Analysis Techniques

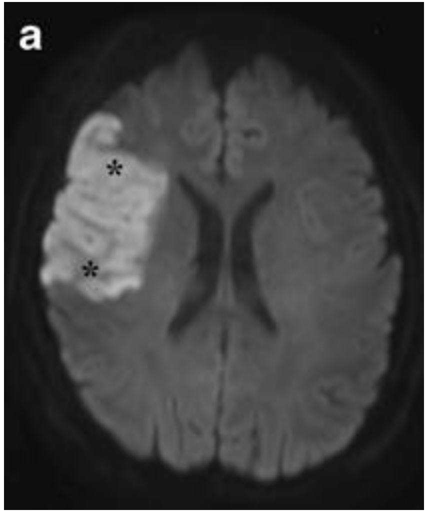
Ellie Thompson and Anna Schroder

Overview

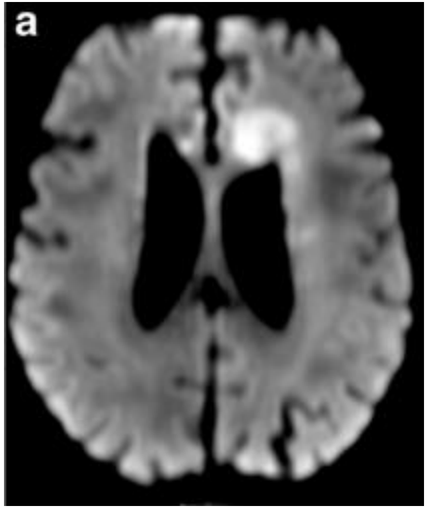
- Lecture
  - Introduction: using analysis techniques to gain biomedical insights from diffusion MRI
  - Diffusion tensor
  - Compartment models
  - Generating fODFs for tractography with constrained spherical deconvolution
- Coding Practicals
  - Practical 1: Diffusion tensor
  - Practical 2: Ball-and-stick model
  - Practical 3: Constrained Spherical Deconvolution
- Summary

Introduction

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

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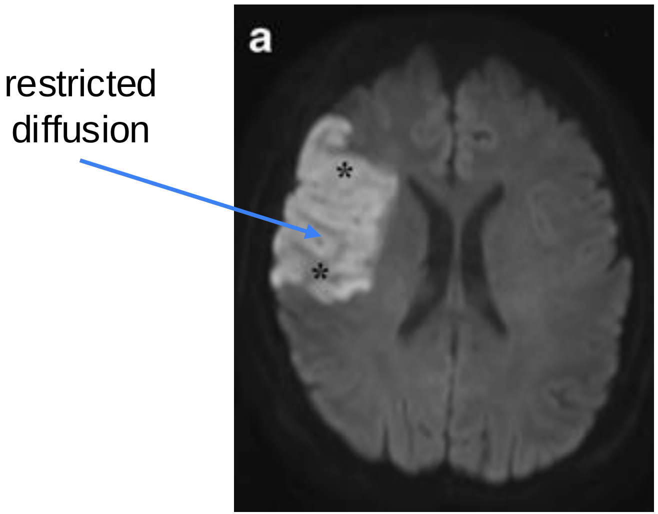

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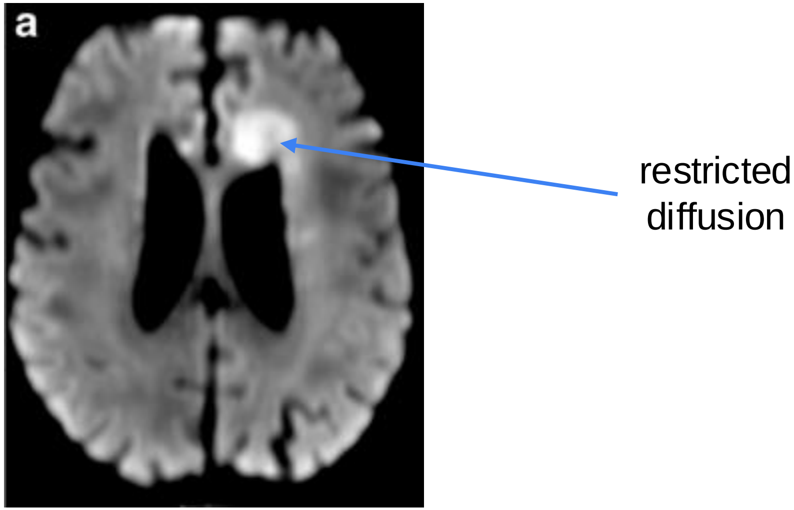

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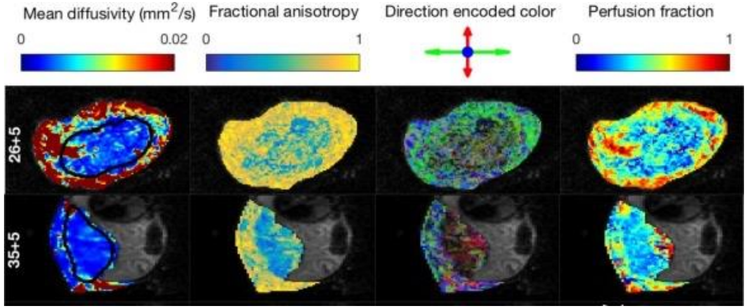
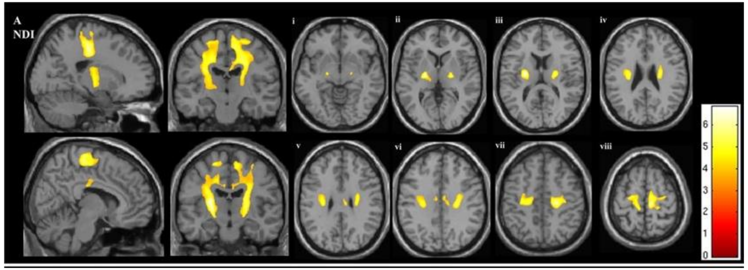
We can use analysis techniques to gain **biomedical insight** from dMRI

Key applications

Microstructure modelling

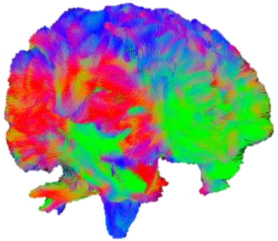


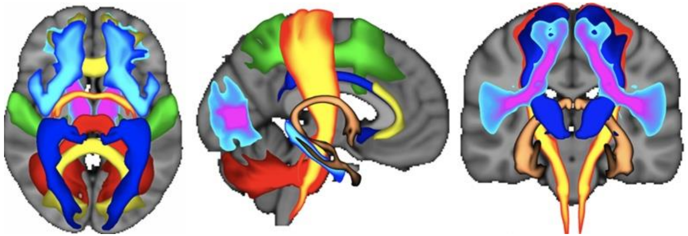
Slator PJ, el al. Placenta microstructure and microcirculation imaging with diffusion MRI. (2018)



Broad RJ, et al. Neurite orientation and dispersion density imaging (NODDI) detects cortical and corticospinal tract degeneration in ALS (2019)

Mapping white matter connections



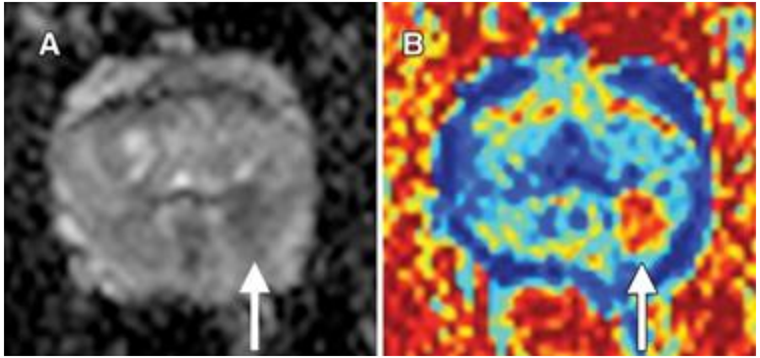


Warrington et al. Concurrent mapping of brain ontogeny and phylogeny within a common space: Standardized tractography and applications. (2022)

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

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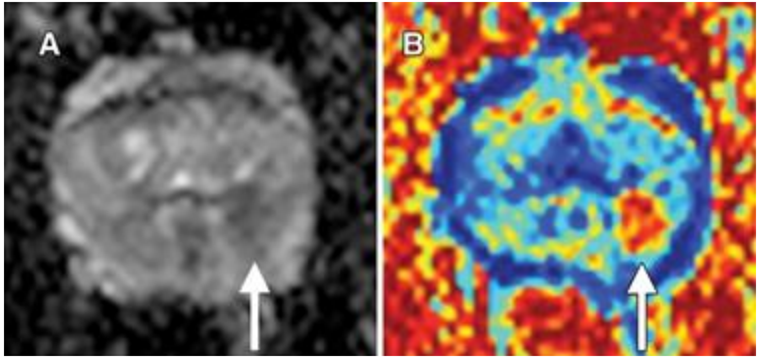


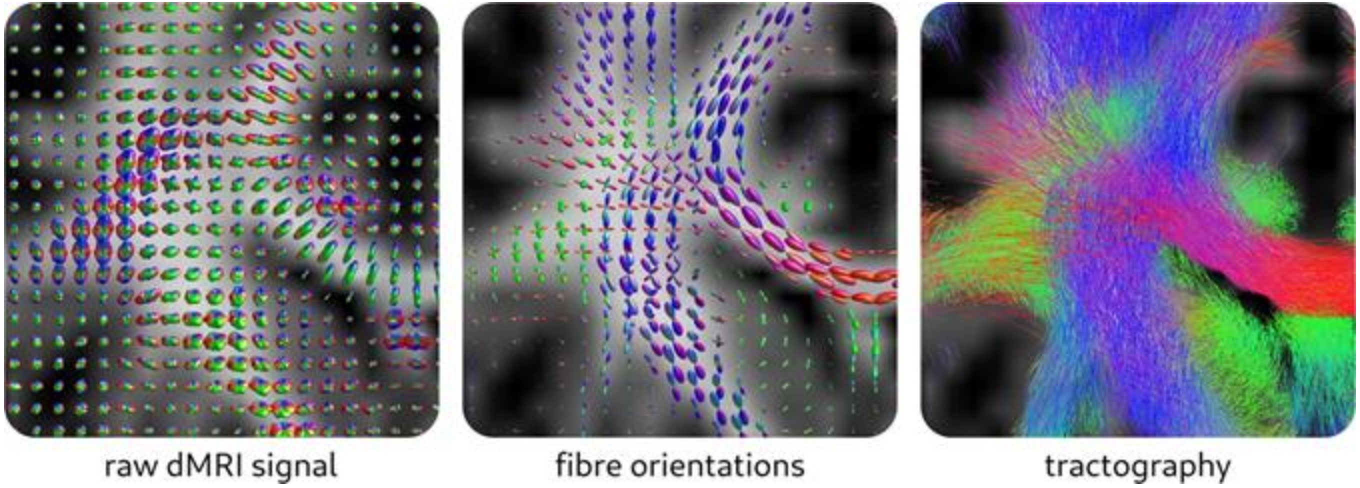
VERDICT intracellular volume fraction map

“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,

The Diffusion Tensor

The Diffusion Tensor

- The diffusion tensor characterises Gaussian diffusion in 3D in each voxel

Stejskal-Tanner equation:

B-value for gradient k (describing pulse sequence)

Unit vector of the direction of gradient k

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

Measured
Imaging parameters
To be estimated

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

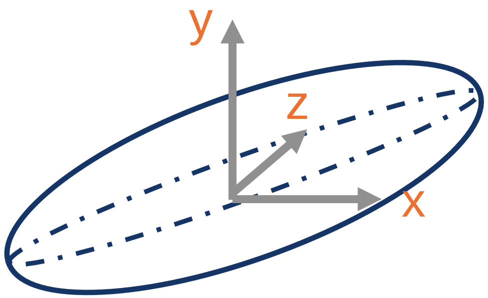
Signal with no diffusion-weighted gradient applied

The diffusion tensor

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 axes (always positive)
- D_{xy}, D_{xz}, D_{yz}: correlation between displacements along these orthogonal axes (positive or negative)

