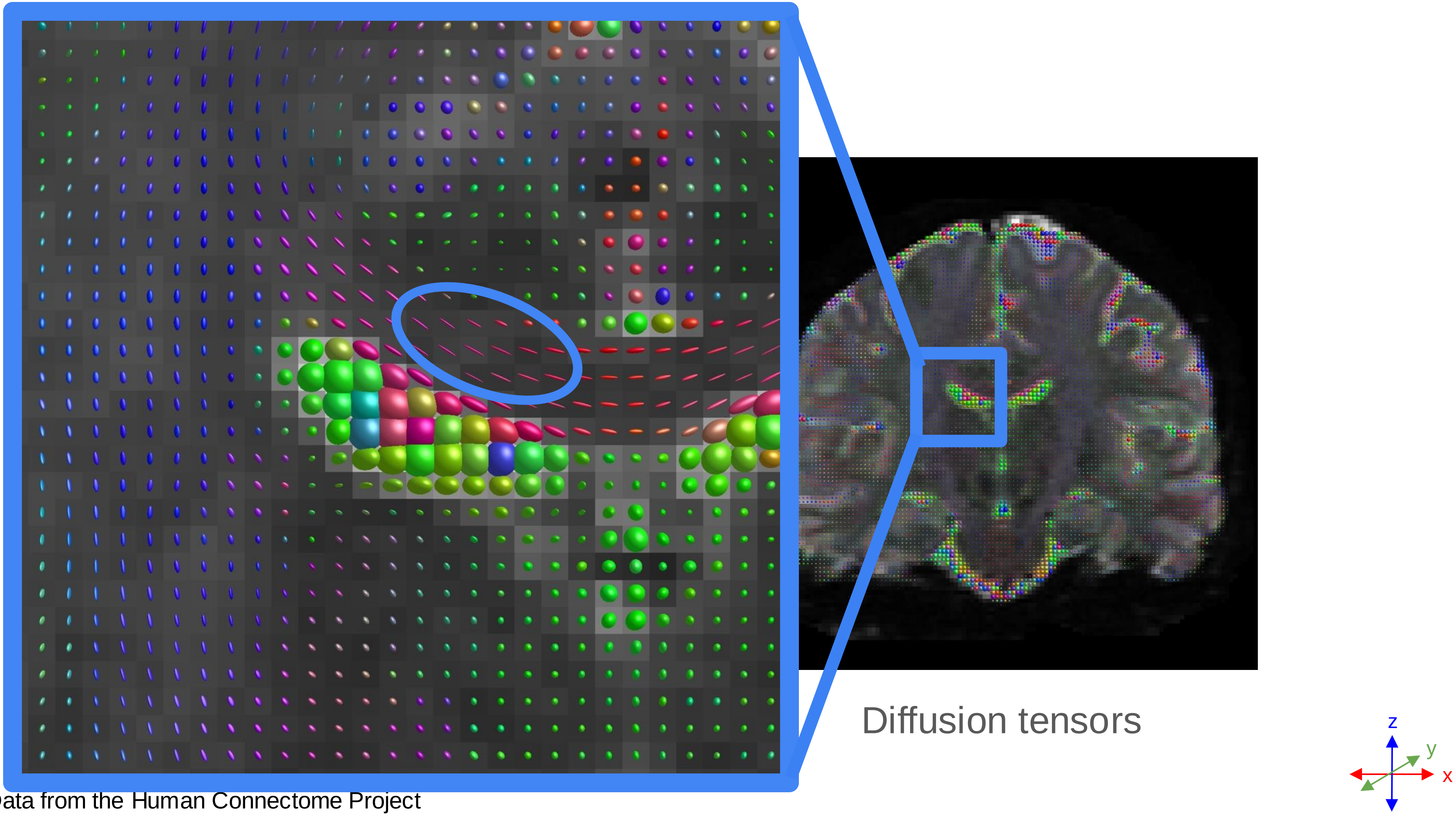
B0 diffusion signal



Diffusion tensors

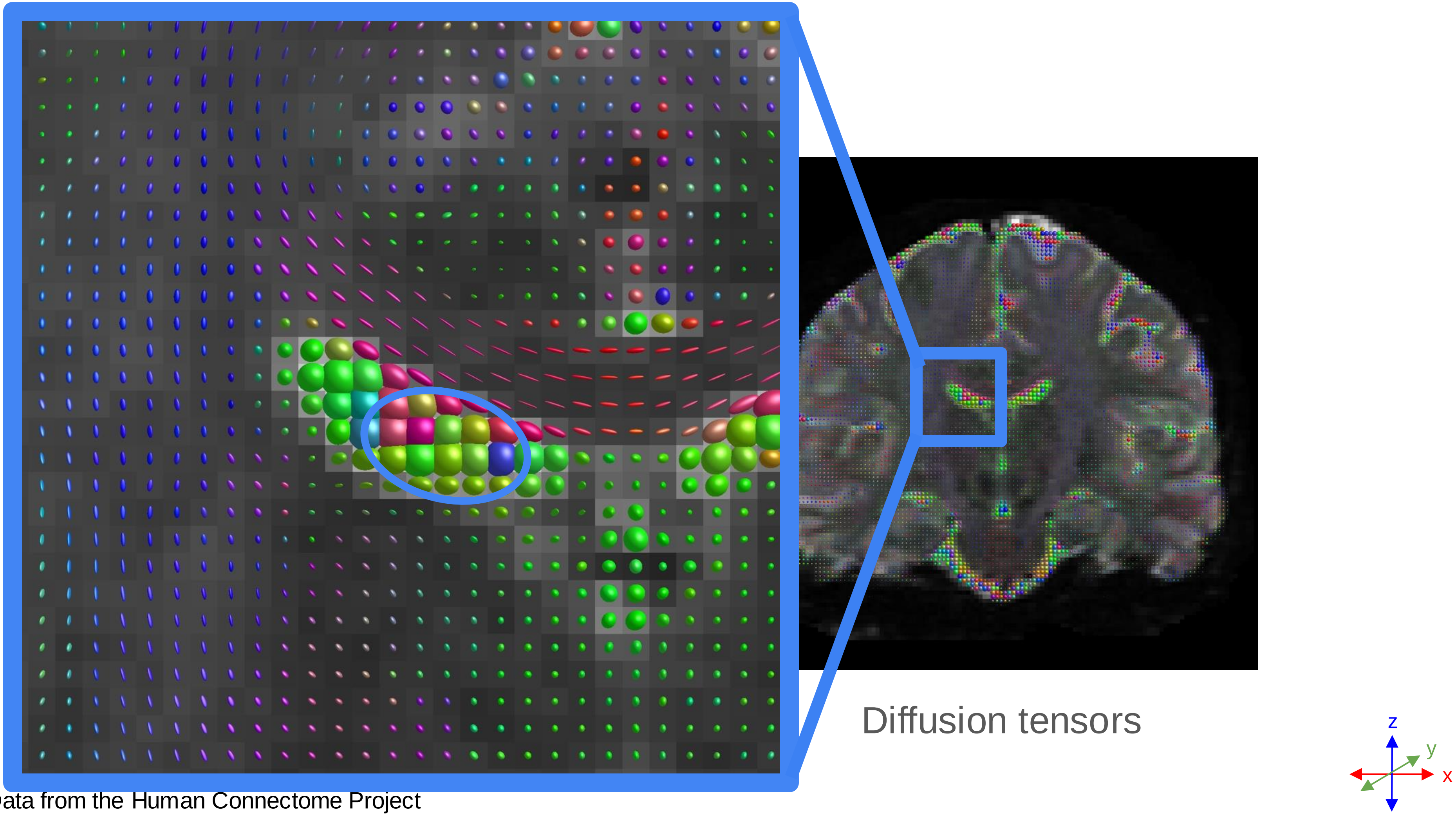


Data from the Human Connectome Project



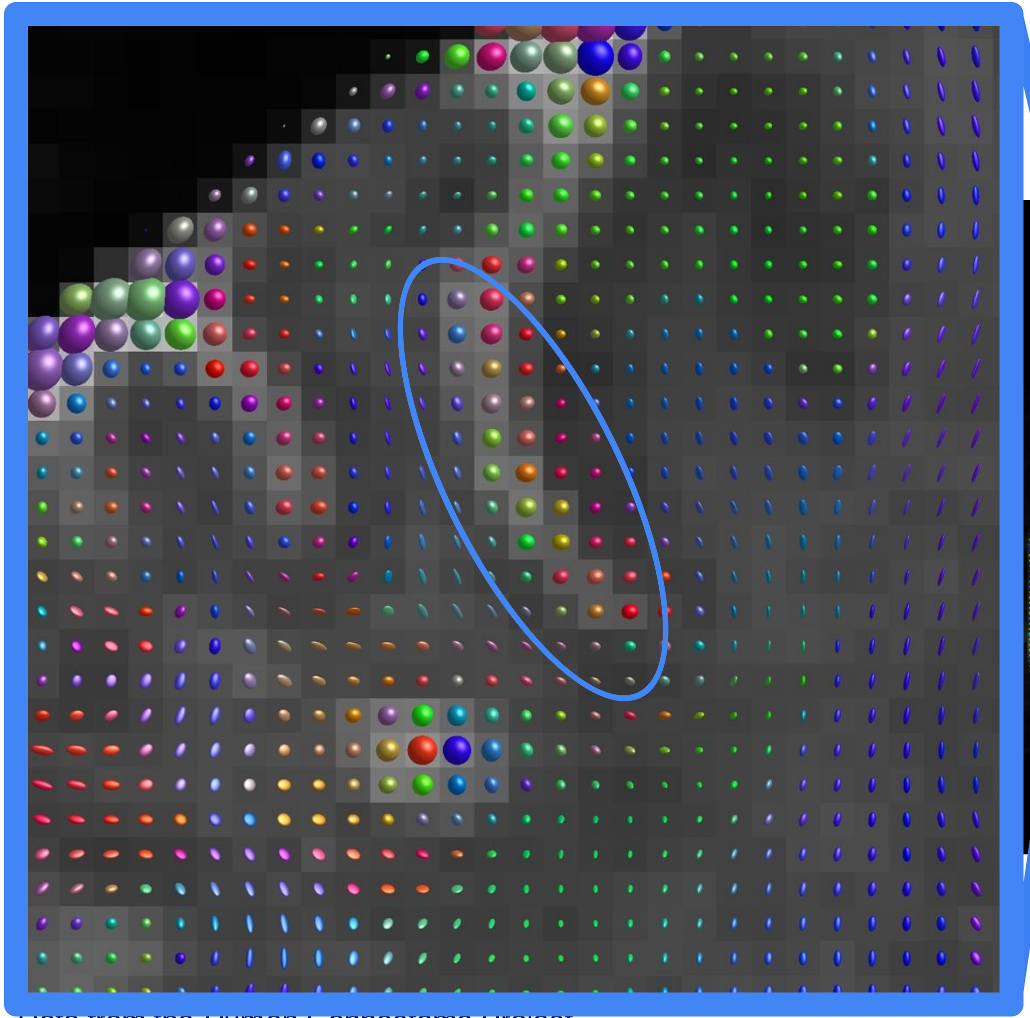
Diffusion tensors

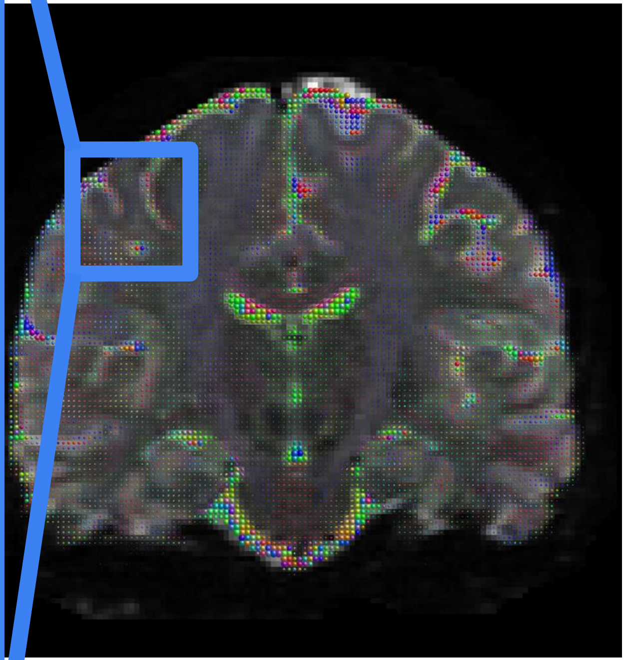
Data from the Human Connectome Project



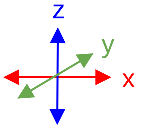
Diffusion tensors

Data from the Human Connectome Project



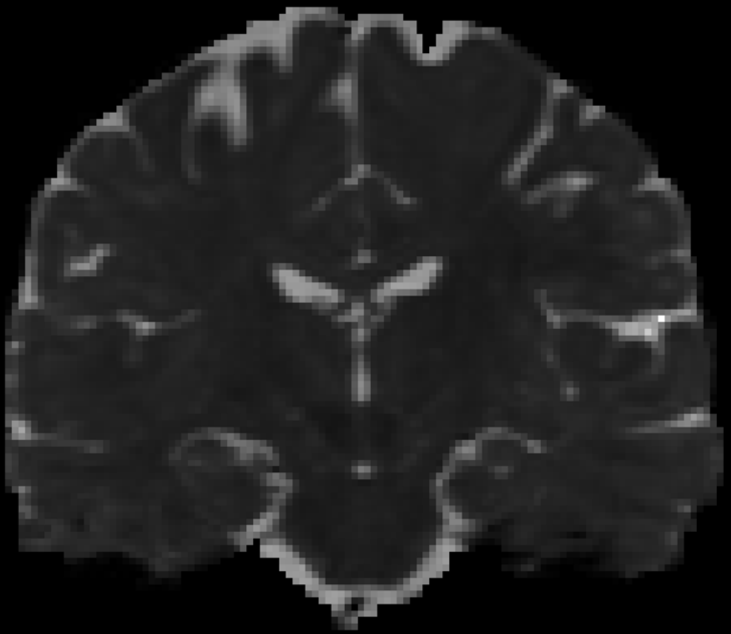


Diffusion tensors

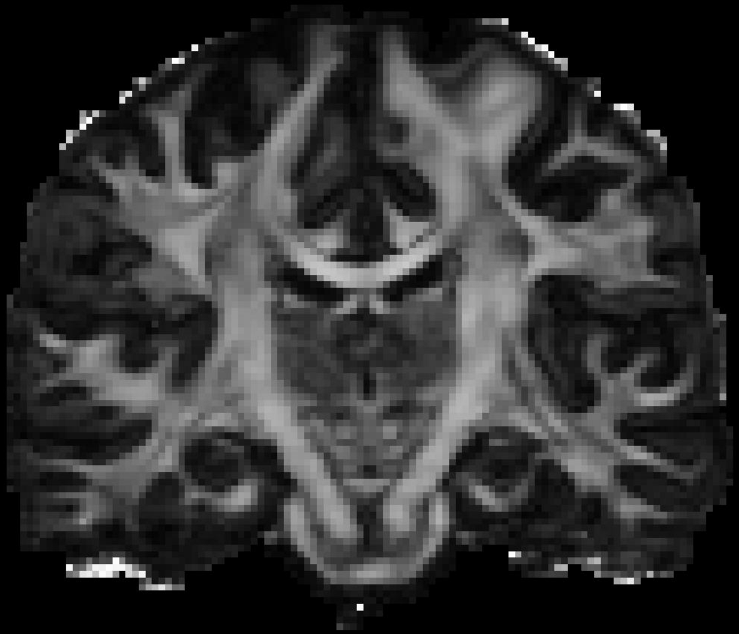


Data from the Human Connectome Project

Measures derived from the diffusion tensor



Mean Diffusivity (MD) = mean of the tensor eigenvalues



Fractional Anisotropy (FA) = normalised variance of tensor eigenvalues

Axial Diffusivity,

Radial Diffusivity

…

Fitting the diffusion tensor from an image

- Fitting the 6 variables of the diffusion tensor (Dxx,Dxy,Dxz,Dyy,Dyz,Dzz) from the diffusion image requires a minimum of 6 diffusion directions (+S(0))
- Methods:
  - Linear least squared
  - Weighted linear least squares
  - Non-linear least squares, etc

Fitting the diffusion tensor from an image

- Fitting the 6 variables of the diffusion tensor (Dxx,Dxy,Dxz,Dyy,Dyz,Dzz) from the diffusion image requires a minimum of 6 diffusion directions (+S(0))
- Methods:
  - Linear least squared
  - Weighted linear least squares
  - Non-linear least squares, etc

- Minimise the following function:

$$S_k - S_0 \exp(-b_k \hat{\boldsymbol{g}}_k^T \boldsymbol{D} \hat{\boldsymbol{g}}_k)$$

Coding practicals

- Three coding practicals:
  - Diffusion tensor
  - Ball-and-stick model
  - Spherical deconvolution
- Estimate model parameters in each voxel of the FiberCup dataset[1]

https://github.com/ethompson93/dmri_analysis_techniques

[1]Poupon, C., Laribiere, L., Tournier, G., Bernard, J., Fournier, D., Fillard, P., Descoteaux, M., et al. (2010). A Diffusion Hardware Phantom Looking Like a Coronal Brain Slice. *Proceedings of the International Society for Magnetic Resonance in Medicine*.

