Diffusion Imaging

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Outline

- What is diffusion and why do we care ?
- How to model diffusion signal?
- What are the pitfalls of modeling ?
- Fiber Tracking using diffusion MRI
- How to pre-process diffusion data?
- How to extract biologically meaningful diffusion measures ?

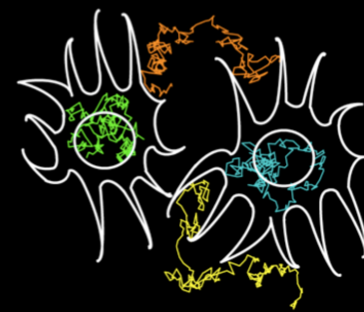
What is diffusion and why do we care ?

- "Diffusion"

Dye diffusing in a gel

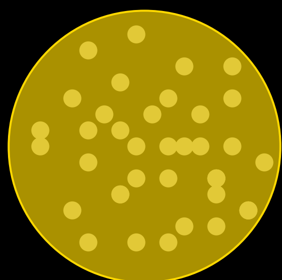
Thermal agitation

Water in biological tissues



Diffusion MRI

- In Unrestricted Medium:



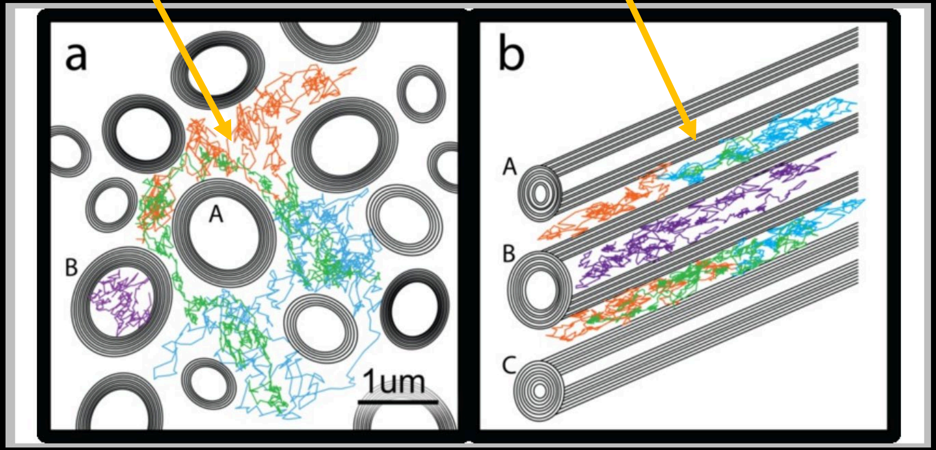
- Isotropic Diffusion

What is diffusion and why do we care ?

IOWA

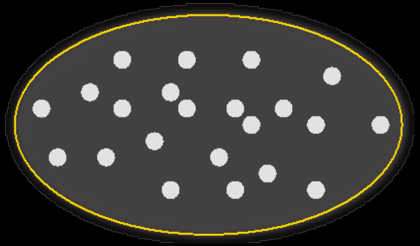
- In Biological Tissues:
  - Presence of tissue boundaries
  - Random walk get modified

Random diffusing motion between the cellular spaces



- Restricted Medium :