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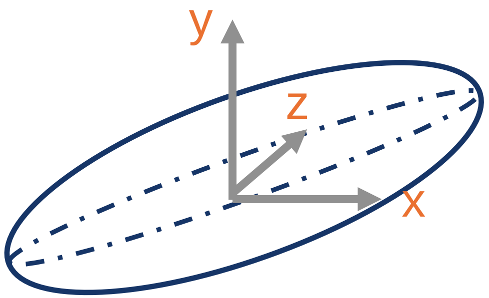

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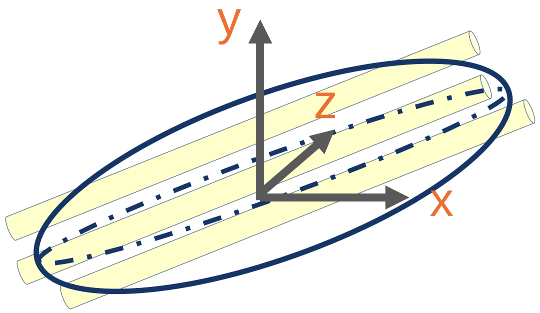
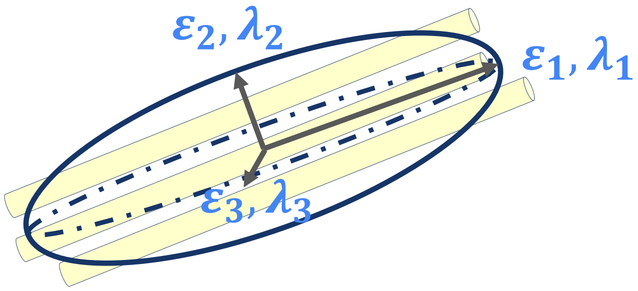
Ellipsoid from DT

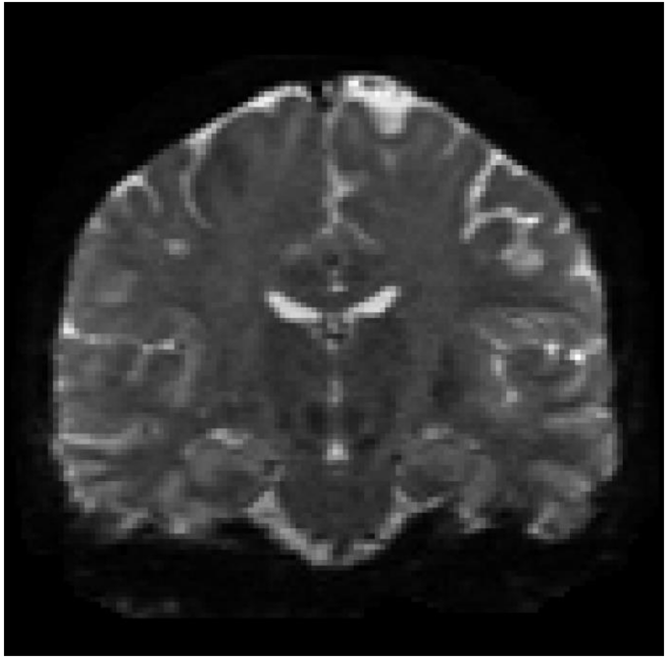
- We can decompose the Diffusion tensor into eigen-values and eigen-vectors

$$\boldsymbol{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix} = [\varepsilon_1 \quad \varepsilon_2 \quad \varepsilon_3] \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{bmatrix}$$

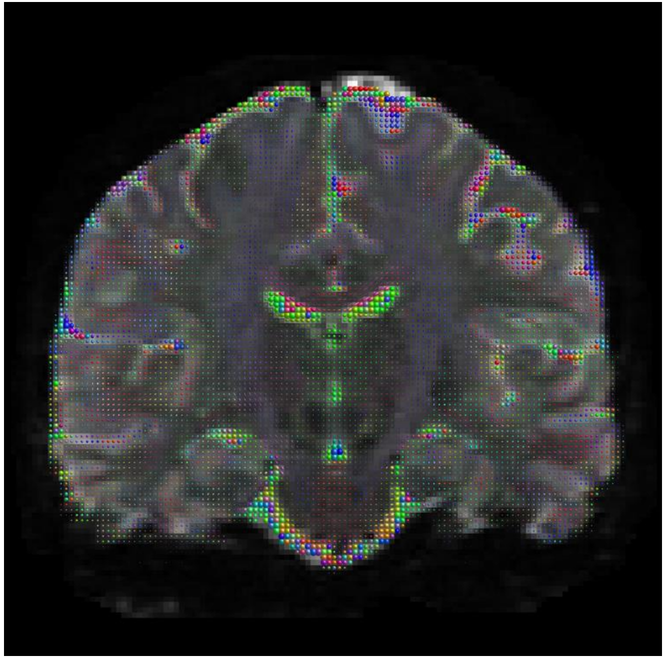




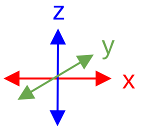
Diffusion Tensor in real data



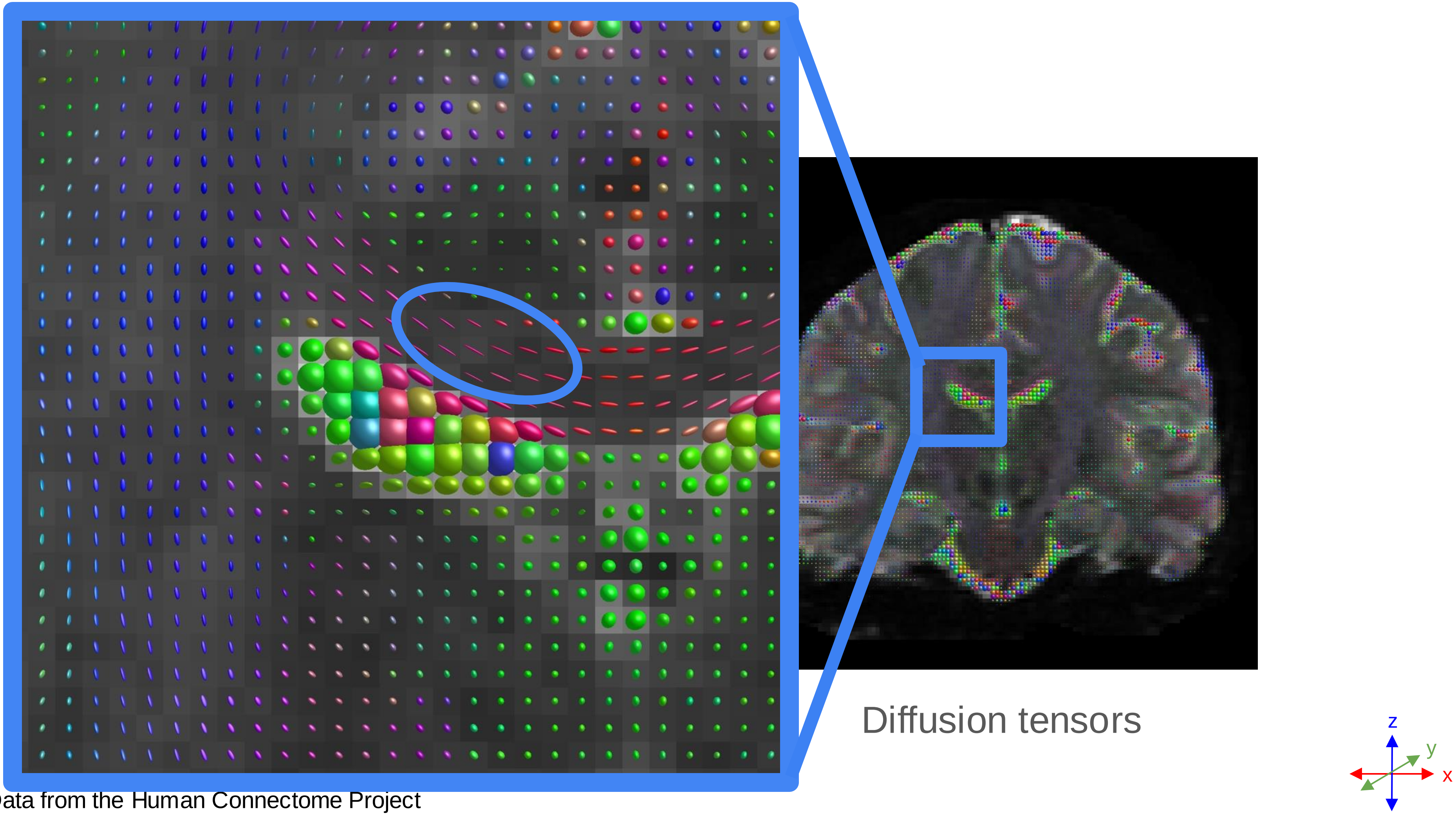
B0 diffusion signal



Diffusion tensors



Data from the Human Connectome Project



Diffusion tensors

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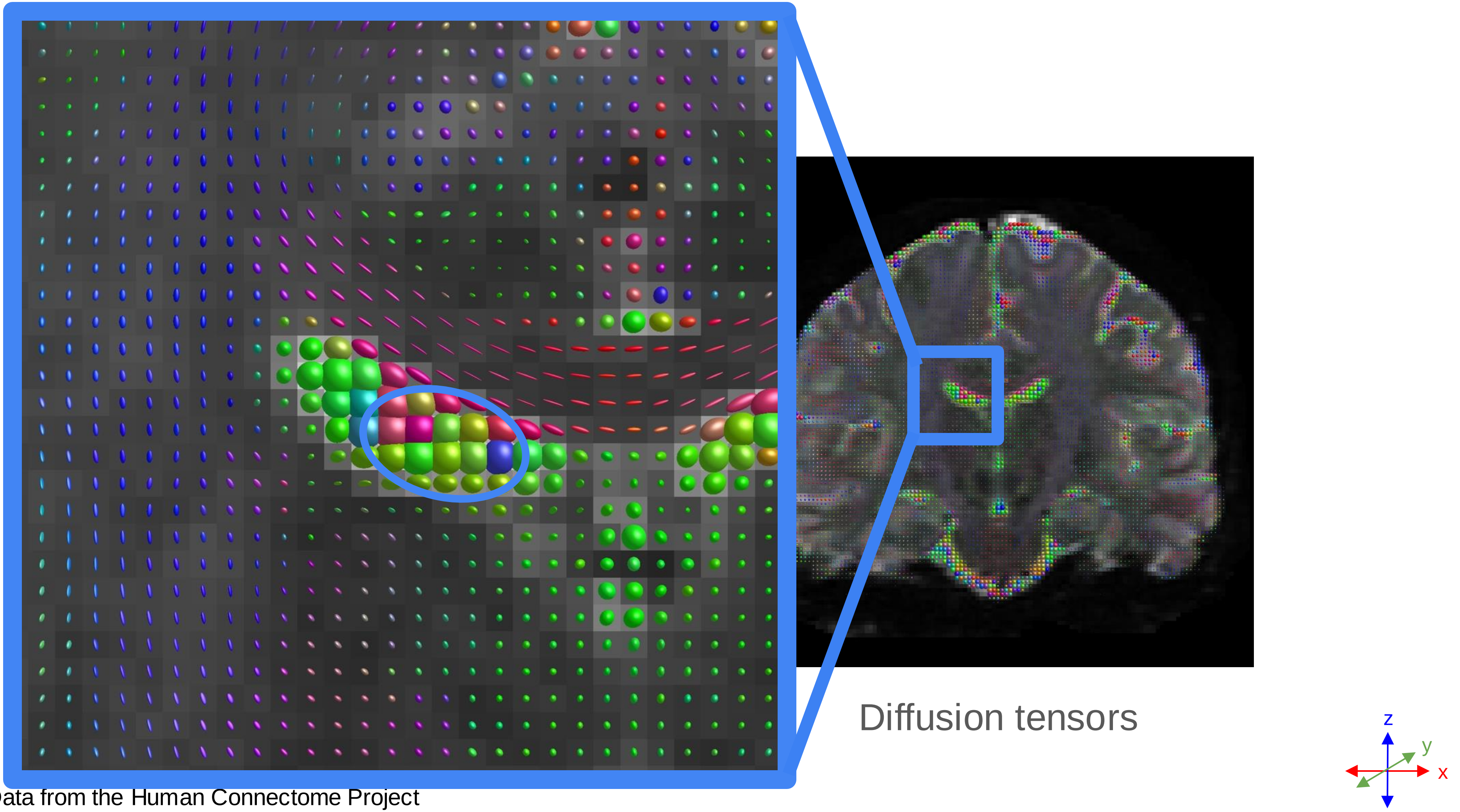