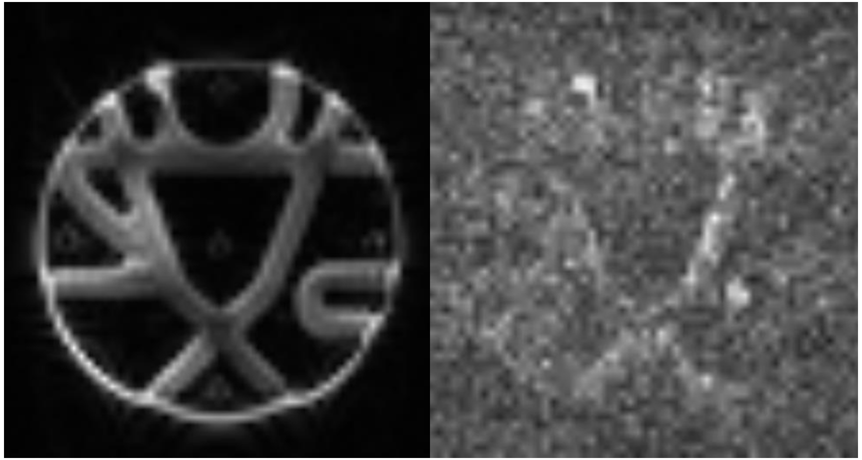
FiberCup Data

- Built as part of a MICCAI challenge and mimics the coronal section (3 slices) of the brain with deep and superficial U-fibre bundles Diffusion MRI simulated from known ground truth fibre bundles

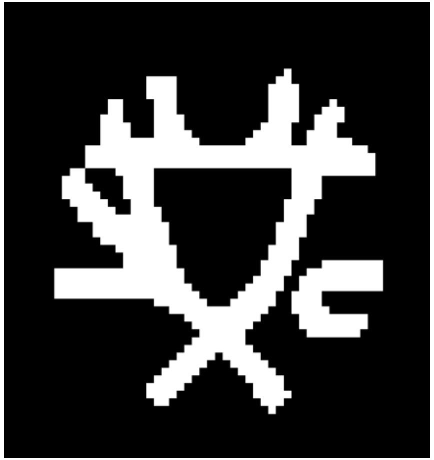
grad.txt

```
0         0         0         0
1         0         0         2000
0         -0.987414         -0.158158         2000
-0.026007         -0.761231         0.64796 2000
0.591136         0.716668         0.370062         2000
-0.236071         0.388148         0.890848         2000
-0.893021         0.197543         0.40434 2000
0.796184         -0.220899         0.56329 2000
0.233964         -0.963062         0.133318         2000
0.935686         -0.189418         0.29768 2000
```

fibrecup.nii.gz



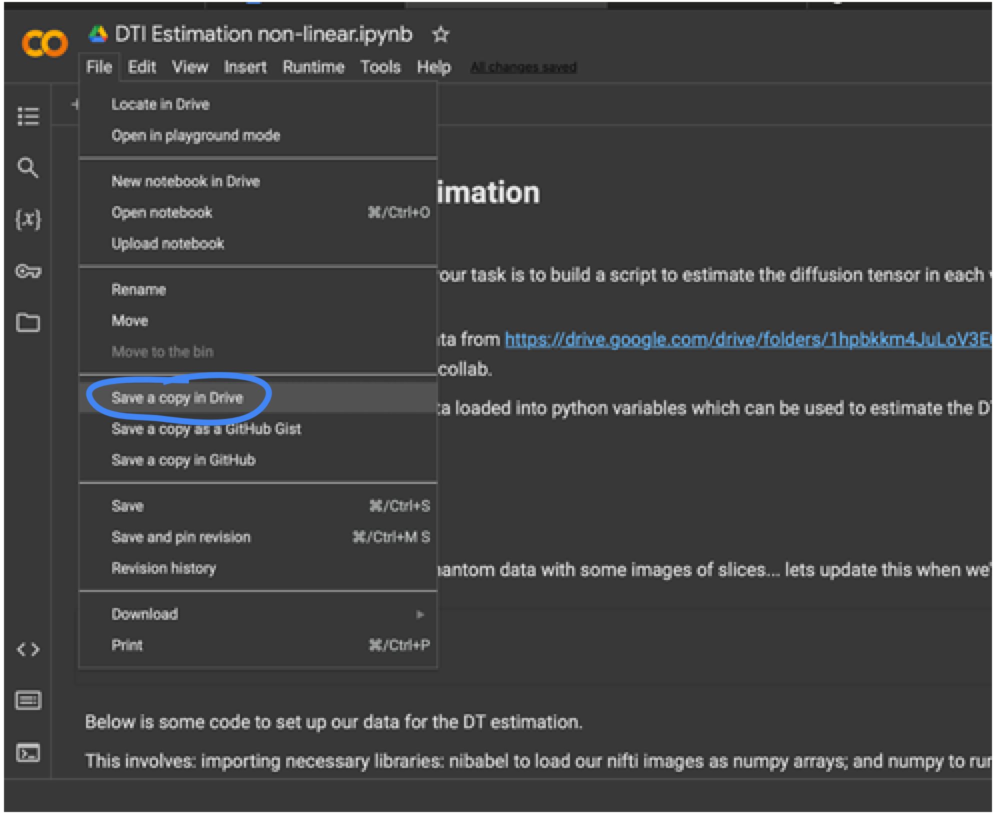
wm_mask.nii.gz



Poupon, C., Laribiere, L., Tournier, G., Bernard, J., Fournier, D., Fillard, P., Descoteaux, M., et al. (2010). A Diffusion Hardware Phantom Looking Like a Coronal Brain Slice. *Proceedings of the International Society for Magnetic Resonance in Medicine.*

Fillard, P., Descoteaux, M., Goh, A., Gouttard, S., Jeurissen, B., Malcolm, J., Ramirez-Manzanares, A., et al. (2011). Quantitative Evaluation of 10 Tractography Algorithms on a Realistic Diffusion MR Phantom. *NeuroImage*, 56(1), 234–220.

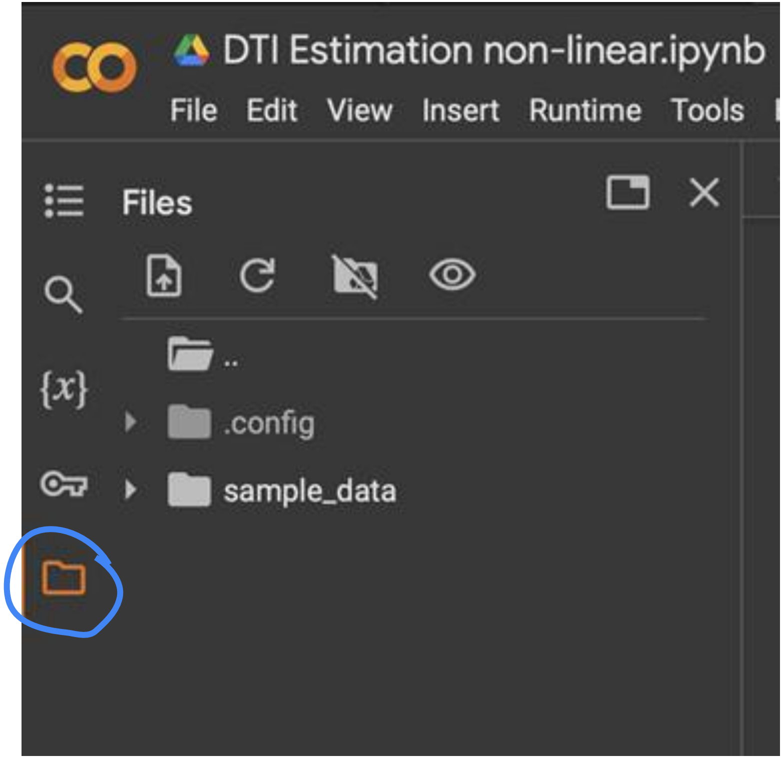
Making your own copy of the practicals



https://github.com/ethompson93/dmri_analysis_techniques

Uploading the data

- Download the sample data from https://drive.google.com/drive/folders/12hHKJoAXDB-AsNTzxXf4ZvSbfq-_7qmX?usp=sharing (link in Colab and on Github)
- Upload to “files”