  Isotropic Diffusion not possible



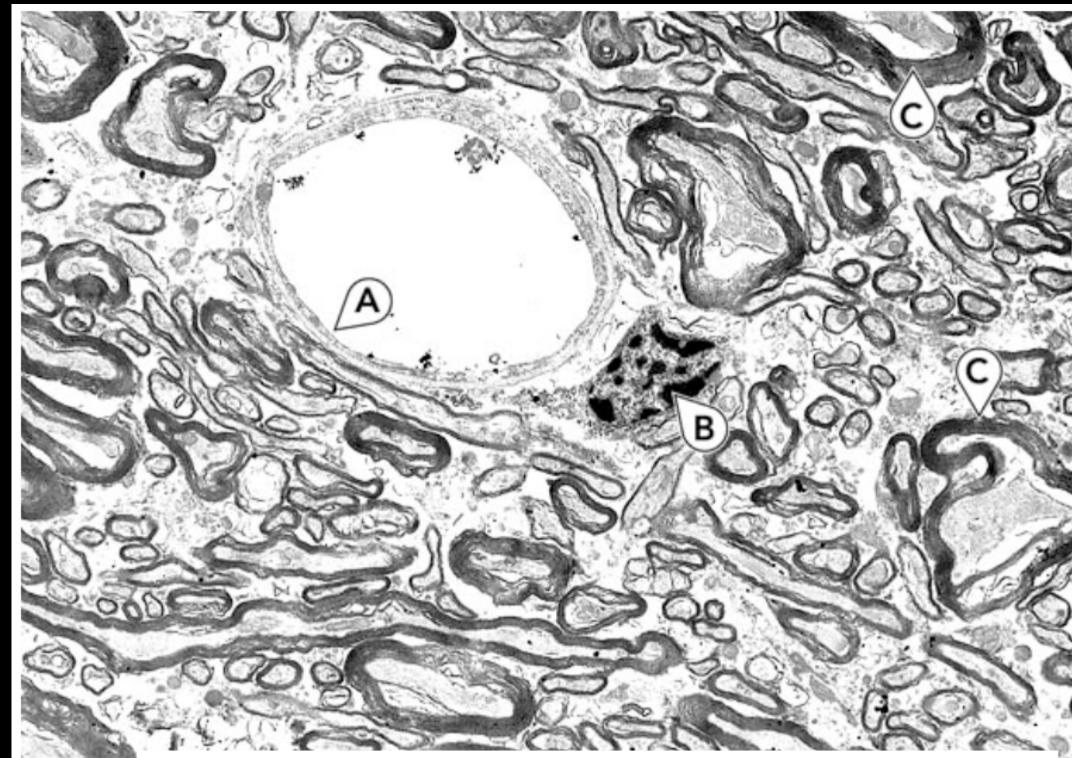
Anisotropic Diffusion

- Patterns of water diffusion in tissue reflect the microstructure of the medium

What is diffusion and why do we care ?

IOWA

- In Biological Tissues:
  - Membrane permeability
  - Macromolecules
  - Packing density
  - Compartment size



Sensitizing the MRI signal to water diffusion is a way to indirectly get information about tissue microstructure and its changes