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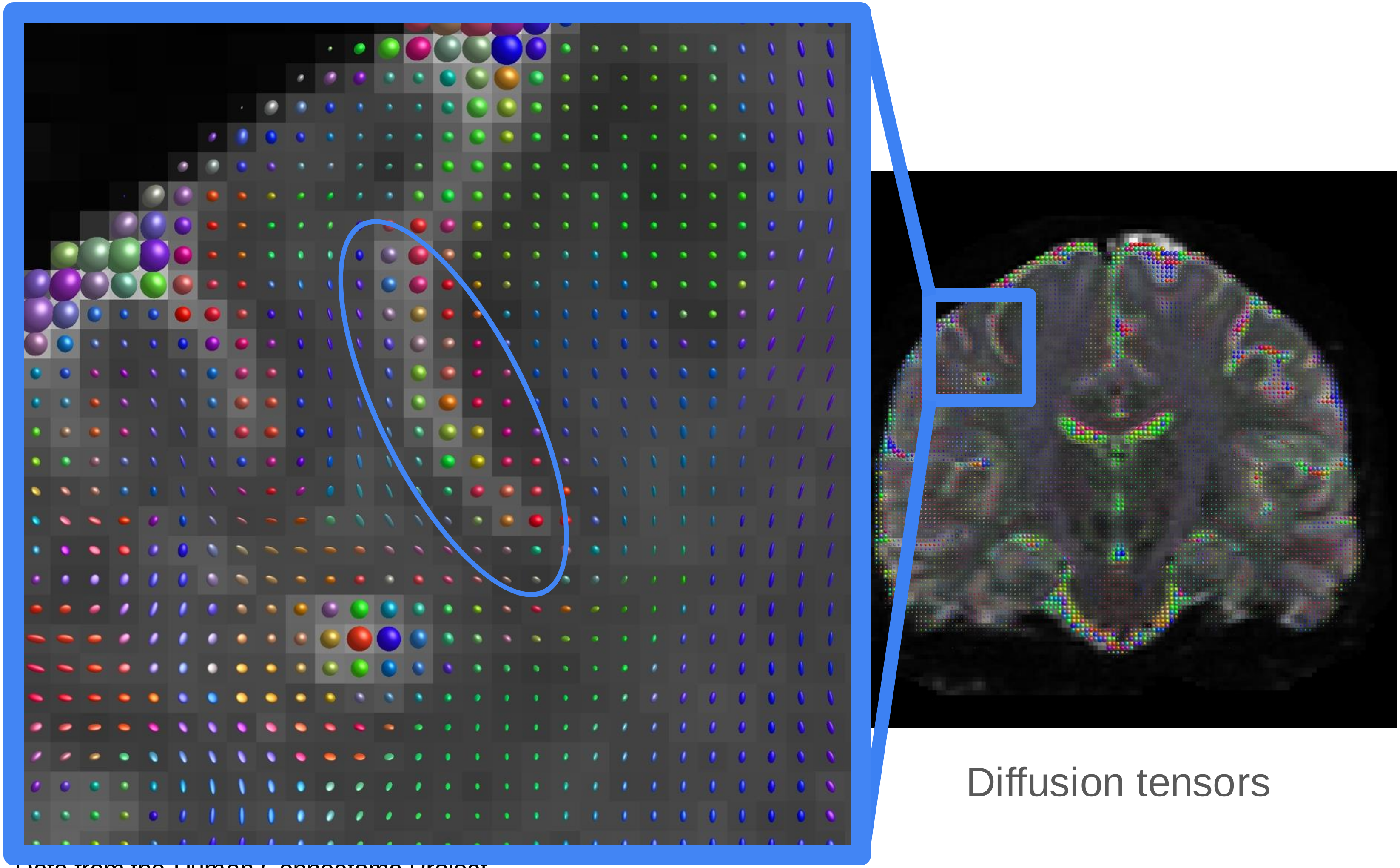

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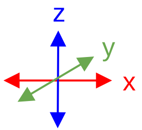

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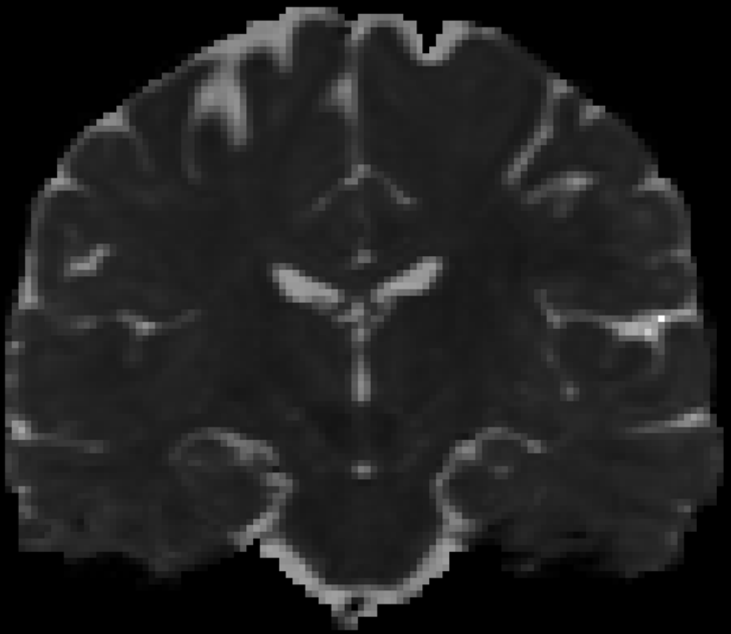
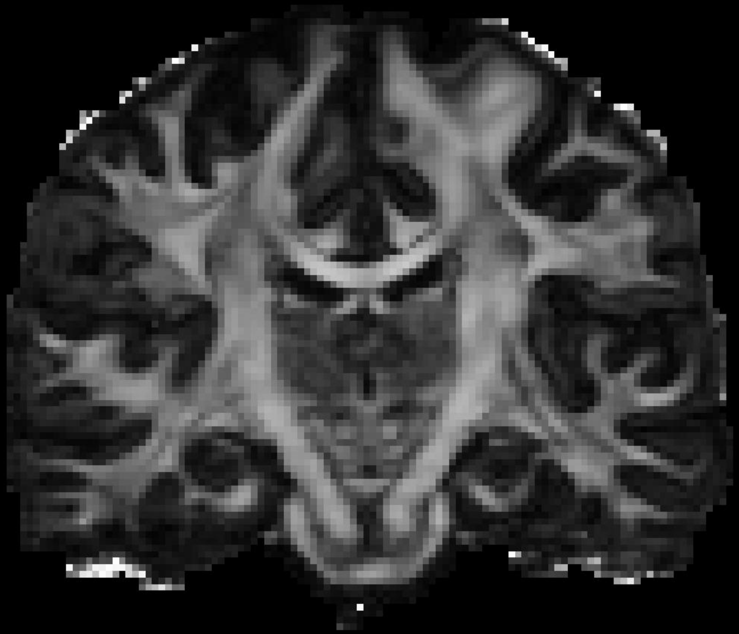
Scalar measures derived from the diffusion tensor



Mean Diffusivity (MD) = mean of the tensor eigenvalues



Fractional Anisotropy (FA) = normalised variance of tensor eigenvalues

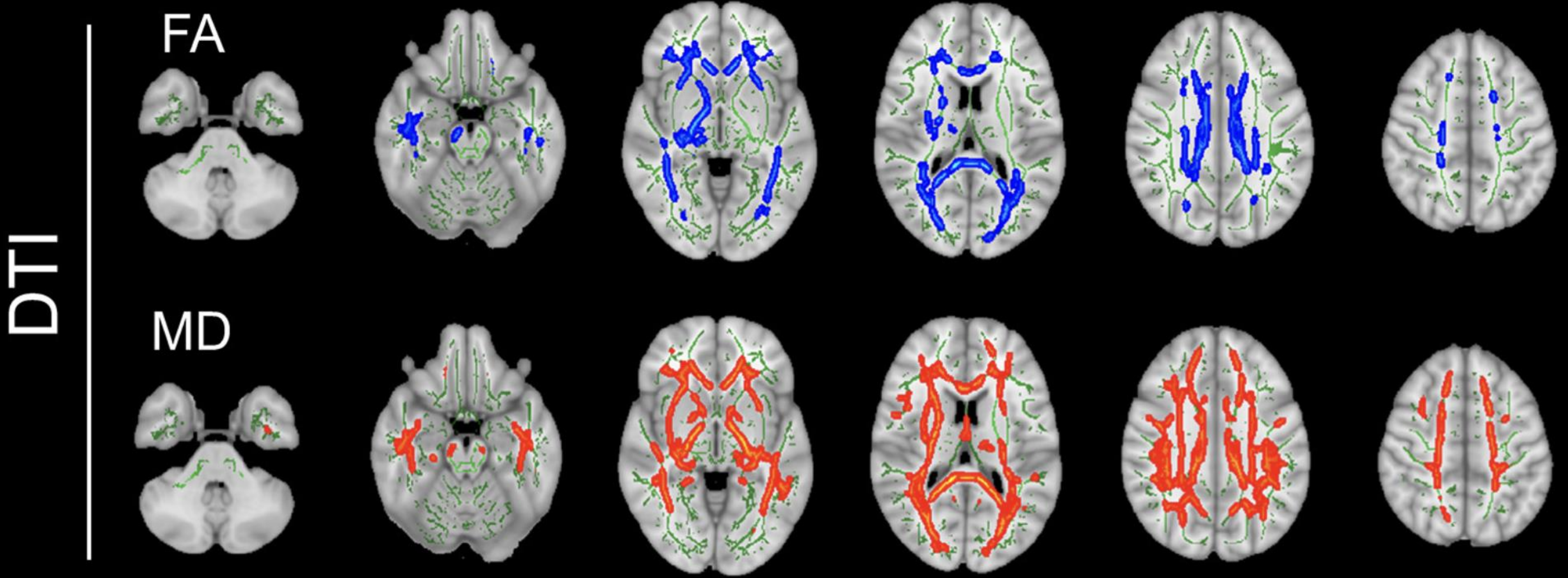
Axial Diffusivity,

Radial Diffusivity

…

Measures derived from the diffusion tensor

Significantly lower in MS
Significantly higher in MS



S. Kato, et al. *Journal of the Neurological Sciences* 436 (2022)

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:
  - least squared (linear, weighted, non-linear)
  - Bayesian MCMC

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- Methods:
    - least squared (linear, weighted, non-linear)
    - Bayesian MCMC

- Minimise the following function:

$$f = \sum_k \left\| S_k - S_0 \exp(-b_k \hat{\boldsymbol{g}}_k^T \boldsymbol{D} \hat{\boldsymbol{g}}_k) \right\|$$