Diffusion Tensor: Coding Exercise

- Estimate the diffusion tensor in each voxel in a phantom dataset

$$S_k = S_0 \exp(-b_k \hat{\boldsymbol{g}}_k^T \boldsymbol{D} \hat{\boldsymbol{g}}_k)$$

Measured
Imaging parameters
To be estimated

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

https://github.com/ethompson93/dmri_analysis_techniques

Compartment models

- Different tissues characterised by different biophysical models
- The signal is represented as a liner combination of the different compartments
- Exchange between compartments assumed to be negligible

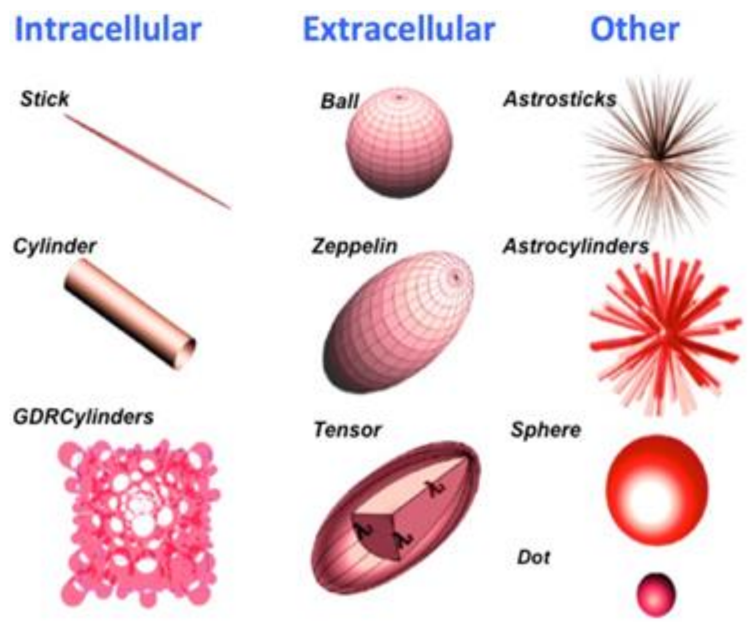
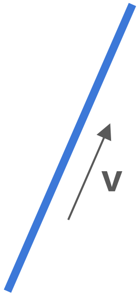


Figure from: Ferizi, U., Schneider, T., Panagiotaki, E., Nedjati-Gilani, G., Zhang, H., Wheeler-Kingshott, C.A.M. and Alexander, D.C. (2014), A ranking of diffusion MRI compartment models with in vivo human brain data. Magn. Reson. Med., 72: 1785-1792. https://doi.org/10.1002/mrm.25080

A simple compartment model: Ball and Stick Model



stick

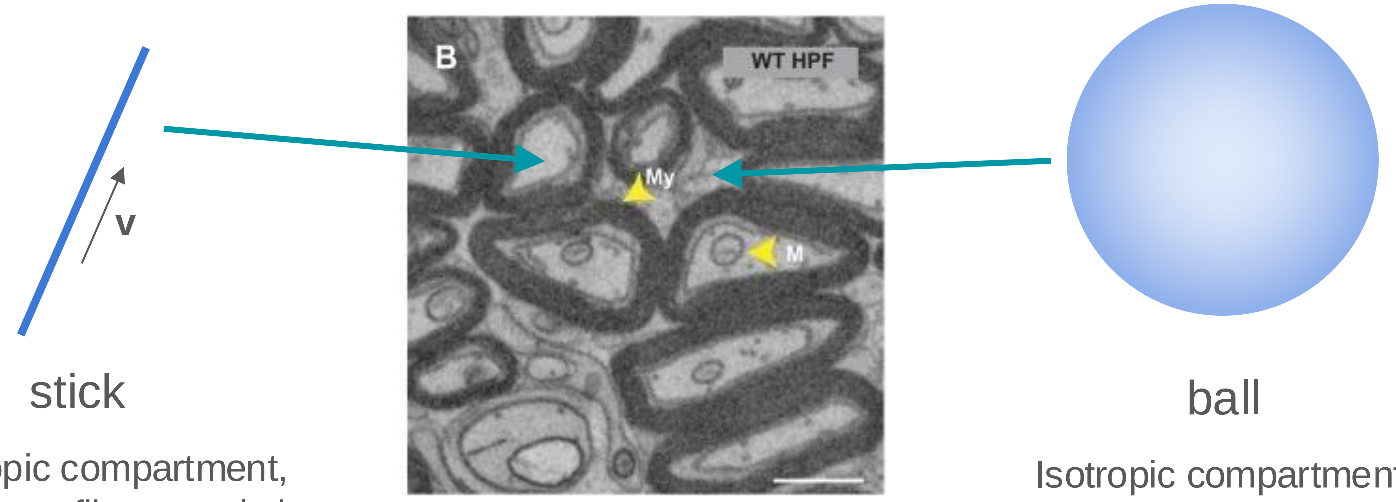
Anisotropic compartment, representing a fibre population with orientation **v**

ball

Isotropic compartment, representing free water in the voxel

Behrens, T.E.J., Woolrich, M.W., Jenkinson, M., Johansen-Berg, H., Nunes, R.G., Clare, S., Matthews, P.M., Brady, J.M. and Smith, S.M. (2003), Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn. Reson. Med., 50: 1077-1088. https://doi.org/10.1002/mrm.10609

A simple compartment model: Ball and Stick Model



stick

Anisotropic compartment, representing a fibre population with orientation **v**

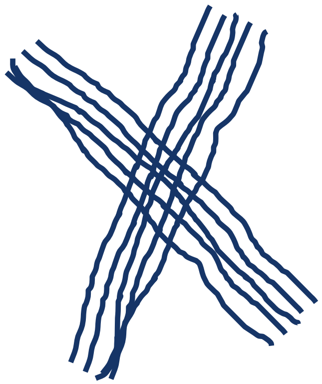
ball

Isotropic compartment, representing free water in the voxel

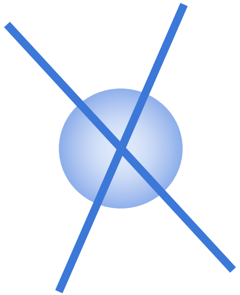
Behrens, T.E.J., Woolrich, M.W., Jenkinson, M., Johansen-Berg, H., Nunes, R.G., Clare, S., Matthews, P.M., Brady, J.M. and Smith, S.M. (2003), Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn. Reson. Med., 50: 1077-1088. https://doi.org/10.1002/mrm.10609

Ball and Stick Model

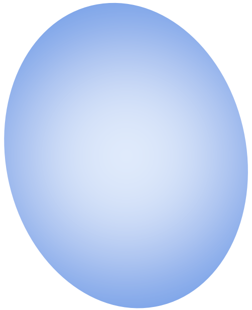
This allows us to model crossing fibre populations, which is not possible with DTI



Intersecting fibre populations



Ball and stick model

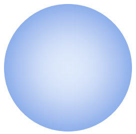


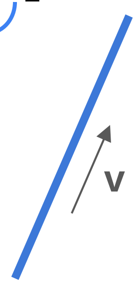
Tensor

Ball and Stick Model

signal measured for a diffusion weighted gradient with direction $\mathbf{g}_k$ and b-value b_k:

$$S_k = S_0[(1 - f)\underbrace{\exp(-b_k d)}_{\text{signal from “ball” compartment}} + f\,\underbrace{\exp(-b_k d(\mathbf{g}_k \cdot \mathbf{v})^2)}_{\text{signal from “stick” compartment: fibre population with direction } \mathbf{v}}]$$





Ball and Stick Model

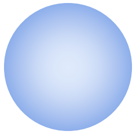
signal measured for a diffusion weighted gradient with direction $\mathbf{g}_k$ and b-value b_k:

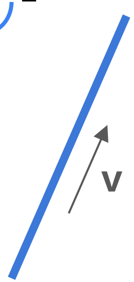
mean diffusivity

volume fraction of anisotropic compartment

$$S_k = S_0[(1-f)\underbrace{\exp(-b_k d)}_{\text{signal from “ball” compartment}} + f\underbrace{\exp(-b_k d(\mathbf{g}_k \cdot \mathbf{v})^2)}_{\text{signal from “stick” compartment: fibre population with direction }\mathbf{v}}]$$

signal when b = 0





Ball and Stick Model

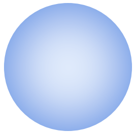
signal measured for a diffusion weighted gradient with direction $\mathbf{g}_k$ and b-value b_k:

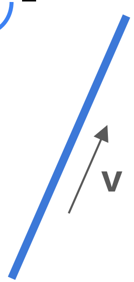
mean diffusivity

volume fraction of anisotropic compartment

$$S_k = S_0[(1-f)\underbrace{\exp(-b_k d)}_{\text{signal from “ball” compartment}} + f\underbrace{\exp(-b_k d(\mathbf{g}_k \cdot \mathbf{v})^2)}_{\text{signal from “stick” compartment: fibre population with direction } \mathbf{v}}]$$

signal when b = 0





Measured

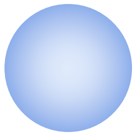
Imaging parameters

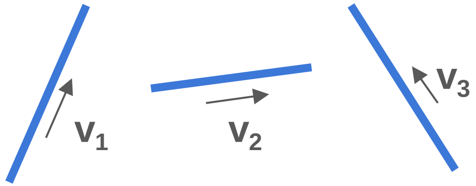
To be estimated

Ball and Stick Model – extending to multiple fibre populations

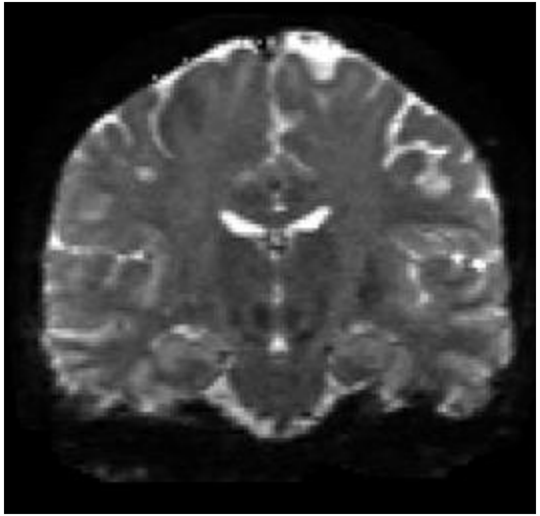
volume fraction of anisotropic compartment i

$$S_k = S_0\left[\left(1-\sum_{i=1}^{N} f_i\right)\underbrace{\exp(-b_k d)}_{\text{signal from “ball”}} + \sum_{i=1}^{N} f_i\,\underbrace{\exp\left(-b_k d(\mathbf{g}_k\cdot\mathbf{v}_{\boldsymbol{i}})^2\right)}_{\text{signal from “stick” compartment: fibre population with direction }\mathbf{v}_\mathrm{i}}\right]$$