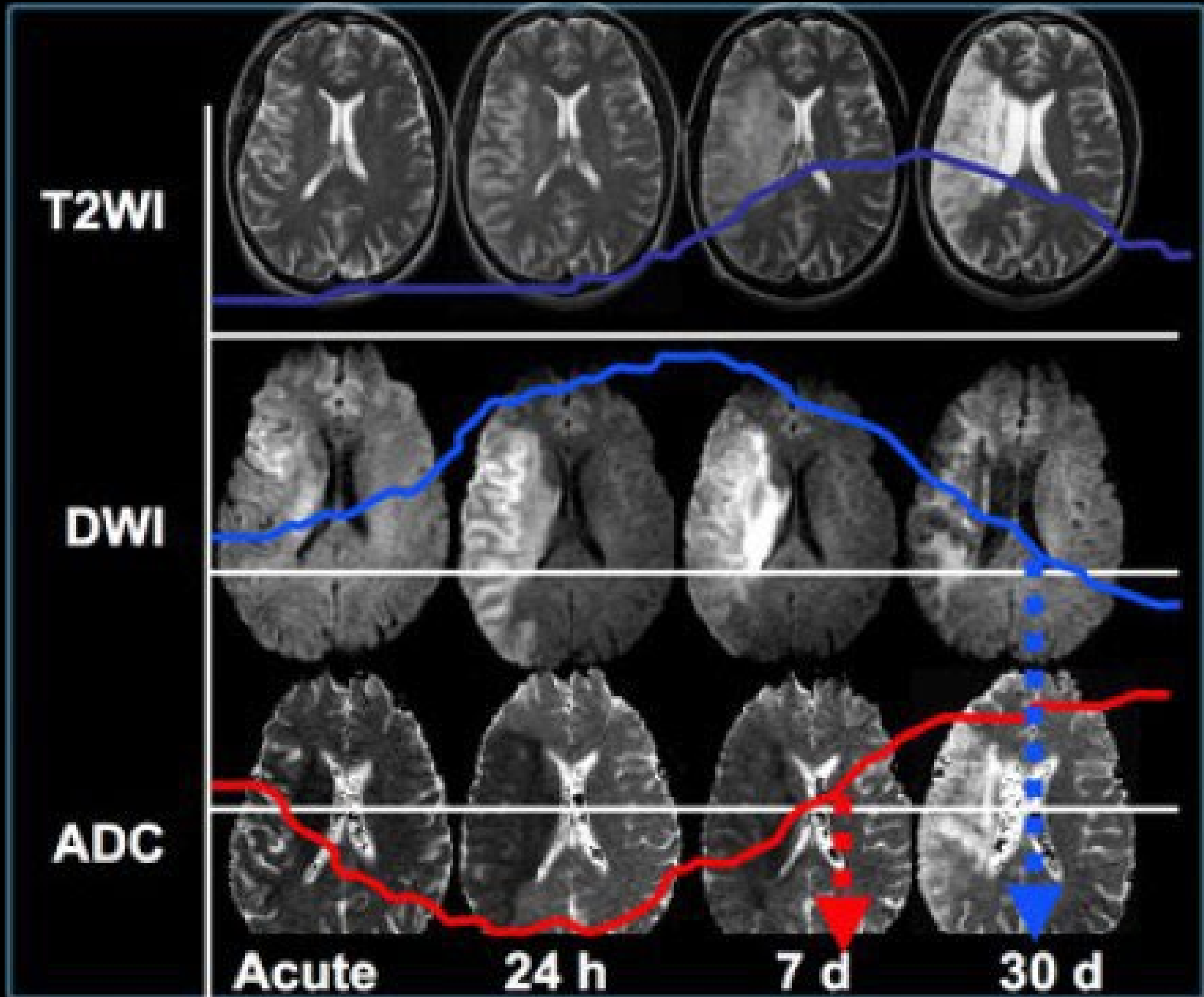
What is diffusion and why do we care ?

IOWA

- Degree of diffusion restriction affected by
  - changes in the cellular density of tissue
  - amount of intracellular versus extracellular water
- Conditions such as :
  - ischemic infarcts, tumor produce highly restricted diffusion
  - cysts and edema yield low degrees of diffusion restriction