Compartment Models

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

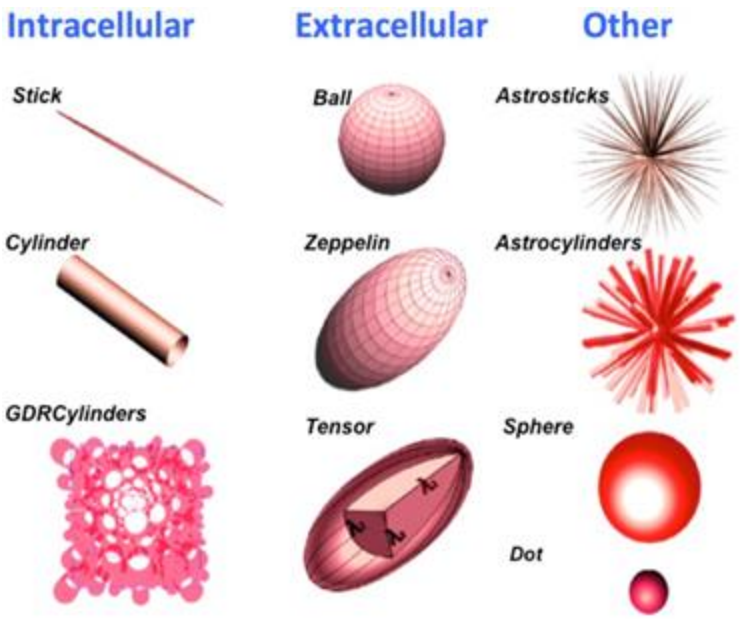
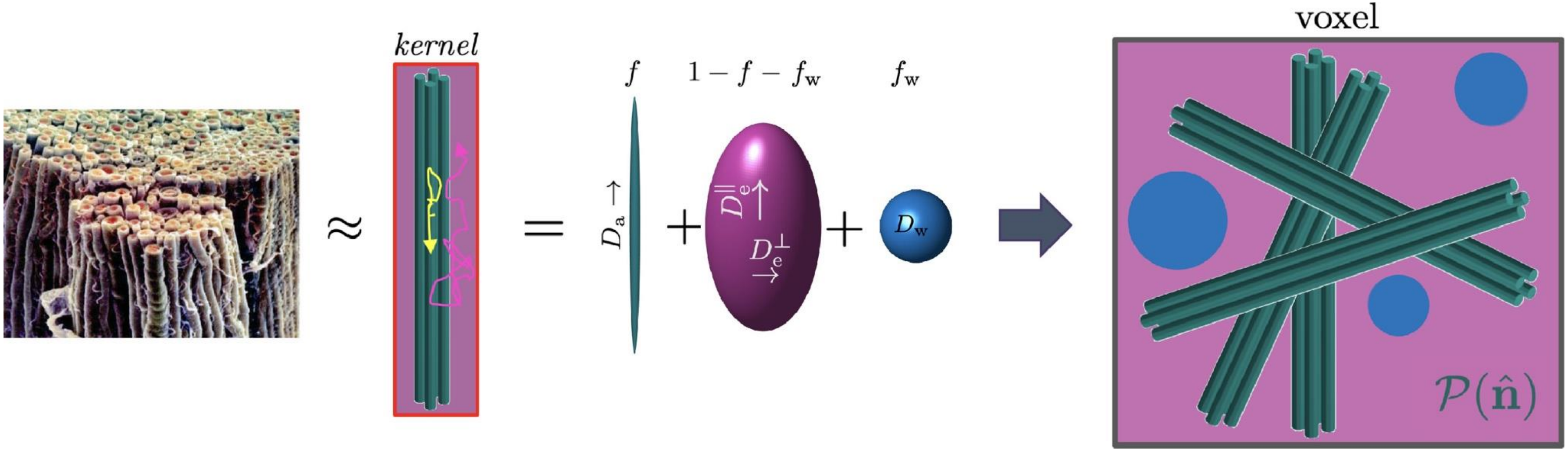


Figure from: Ferizi, U., Schneider, T., Panagiotaki, E., Nedjati-Gilani, G., Zhang, H., Wheeler-Kingshott, C.A.M. and Alexander, D.C. (2014), A ranking of diffusion MRI compartment models with in vivo human brain data. Magn. Reson. Med., 72: 1785-1792. https://doi.org/10.1002/mrm.25080

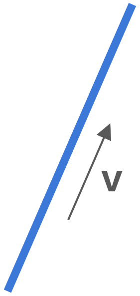
The standard model for dMRI



- Stick compartment: axons
- Zeppelin compartment: hindered diffusion in the extra-axonal space
- Free water compartment: partial volume contributions from the CSF

Novikov DS, Fieremans E, Jespersen SN, Kiselev VG. Quantifying brain microstructure with diffusion MRI: Theory and parameter estimation. NMR Biomed. 2019 Apr;32(4):e3998. doi: 10.1002/nbm.3998. Epub 2018 Oct 15.
Coelho S, Baete SH, Lemberskiy G, Ades-Aron B, Barrol G, Veraart J, Novikov DS, Fieremans E. Reproducibility of the Standard Model of diffusion in white matter on clinical MRI systems. Neuroimage. 2022 Aug 15;257:119290. doi: 10.1016/j.neuroimage.2022.119290. Epub 2022 May 8.

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

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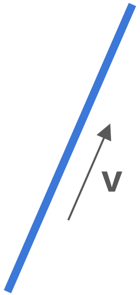

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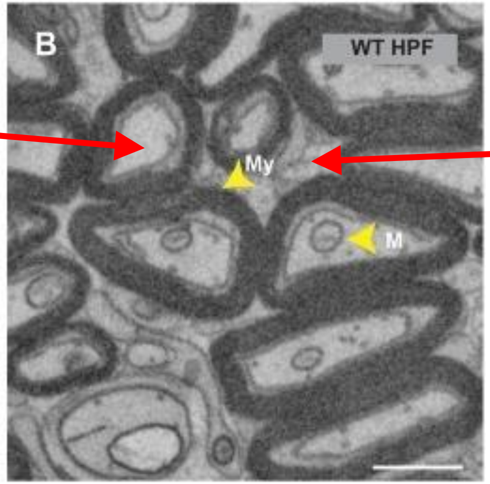

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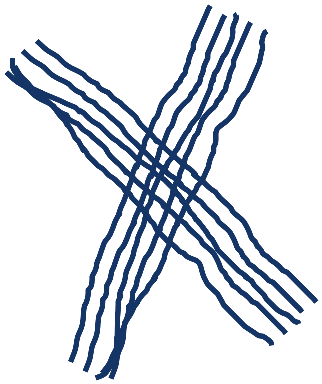
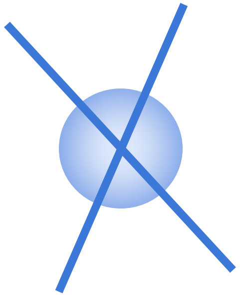
Ball and Stick Model

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



Intersecting fibre populations



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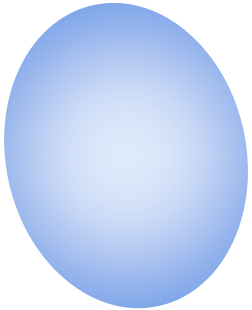
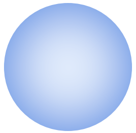


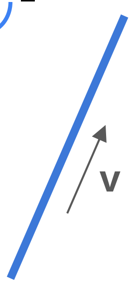
Tensor

Ball and Stick Model

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

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





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

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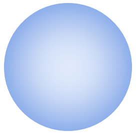
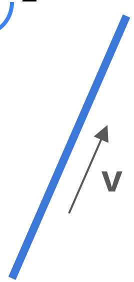
signal when b = 0





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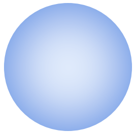
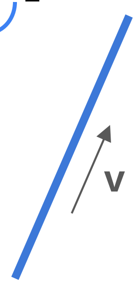


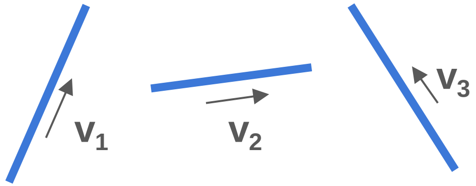


Measured
Imaging parameters
To be estimated

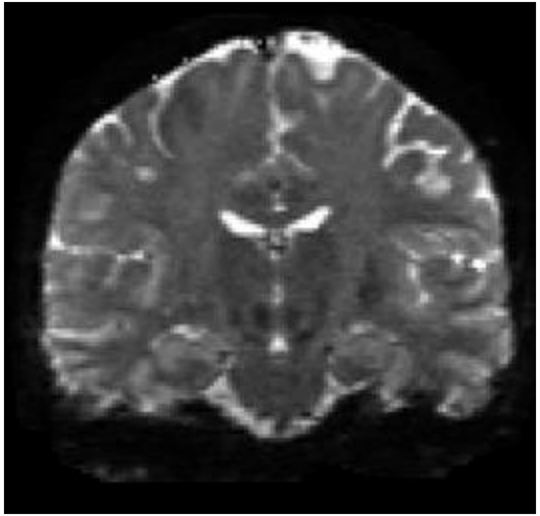
Ball and Stick Model – extending to multiple fibre populations

volume fraction of anisotropic compartment i

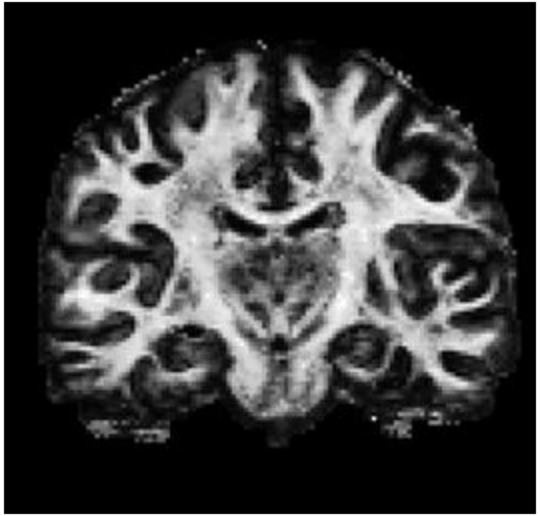
$$S_k = S_0\left[\left(1-\sum_{i=1}^{N} f_i\right)\underbrace{\exp(-b_k d)}_{\text{signal from “ball”}} + \sum_{i=1}^{N} f_i \underbrace{\exp\left(-b_k d(\mathbf{g}_k\cdot\mathbf{v}_i)^2\right)}_{\text{signal from “stick” compartment: fibre population with direction } \mathbf{v}_i}\right]$$