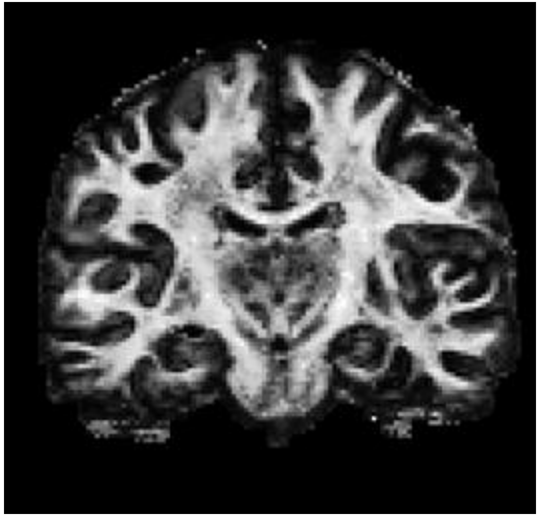




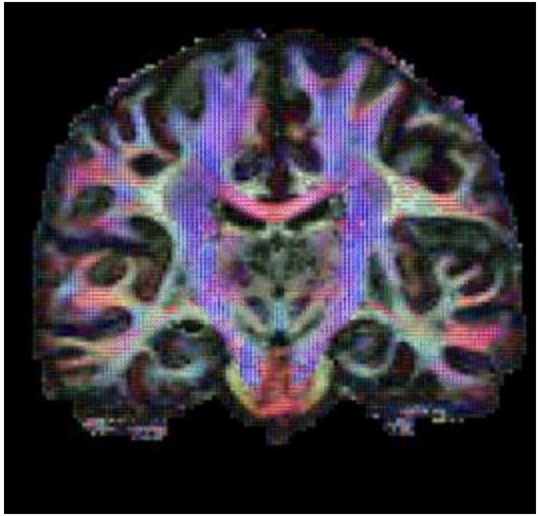
Ball and Stick Model in real data



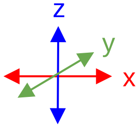
B0 diffusion signal



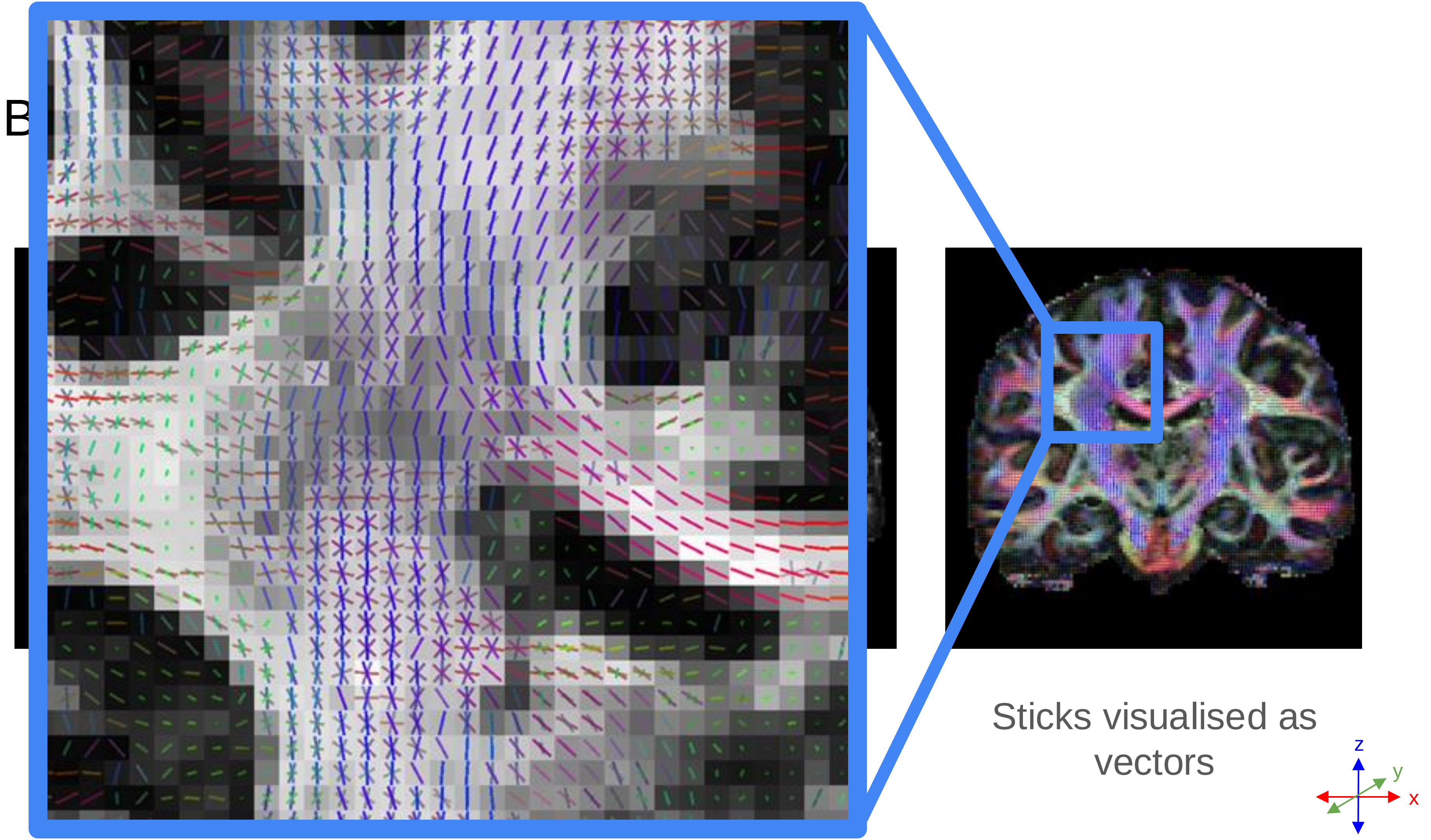
Fibre volume fraction



Sticks visualised as vectors



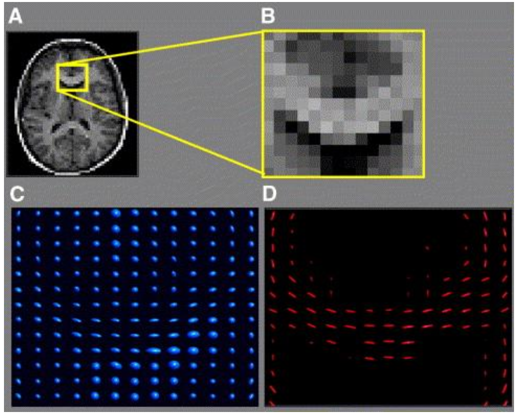
Data from the Human Connectome Project


B
Sticks visualised as vectors
z
y
x

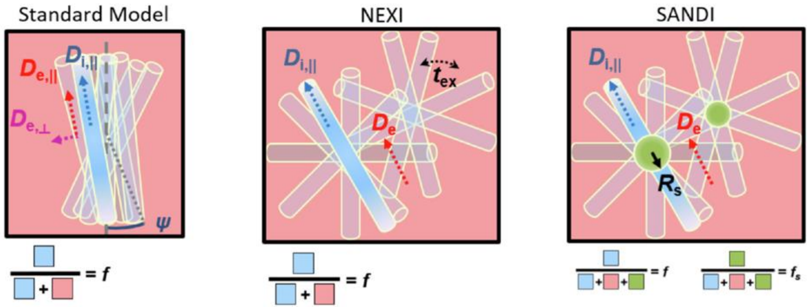
More advanced compartment models

- White matter
  - CHARMED: Composite hindered and restricted model of diffusion. *Assaf and Basser (2005) NeuroImage*
  - NODDI: Neurite orientation dispersion and density imaging. *Zhang et al (2012) NeuroImage*
- Grey matter
  - SANDI: Soma and neurite density imaging. *Palombo et al (2020) NeuroImage*
  - NEXI: neurite exchange imaging. *Jelescu et al (2022) NeuroImage*
- Tumours
  - VERDICT: Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumours. *Panagiotaki et al (2014), Cancer Res*

CHARMED



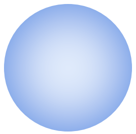
hindered restricted

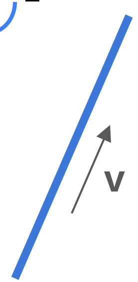


Ball and Stick Model: Coding Exercise

- Open up the second colab notebook to begin the exercise
- You will need to upload the data again, either from gdrive or github
- This time we will be fitting the ball-and-stick model to our data

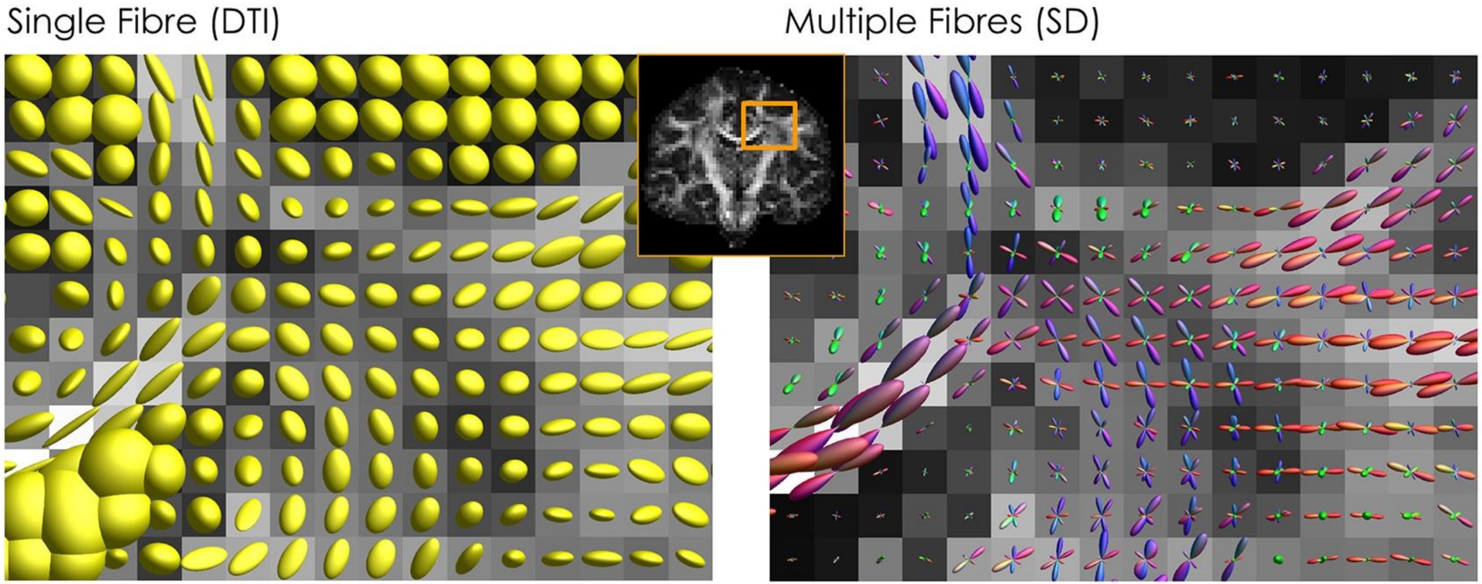
$$S_k = S_0[(1-f)\underbrace{\exp(-b_k d)}_{\text{signal from “ball” compartment}} + f\underbrace{\exp(-b_k d(\mathbf{g}_k \cdot \mathbf{v})^2)}_{\text{signal from “stick” compartment: fibre population with direction } \mathbf{v}}]$$





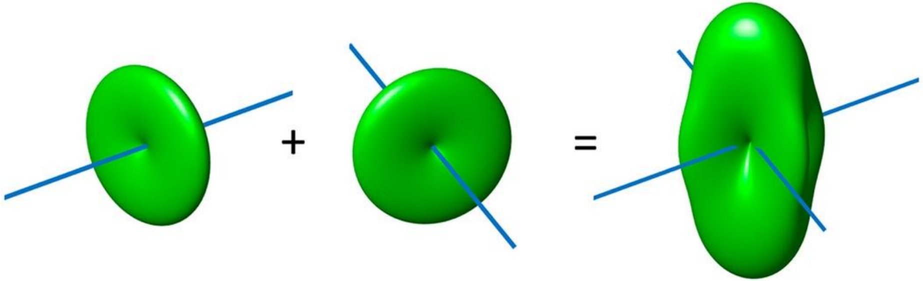
Spherical Deconvolution

- Method for obtaining a continuous fibre orientation distribution function: fODF
- Provides fibre orientations for tractography



Dell'Acqua F, Tournier JD. Modelling white matter with spherical deconvolution: How and why? *NMR in Biomedicine*. 2019; 32:e3945. https://doi.org/10.1002/nbm.3945

Spherical Deconvolution

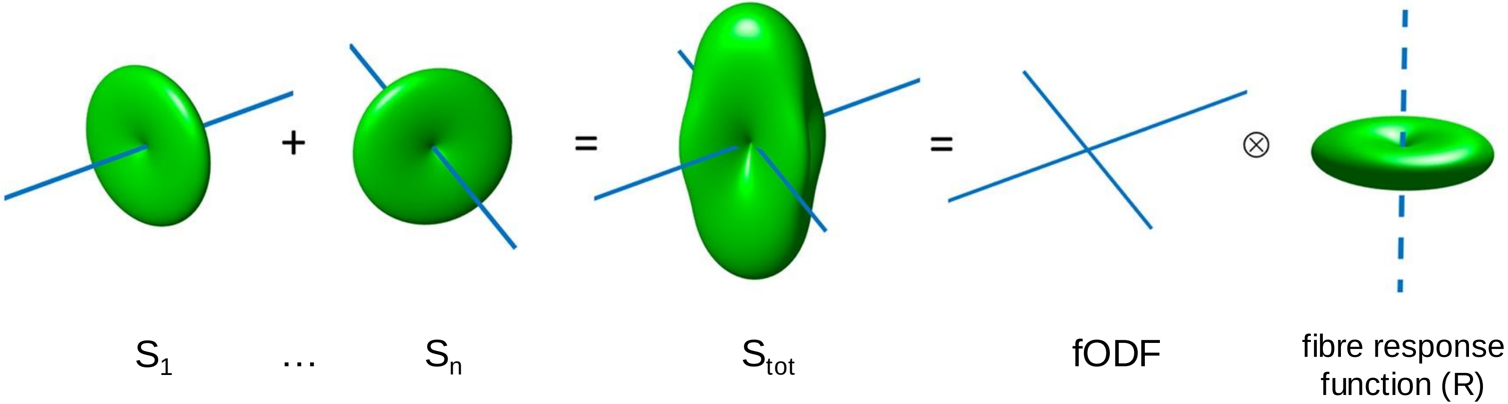


S_1 … S_n S_{tot}

- We assume that the diffusion-weighted signal is equivalent for all fibre populations in the brain (fibre response function)
- The measured signal is a linear combination of signals from all the fibre populations within a voxel