Diagnosis of pathological and histological information

Diffusion Weighted MRI in clinic



Diffusion Weighted MRI in clinic

IOWA

- Many pathologies cause restricted extracellular water diffusion

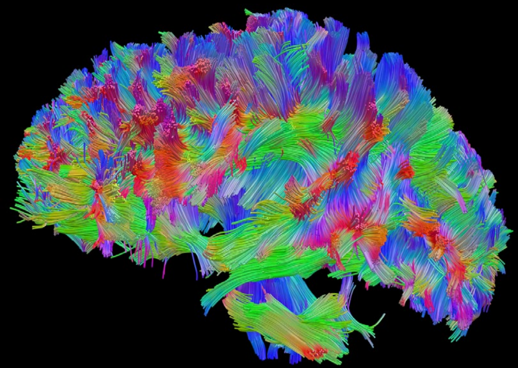
- Vascular Etiologies
  - *Ischemia-infarction*
  - *Hypoxic-ischemic Injury*
  - *Acute Hypertensive Encephalopathy*
  - *Venous Infarction*
- Infectious Etiologies
  - *Abscess*
  - *Empyema*
  - *Ventriculitis*
  - *Viral Encephalitis (Herpes, HIV, etc.)*
  - *Progressive Multifocal Leukoencephalopathy*
  - *Creutzfeldt-Jakob Disease*
  - *Toxoplasmosis*
- Neoplastic Etiologies
  - *Meningioma*
  - *Primary CNS Lymphoma*
  - *Glioblastoma*
  - Demyelinating Etiologies
  - *Tumefactive Multiple Sclerosis*
  - *Neuromyelitis Optica*
  - *Acute Disseminated Encephalomyelitis*
- Metabolic/Toxic Etiologies
  - *Osmotic Demyelination Syndrome*
  - *Hypoglycemic Encephalopathy*
  - *Wernicke Encephalopathy*
  - *Carbon Monoxide Poisoning*
  - *Ethylene Glycol and Methanol Toxicity*
- Trauma
  - *Diffuse Axonal Injury*
- Miscellaneous Etiologies
  - *Epidermoid Cyst*
  - *Choroid Plexus Cyst*
  - *Status Epilepticus*
  - *Wallerian Degeneration*

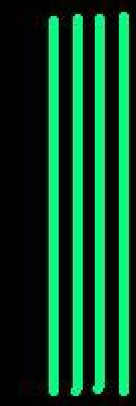
Daniel J, *J Am Osteopath Coll Radiol.* 2020;9(3):20-31.

Biological Significance

- Anisotropy of water diffusion

  Axonal pathways





- in vivo connectivity (e.g., orientation, density)

- in vivo white matter integrity

(e.g.:, maturation/myelination, neurodegeneration)

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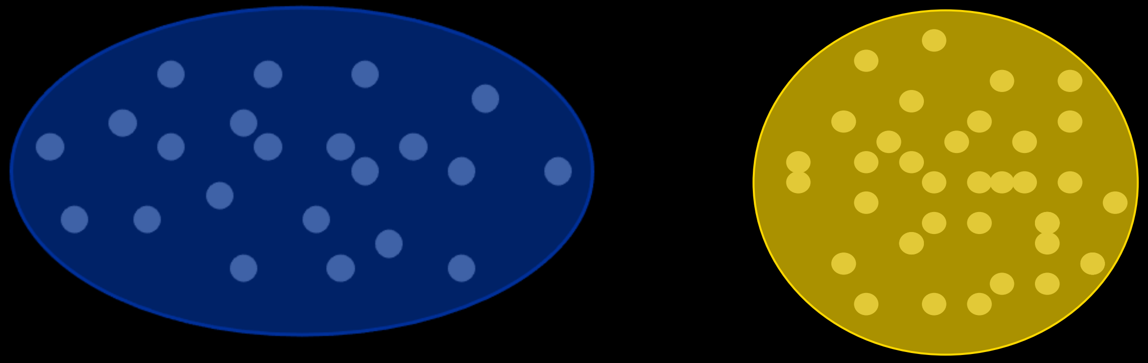
Modeling diffusion

- Full diffusion behavior in 3D space



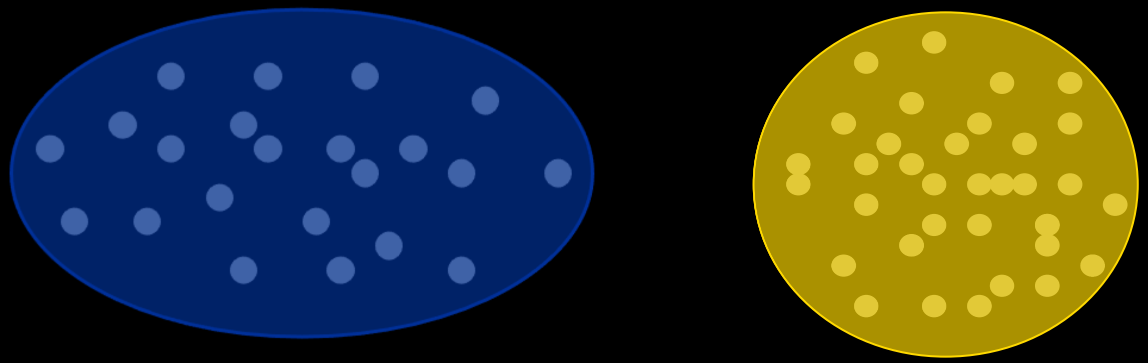
- described using ellipsoids (Tensor)