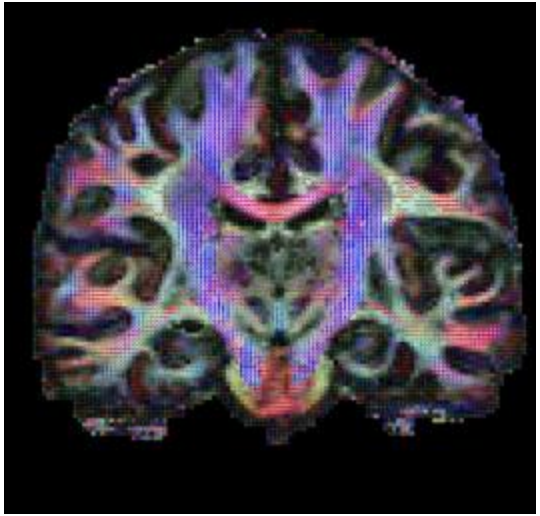
Ball and Stick Model in real data



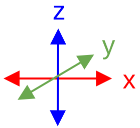
B0 diffusion signal



Fibre volume fraction

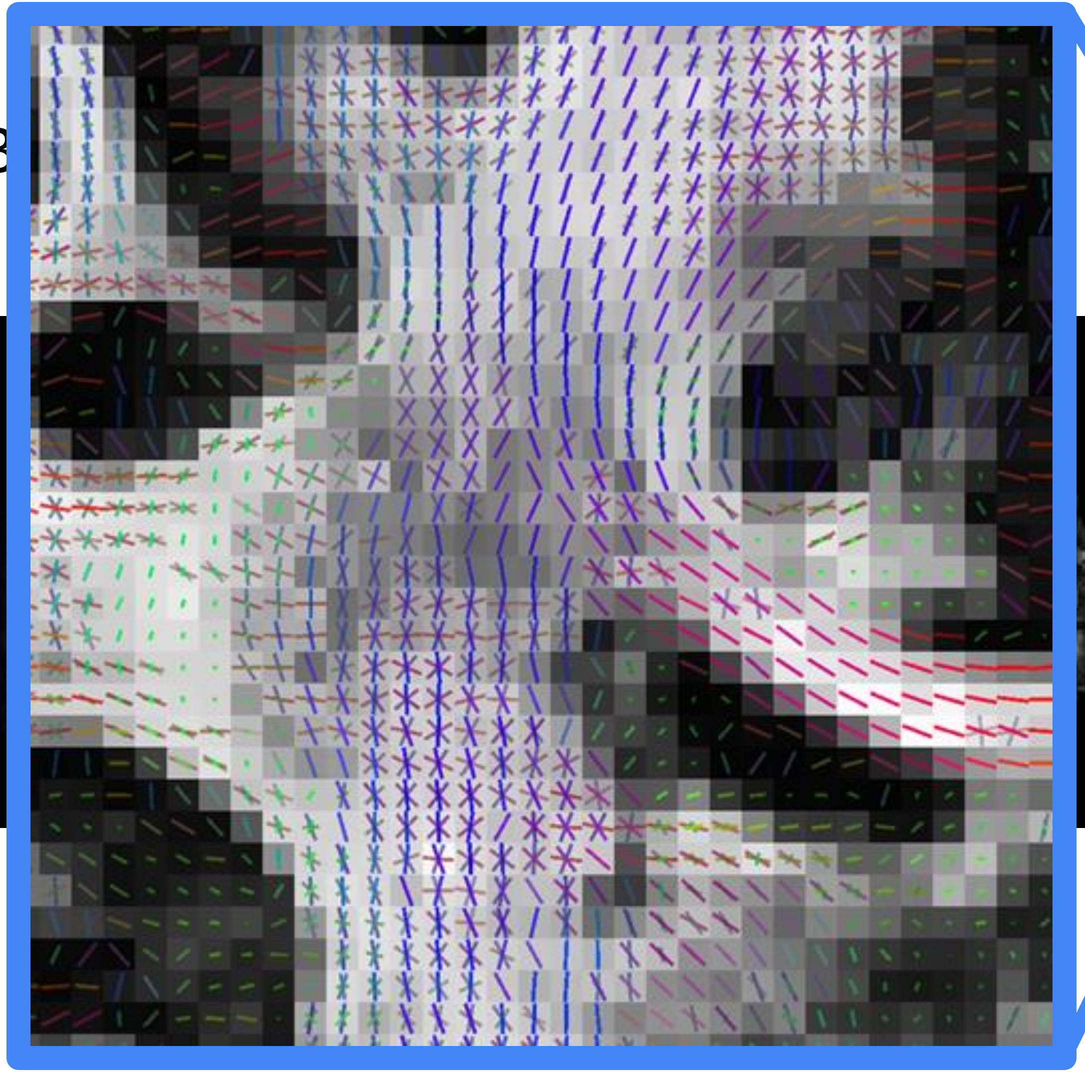


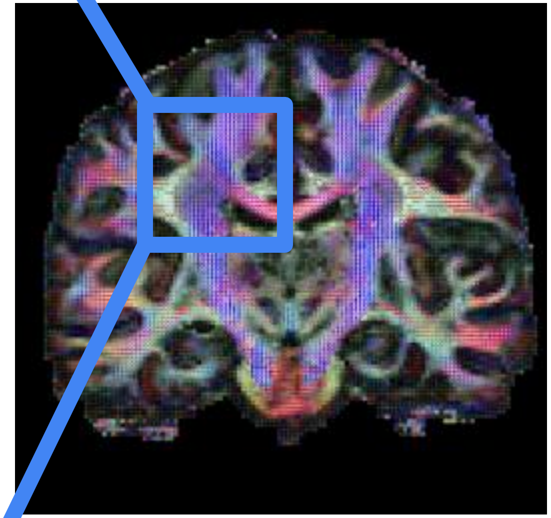
Sticks visualised as vectors



Data from the Human Connectome Project

B





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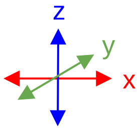
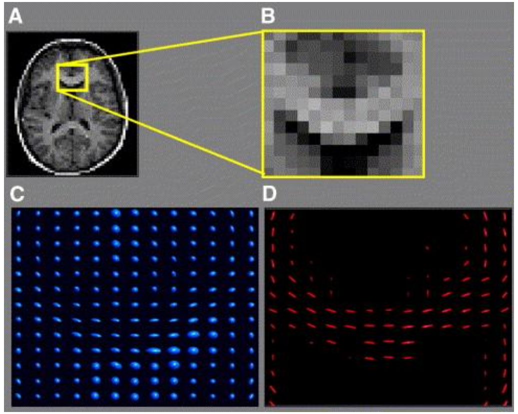


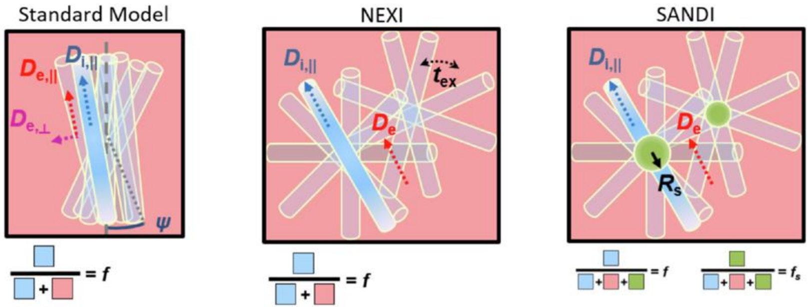
More advanced compartment models

- 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



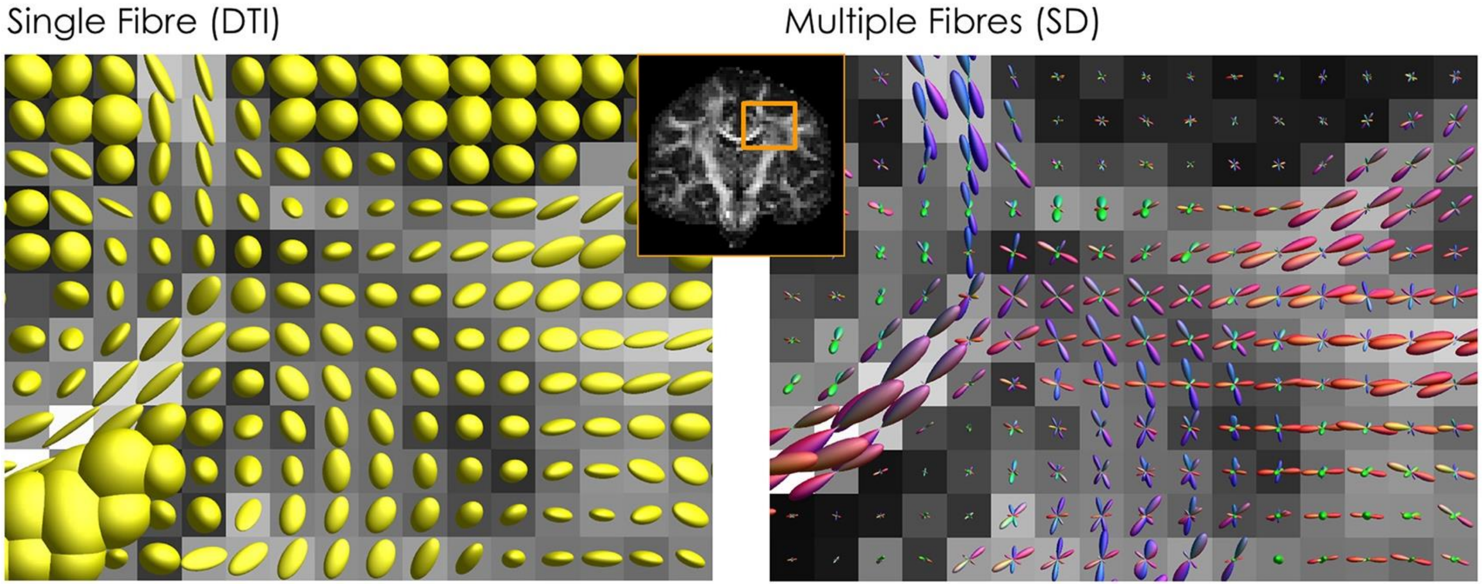
hindered restricted



Generating fibre orientation distribution functions (fODFs) with constrained spherical deconvolution

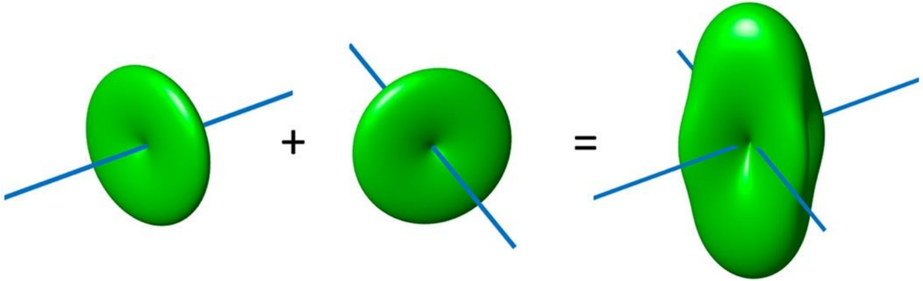
Spherical Deconvolution

- 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

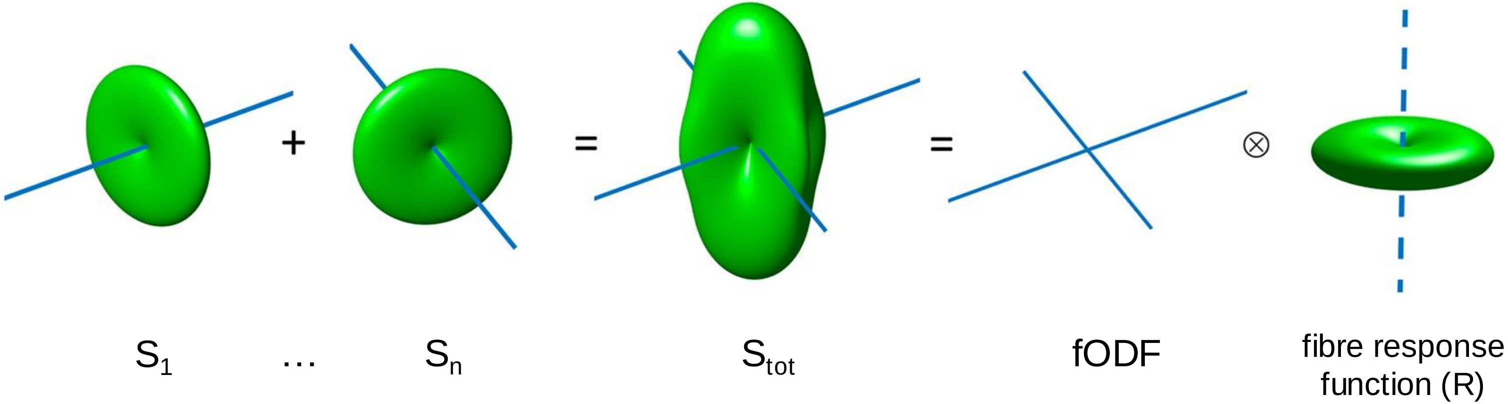


S_1 … S_n S_{tot}

- The diffusion-weighted signal is a linear combination of signals from the different fibre populations in 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



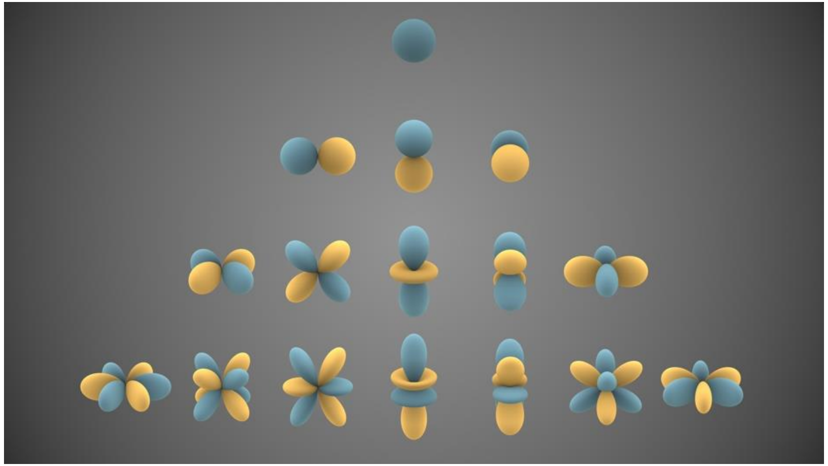
- The diffusion-weighted signal is a linear combination of signals from the different fibre populations in a voxel
- The measured signal is the convolution of the *fibre response function* (signal from a single, coherently-oriented fibre bundle) with the fODF
- The fODF is obtained by deconvolving the 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