Dell'Acqua F, Tournier JD. Modelling white matter with spherical deconvolution: How and why? *NMR in Biomedicine*. 2019; 32:e3945. https://doi.org/10.1002/nbm.3945

Spherical Deconvolution



- We assume that the diffusion-weighted signal is equivalent for all fibre populations in the brain (fibre response function)
- The measured signal is a linear combination of signals from all the fibre populations within a voxel
- The fODF is obtained by deconvolving the measured signal with the fibre response function

Dell'Acqua F, Tournier JD. Modelling white matter with spherical deconvolution: How and why? *NMR in Biomedicine*. 2019; 32:e3945. https://doi.org/10.1002/nbm.3945

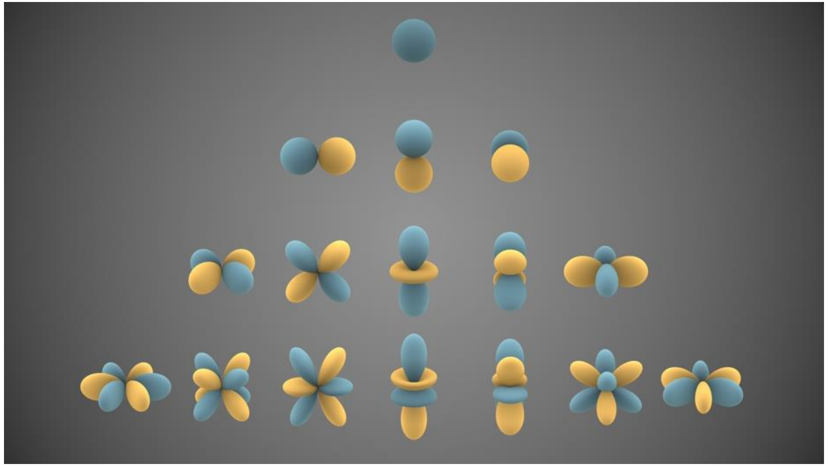
Spherical Harmonic Basis

- We can represent the fODF as a weighted sum of spherical harmonics up to a degree l_{max}:

$$f(\theta,\phi) = \sum_{l}^{l_{\max}} \sum_{m=-l}^{l} \color{red}{c_{lm}} \color{blue}{Y_{lm}}(\theta,\phi)$$

coefficients to be estimated

spherical harmonics

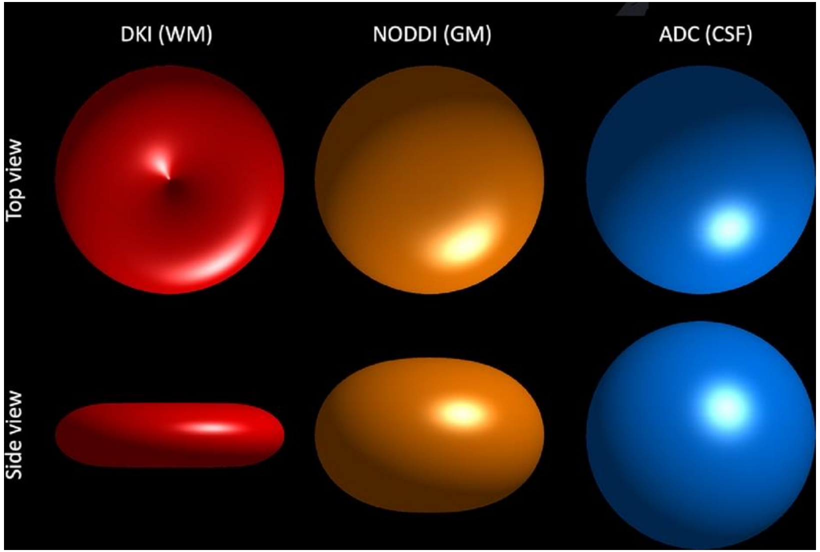


Advantages:

- compact representation reduces noise
- convolution is a simple product in spherical harmonic domain – easier computation

Step 1: Estimating the fibre response function

- The DW signal that would be acquired for single coherent fibre population
- Model based approaches: eg. axially symmetric tensor
- Direct empirical measurements from single-fibre voxels
- Response function can be derived for each tissue type (multi-tissue)

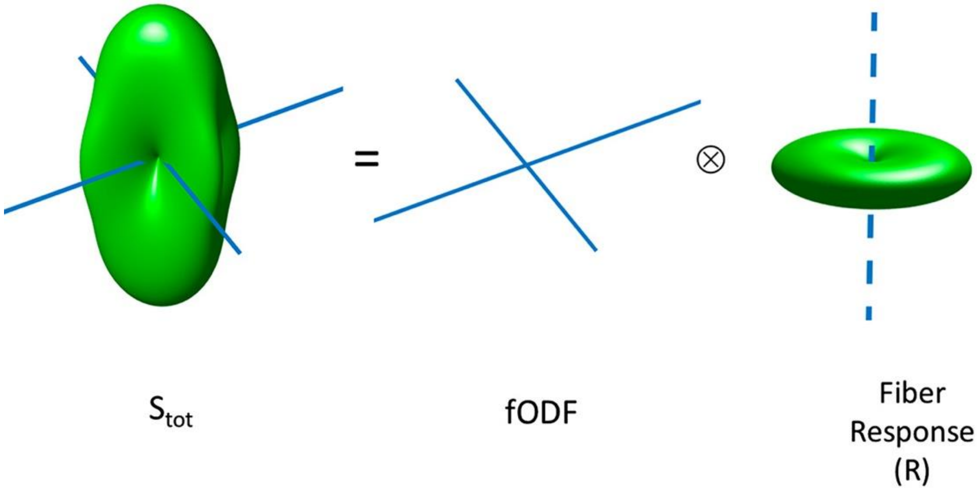


Examples of Response Functions derived from different models

Spherical deconvolution with tissue-specific response functions and multi-shell diffusion MRI to estimate multiple fiber orientation distributions (mFODs)":https://www.sciencedirect.com/science/article/pii/S1053811920306923

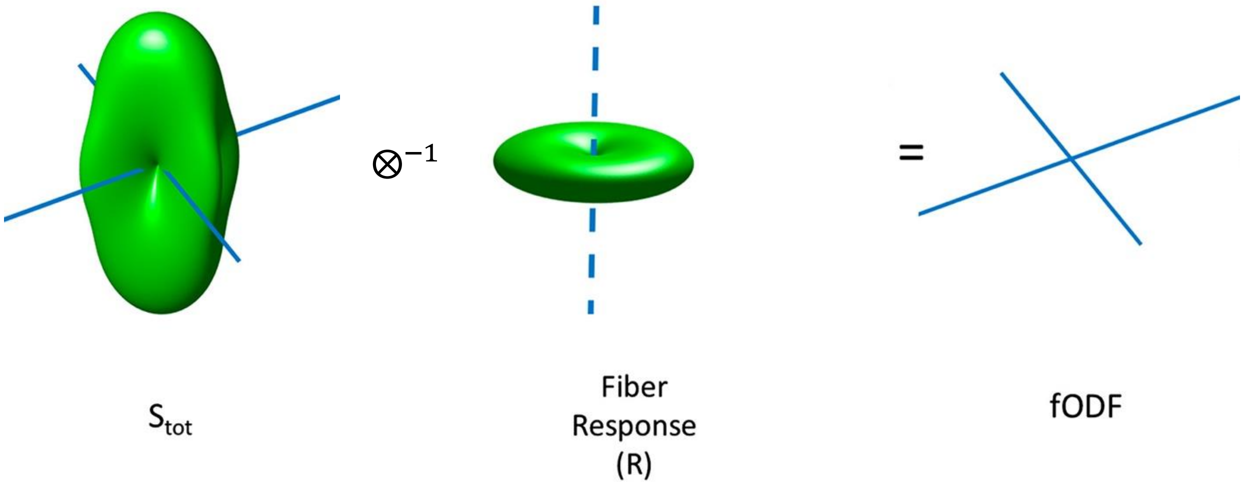
Step 2: Using the fibre response function to determine the fODF

- We can deconvolve the measured signal with the response function, R, to obtain the fODF