$$\underline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

- Each element captures the variance of the diffusion process

Modeling diffusion

- Full diffusion behavior in 3D space



- Diffusion Tensor

$$\underline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

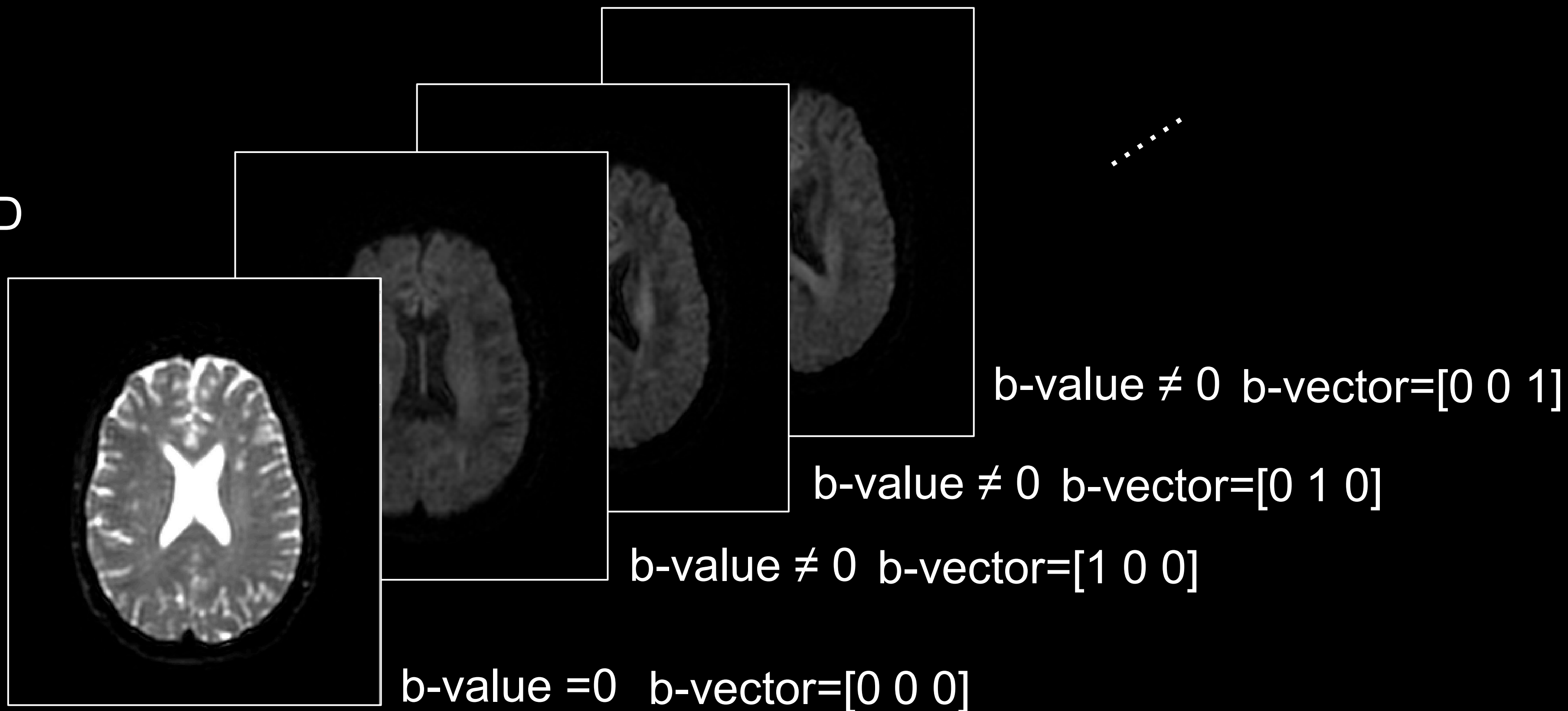
- Symmetric positive definite matrix
- 6 unknowns
- At least six measurements needed
- > 6 measurements will provide robustness to noise