- The fODF is typically expressed as a weighted sum of spherical harmonics up to degree l_{max}:

$$f(\theta,\phi) = \sum_{l}^{l_{\max}} \sum_{m=-l}^{l} \underbrace{c_{lm}}_{\text{coefficients to be estimated}} \underbrace{Y_{lm}}_{\text{spherical harmonics}}(\theta,\phi)$$

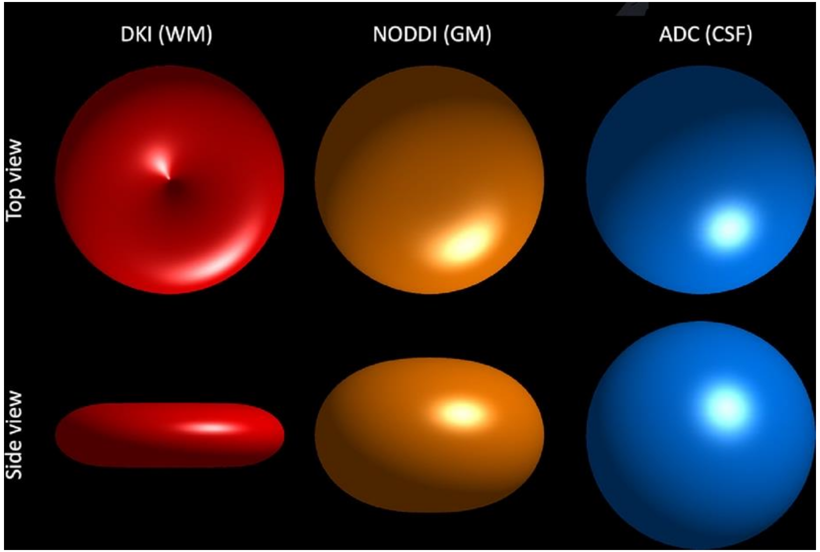


By Inigo.quilez - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=32782753

- compact representation reduces noise
- convolution is a simple product in spherical harmonic domain – computationally efficient

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)

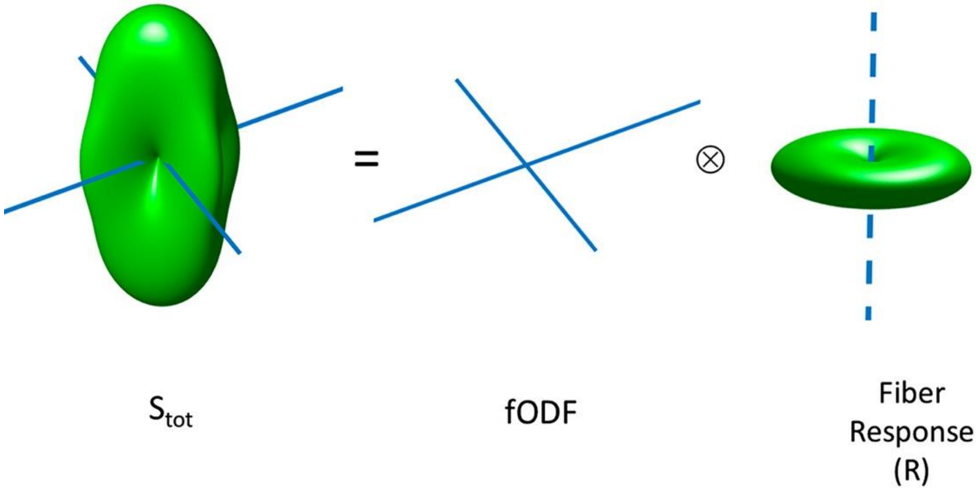


Examples of tissue-specific response functions derived from different models

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

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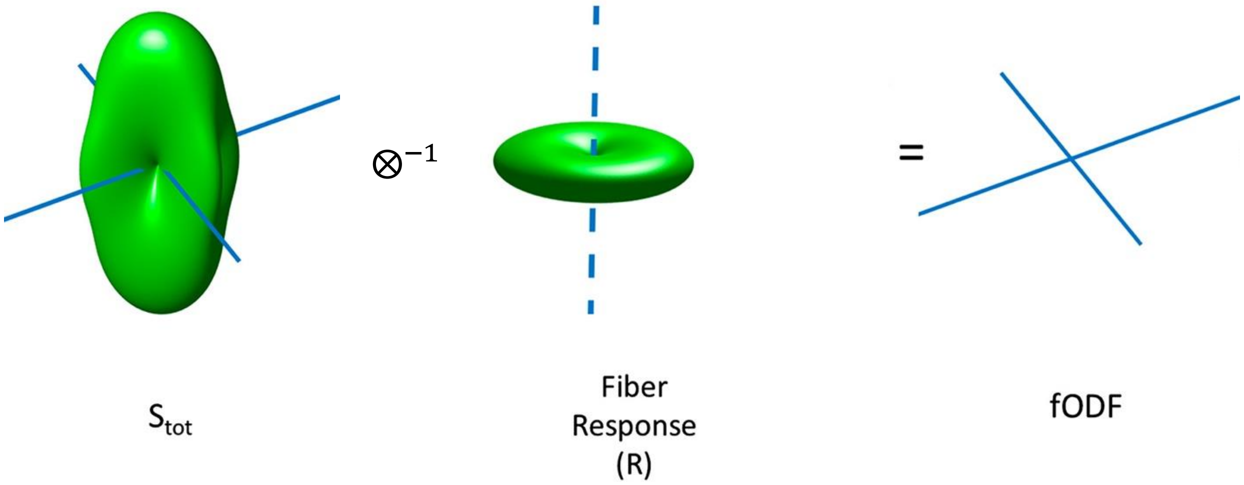
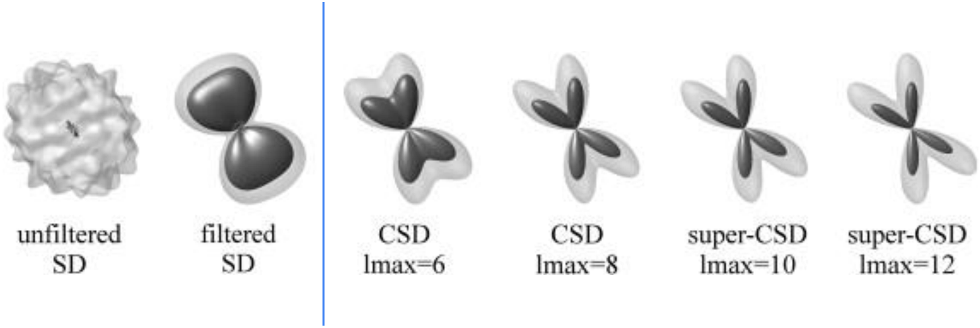


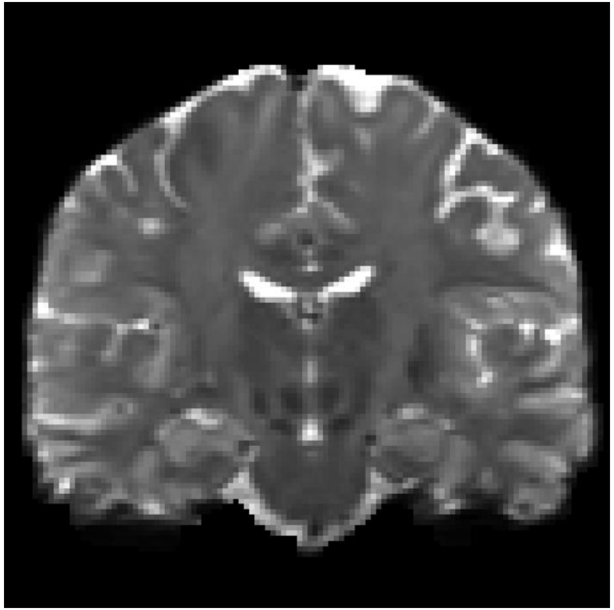
Constrained Spherical Deconvolution

- 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

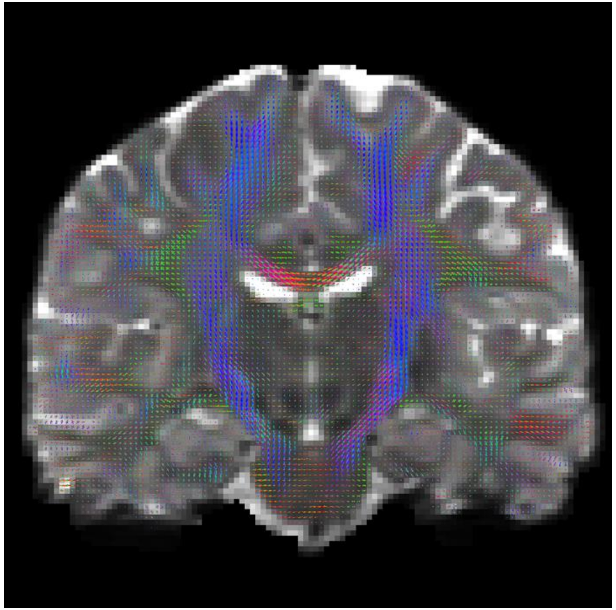


Tournier, J. D., Calamante, F., & Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. NeuroImage, 35(4), 1459–1472. https://doi.org/10.1016/j.neuroimage.2007.02.016