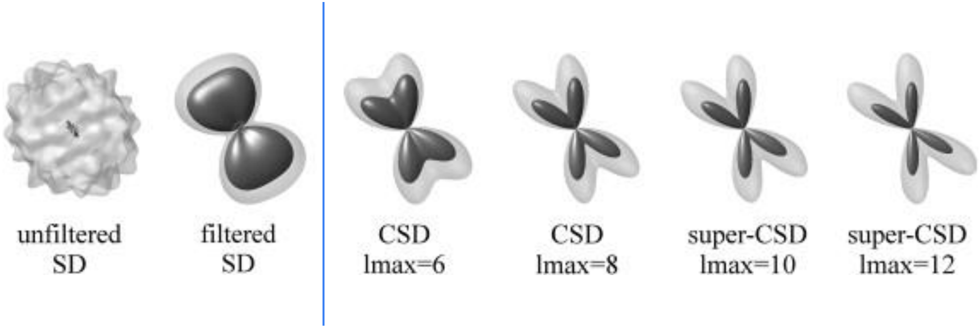
Step 2: Using the fibre response function to determine the fODF

- We can deconvolve the measured signal with the response function, R, to obtain the fODF



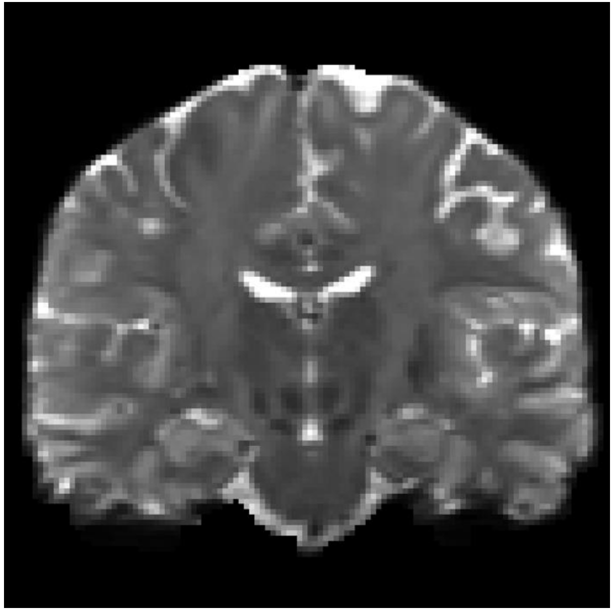
Constrained Spherical Deconvolution

- The spherical deconvolution operation is ill-posed and susceptible to noise
- Tournier et al (2007) introduced a **non-negativity constraint** to the reconstructed fODF
- This drastically improves the robustness to noise and improves angular resolution

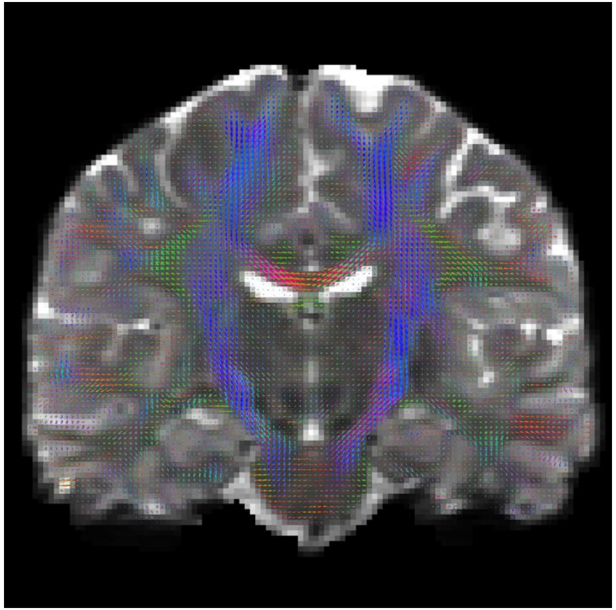


Tournier, J. D., Calamante, F., & Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. NeuroImage, 35(4), 1459–1472. https://doi.org/10.1016/j.neuroimage.2007.02.016

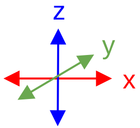
CSD in real data



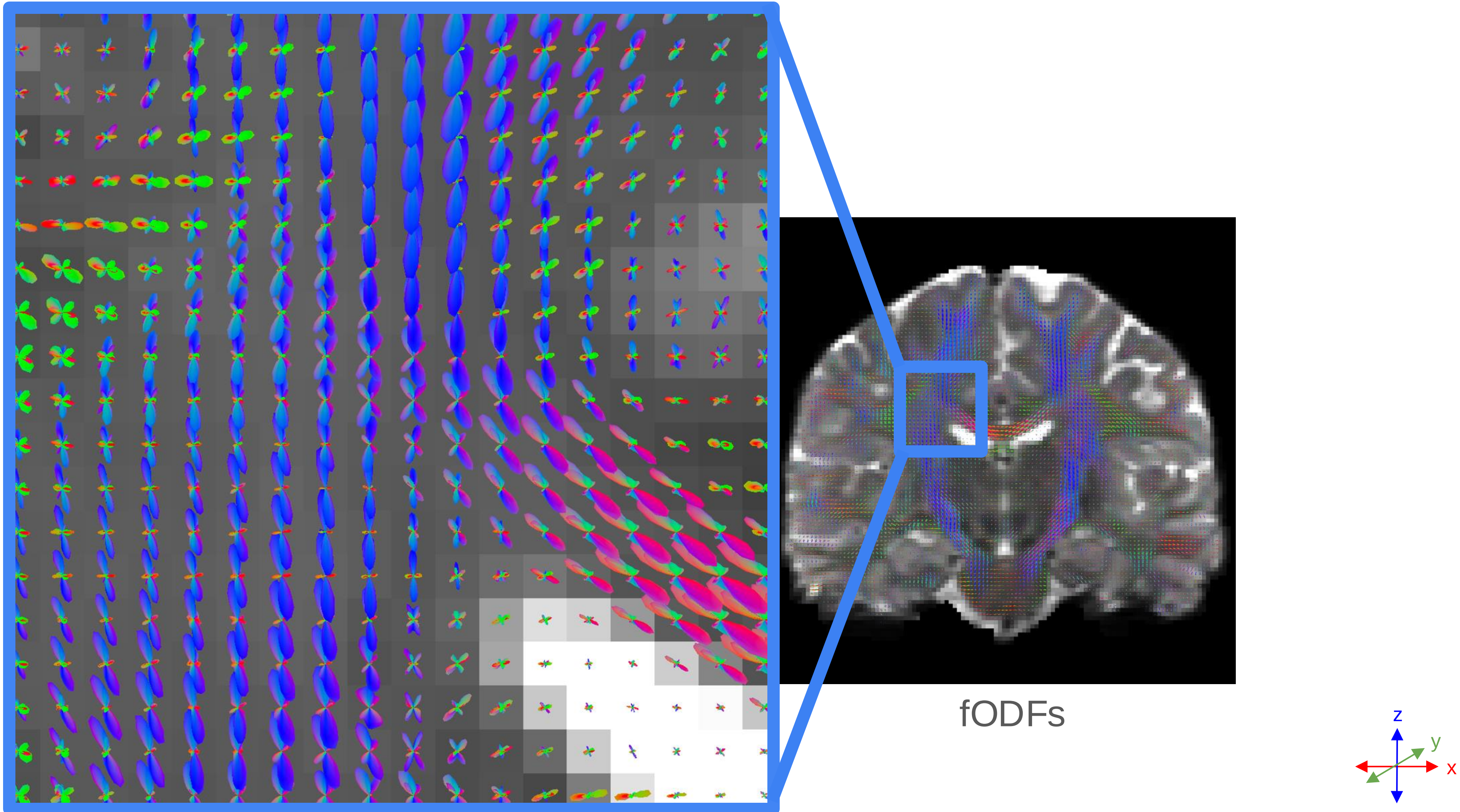
B0 diffusion signal



fODFs



Data from the Human Connectome Project


fODFs
z
y
x

CSD coding exercise

- We will use DIPY – an open-source python library for diffusion MRI analysis
- We perform constrained spherical deconvolution on the Fibercup phantom
- The notebook will take you through the steps of estimating the fibre response function and running the constrained spherical deconvolution

Conclusions

- Analysis techniques unlock biological insight from diffusion MRI scans
  - e.g. microstructural metrics and fibre orientations for tractography
- The diffusion tensor provides insight into the diffusion signal, but lacks microstructural specificity
- Compartment models, such as ball-and-stick, characterise different tissue environments with biophysical models
- Constrained spherical deconvolution is a method for estimating the fibre orientation distribution function

Acknowledgements

Professor Danny Alexander and the CU-MONDAI group at UCL Hawkes Institute