Modeling diffusion

b-value, b-vector

$$S_{u_i} = S_{ref} \exp(-b u_i^T \mathbb{D} u_i)$$

Dataset : 4D

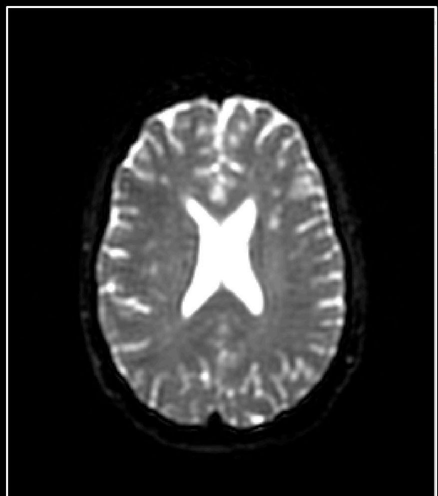


Modeling diffusion

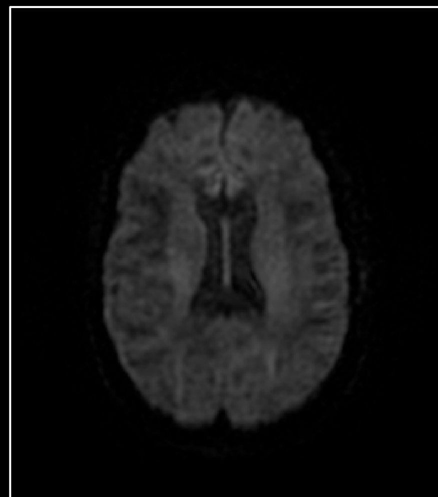
b-value, b-vector

$$S_{u_i} = S_{ref} \exp(-b u_i^T \mathbb{D} u_i)$$

S_{ref}



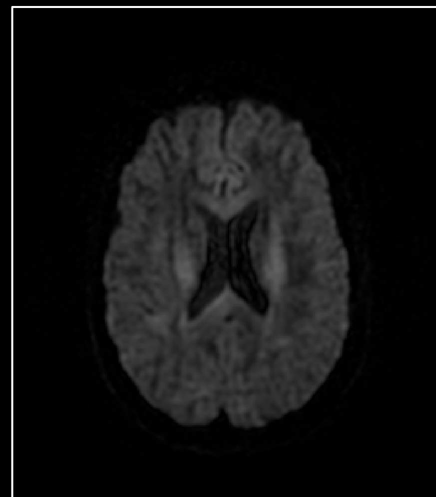
S_{u_1}



b-vector = $[u_{x1} \quad u_{y1} \quad u_{z1}]$

E.g.: [1 0 0]

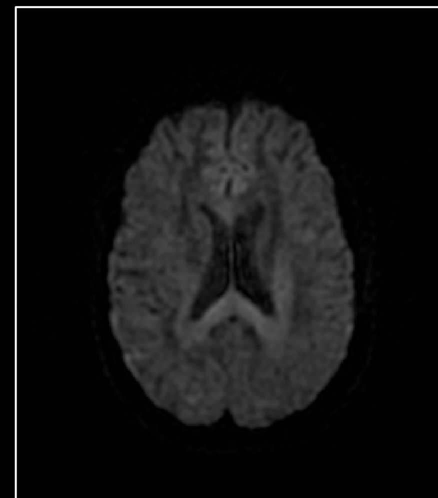
S_{u_2}



b-vector = $[u_{x2} \quad u_{y2} \quad u_{z2}]$

E.g.: [0 1 0]