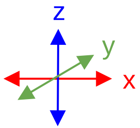
CSD in real data



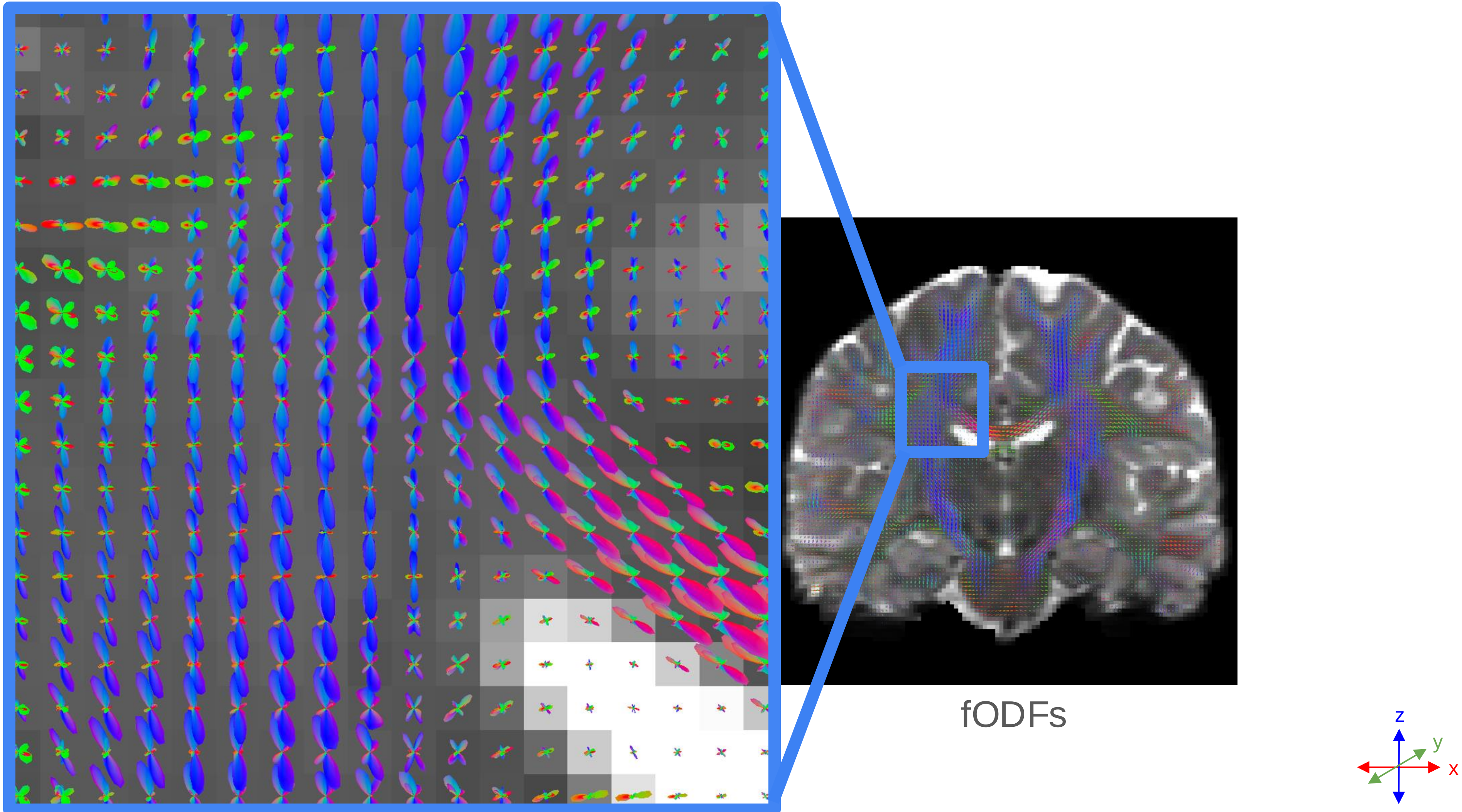
B0 diffusion signal



fODFs



Data from the Human Connectome Project


fODFs
z
y
x

Coding Practicals

Coding practicals

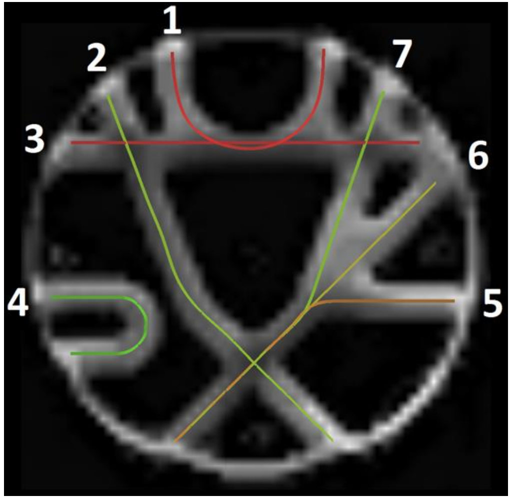
- Three coding practicals:
    - Diffusion tensor
    - Ball-and-stick model
    - Spherical deconvolution
- Estimate model parameters in each voxel of the FiberCup dataset[1]

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 a coronal section (3 slices) of the brain
- Diffusion MRI simulated from known ground truth fibre bundles



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.

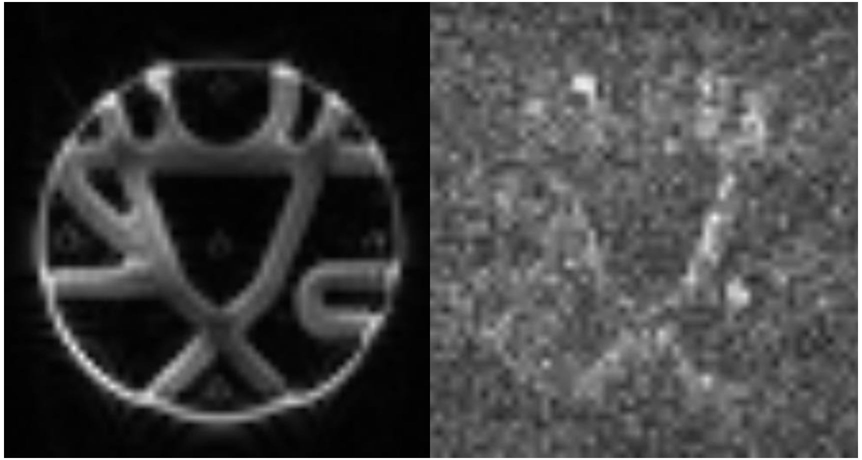
FiberCup Data

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

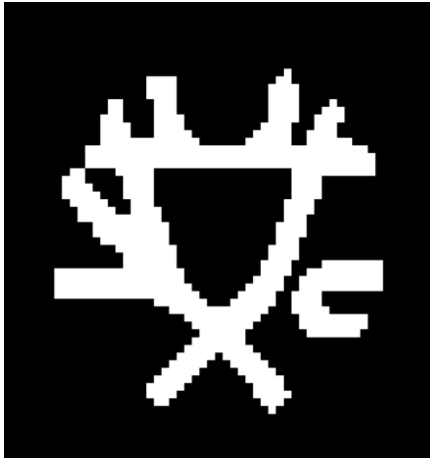
Files:

- Diffusion weighted images "fibrecup.nii.gz"
- White matter mask "wm_mask.nii.gz"
- B-values and b-vectors in the 'grad.txt' file

fibrecup.nii.gz



wm_mask.nii.gz



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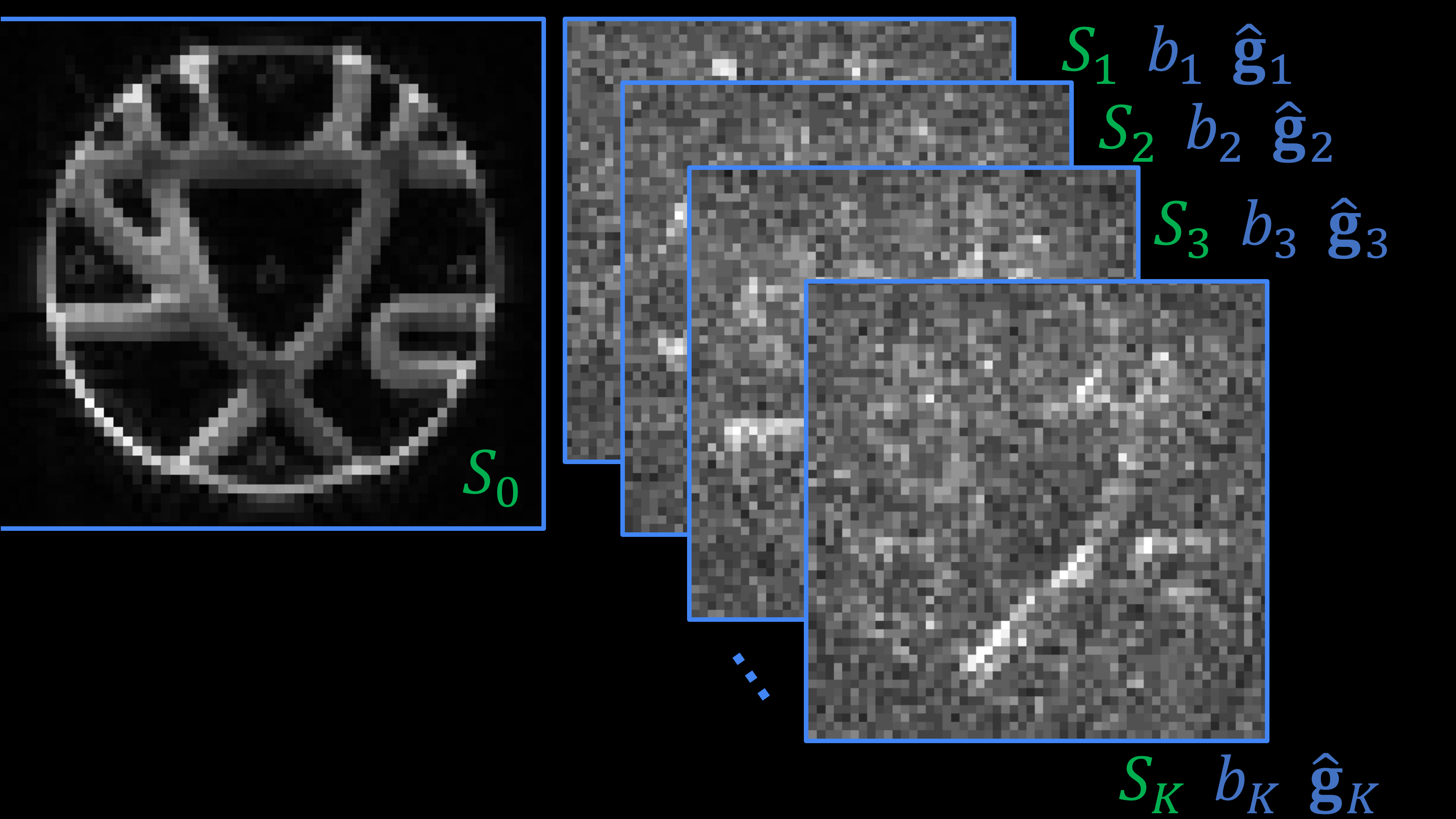
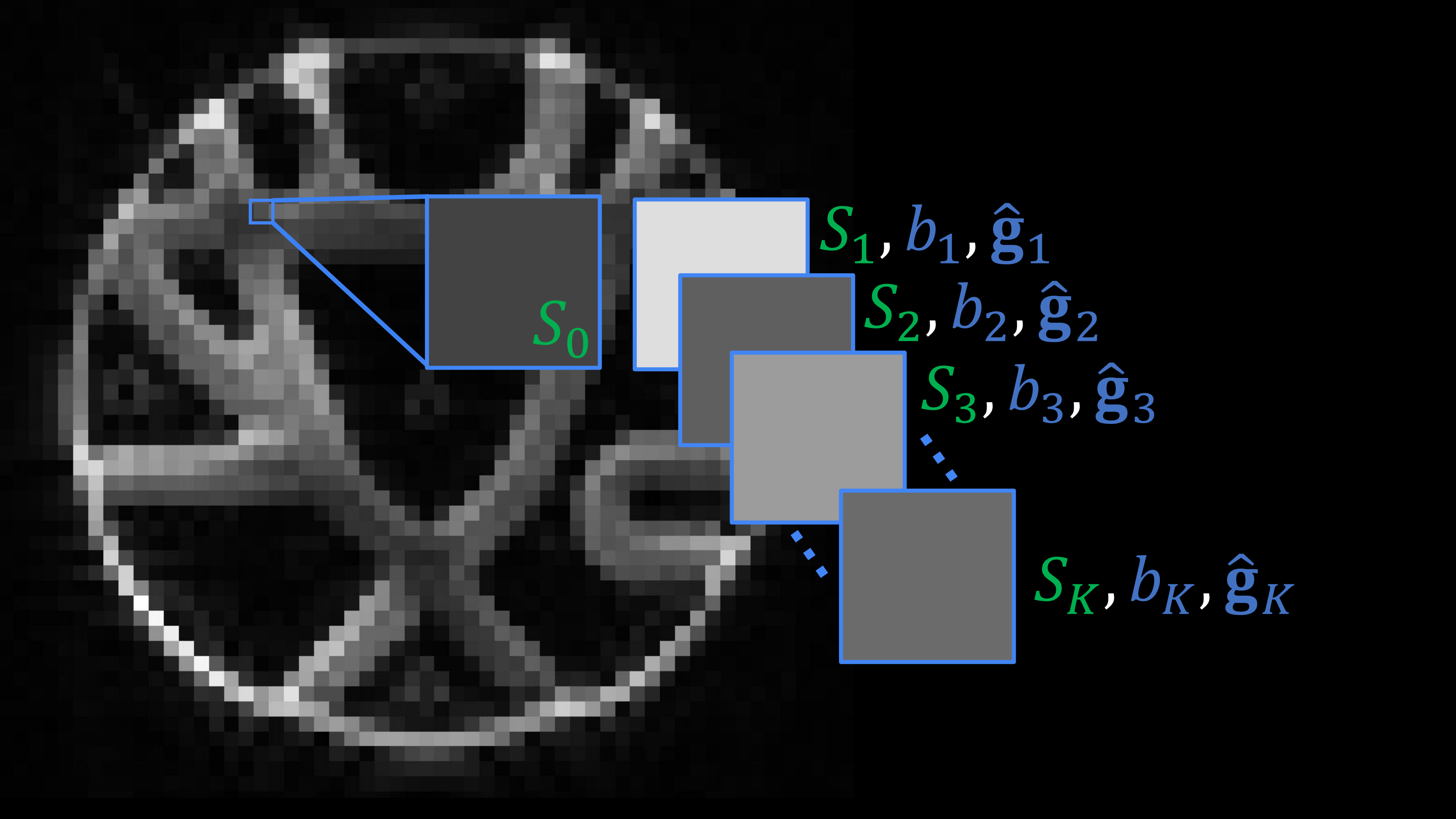
Summary of the practical – overall picture + specific aims of the tasks