S_{u_3}



b-vector = $[u_{x3} \quad u_{y3} \quad u_{z3}]$

E.g.: [0 0 1]

……

Modeling diffusion

b-value, b-vector

$$S_{u_i} = S_{ref}\exp(-bu_i^T \mathbb{D} u_i)$$

$$-\frac{1}{b}\ln\left(\frac{S_{u_i}}{S_{ref}}\right) = \begin{bmatrix} u_{xi} & u_{yi} & u_{zi} \end{bmatrix} \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \begin{bmatrix} u_{xi} \\ u_{yi} \\ u_{zi} \end{bmatrix}$$

$$y_i = u_{xi}u_{xi}D_{xx} + u_{yi}u_{yi}D_{yy} + u_{zi}u_{zi}D_{zz} + 2u_{xi}u_{yi}D_{xy} + 2u_{yi}u_{zi}D_{yz} + 2u_{zi}u_{xi}D_{zx}$$

Modeling diffusion

$$y_1 = u_{x1}u_{x1}D_{xx} + u_{y1}u_{y1}D_{yy} + u_{z1}u_{z1}D_{zz} + 2u_{x1}u_{y1}D_{xy} + 2u_{y1}u_{z1}D_{yz} + 2u_{z1}u_{x1}D_{zx}$$

$$y_2 = u_{x2}u_{x2}D_{xx} + u_{y2}u_{y2}D_{yy} + u_{z2}u_{z2}D_{zz} + 2u_{x2}u_{y2}D_{xy} + 2u_{y2}u_{z2}D_{yz} + 2u_{z2}u_{x2}D_{zx}$$

$$\vdots$$

$$y_6 = u_{x6}u_{x6}D_{xx} + u_{y6}u_{y6}D_{yy} + u_{z6}u_{z6}D_{zz} + 2u_{x6}u_{y6}D_{xy} + 2u_{y6}u_{z6}D_{yz} + 2u_{z6}u_{x6}D_{zx}$$

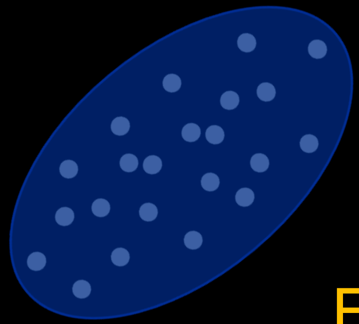
$$\underbrace{\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_6 \end{bmatrix}}_{Y} = \underbrace{\begin{bmatrix} u_{x1}u_{x1} & u_{y1}u_{y1} & \ldots\ldots & 2u_{z1}u_{x1} \\ u_{x2}u_{x2} & u_{y2}u_{y2} & \ldots\ldots & 2u_{z2}u_{x2} \\ \vdots & \vdots & & \vdots \\ u_{x6}u_{x6} & u_{y6}u_{y6} & \ldots\ldots & 2u_{z6}u_{x6} \end{bmatrix}}_{A} \underbrace{\begin{bmatrix} D_{xx} \\ D_{yy} \\ \vdots \\ D_{zx} \end{bmatrix}}_{X}$$