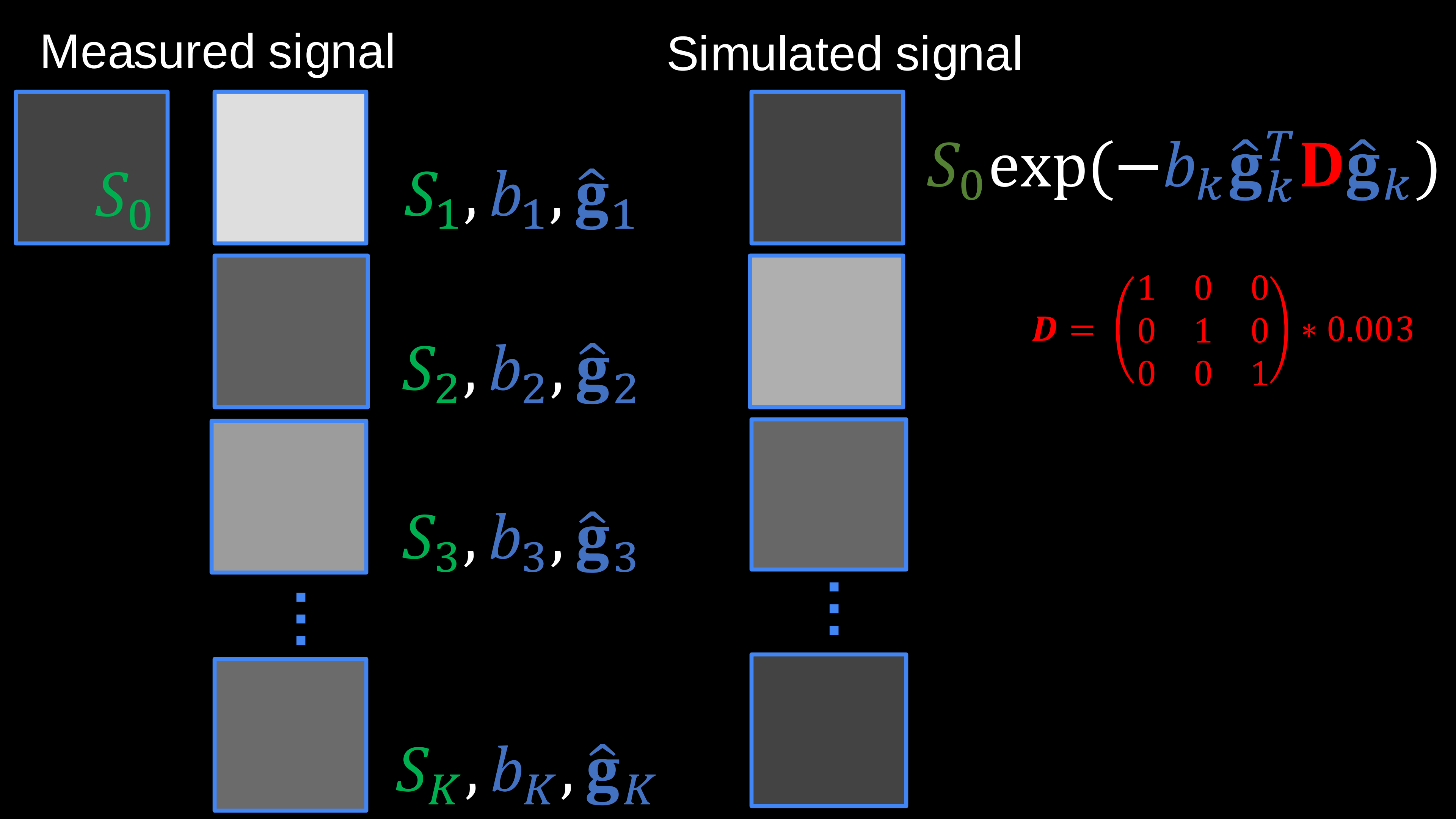
- **Aim:** fit parameters of interest
  - Diffusion tensor: D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}
  - Ball and stick: stick volume fraction f, and direction in terms of θ, ϕ

- **How?** Find parameter values **for each voxel** that minimise error between model and measurements
- We'll use non-linear least squares – scipy optimise least-squares
- In each voxel we use measurements from all gradient directions to fit the model


S_0
S_1 b_1 $\hat{\mathbf{g}}_1$
S_2 b_2 $\hat{\mathbf{g}}_2$
S_3 b_3 $\hat{\mathbf{g}}_3$
S_K b_K $\hat{\mathbf{g}}_K$



S_0
$S_1, b_1, \hat{\mathbf{g}}_1$
$S_2, b_2, \hat{\mathbf{g}}_2$
$S_3, b_3, \hat{\mathbf{g}}_3$
$S_K, b_K, \hat{\mathbf{g}}_K$


Measured signal
Simulated signal
S_0
$S_1, b_1, \hat{\mathbf{g}}_1$
$S_2, b_2, \hat{\mathbf{g}}_2$
$S_3, b_3, \hat{\mathbf{g}}_3$
$S_K, b_K, \hat{\mathbf{g}}_K$
$S_0 \exp(-b_k \hat{\mathbf{g}}_k^T \mathbf{D} \hat{\mathbf{g}}_k)$
$\boldsymbol{D} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} * 0.003$

Measured signal

Simulated signal

$$SSE\left(\; S_1, b_1, \hat{\mathbf{g}}_1 \;,\; S_2, b_2, \hat{\mathbf{g}}_2 \;,\; S_3, b_3, \hat{\mathbf{g}}_3 \;,\; \vdots \;\; S_K, b_K, \hat{\mathbf{g}}_K \;, \; \right)$$

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

$$\boldsymbol{D} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} * 0.003$$

Measured signal

Simulated signal

$$SSE\left(\square,\ S_1, b_1, \hat{\mathbf{g}}_1,\ \square;\ \square,\ S_2, b_2, \hat{\mathbf{g}}_2,\ \square;\ \square,\ S_3, b_3, \hat{\mathbf{g}}_3,\ \square;\ \vdots;\ \square,\ S_K, b_K, \hat{\mathbf{g}}_K,\ \square \right)$$

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

$$\boldsymbol{D} = \begin{pmatrix} 0.5 & 0.1 & 0 \\ 0.1 & 1 & 0.2 \\ 0 & 0.2 & 1 \end{pmatrix} * 0.003$$

SciPy

Measured signal

Simulated signal

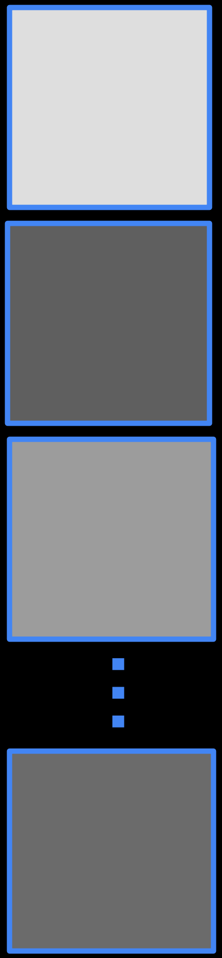
$$SSE\left(\begin{array}{ccc} \square & S_1, b_1, \hat{\mathbf{g}}_1, & \square \\ \square & S_2, b_2, \hat{\mathbf{g}}_2, & \square \\ \square & S_3, b_3, \hat{\mathbf{g}}_3, & \square \\ \vdots & & \vdots \\ \square & S_K, b_K, \hat{\mathbf{g}}_K, & \square \end{array} \right)$$

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

$$\boldsymbol{D} = \begin{pmatrix} 0.8 & 0.1 & 0.3 \\ 0.1 & 0.5 & 0.1 \\ 0.3 & 0.1 & 0.6 \end{pmatrix} * 0.003$$

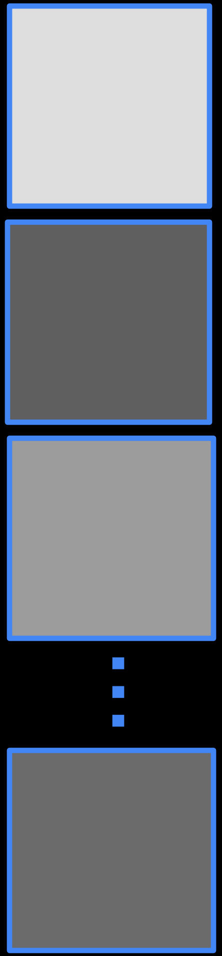
SciPy

Simulated signal



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

Simulated signal



$$S_0 \exp(-b_1 \hat{\mathbf{g}}_1^T \mathbf{D} \hat{\mathbf{g}}_1)$$

$$S_0 \exp(-b_2 \hat{\mathbf{g}}_2^T \mathbf{D} \hat{\mathbf{g}}_2)$$

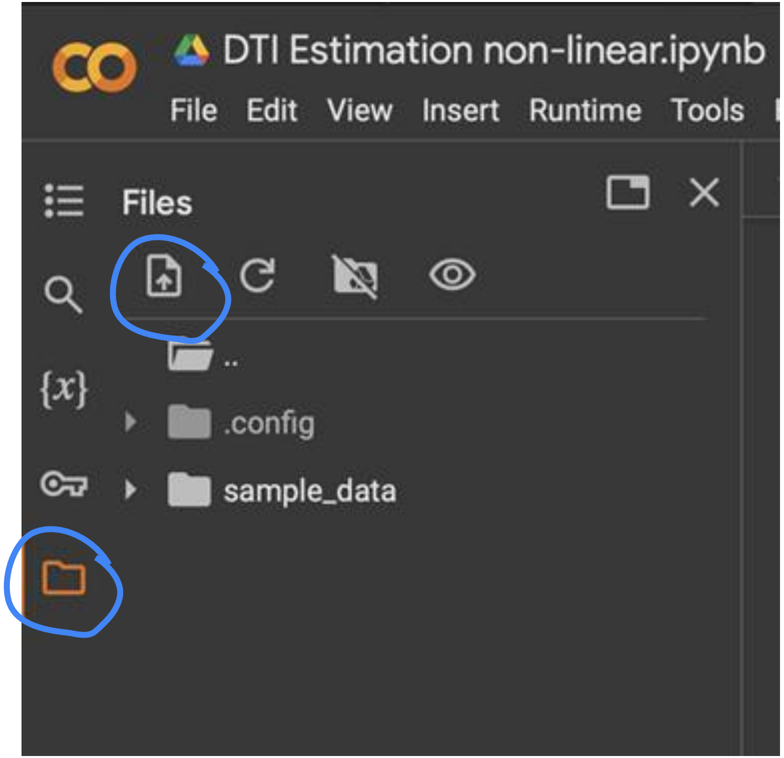
$$S_0 \exp(-b_3 \hat{\mathbf{g}}_3^T \mathbf{D} \hat{\mathbf{g}}_3)$$

$$S_0 \exp(-b_K \hat{\mathbf{g}}_K^T \mathbf{D} \hat{\mathbf{g}}_K)$$

Get into groups! (2 or 3 people)

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

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

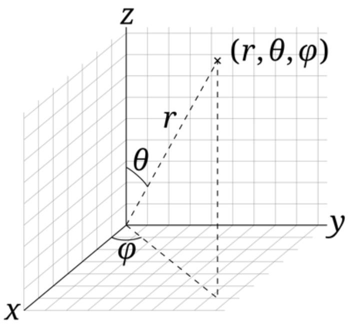
https://github.com/ethompson93/dmri_analysis_techniques

Ball and Stick Model: Coding Exercise

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

- We want to estimate f and $\mathbf{v}$ in each voxel
- We express $\mathbf{v}$ in spherical coordinates (θ,ϕ) for efficiency
- Need to convert to Cartesian coordinates for dot product with $\mathbf{g}$:

$$x = \sin\theta\cos\varphi$$
$$y = \sin\theta\sin\varphi$$
$$z = \cos\theta$$



CSD coding exercise

- We will use DIPY, an open-source python library, to 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

Different Software for dMRI analysis

Not an exhaustive list!

DIPY

Slicer dMRI

MRtrix3

FSL

dmipy Public

DSI Studio

Conclusions

- Analysis techniques unlock biological insight from dMRI
    - e.g. microstructural information and fibre orientations for tractography
- The diffusion tensor quantifies anisotropy in 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

wellcome

UKRI Engineering and Physical Sciences Research Council

NIHR | University College London Hospitals Biomedical Research Centre

UCL

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

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