$$X = A^{-1}Y$$

Many software programs have built-in tools to perform a DTI fitting

Anisotropy : Major axis of the ellipsoid

$$\underline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$



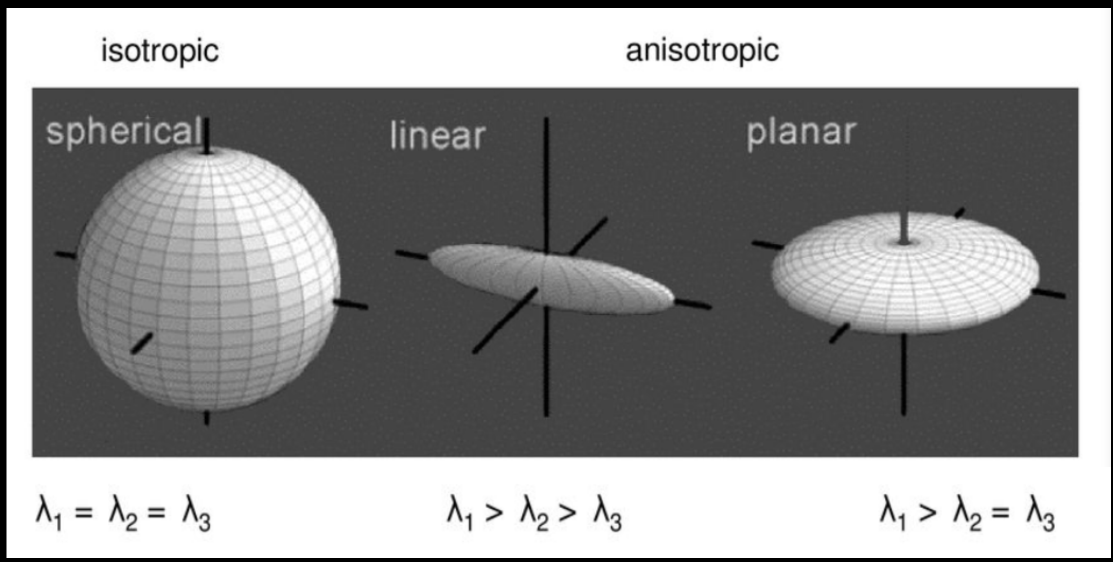
$$\mathbb{D} = E\,\Lambda\,E^T$$

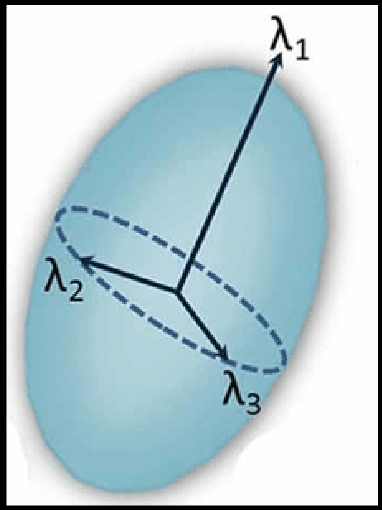
Eigen Decomposition

$$= E^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} E$$

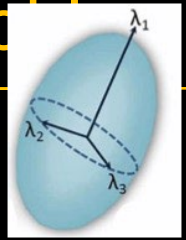
Eigenvectors

$$E = \begin{bmatrix} e_{1x} & e_{2y} & e_{3z} \\ e_{1x} & e_{2y} & e_{3z} \\ e_{1x} & e_{2y} & e_{3z} \end{bmatrix}$$

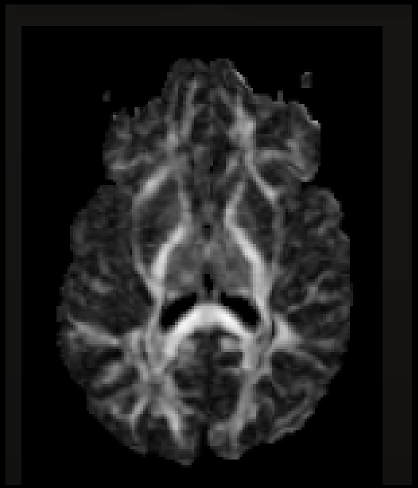




Anisotropy : Major axis of the ellipso



For every voxel



$$\underline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \longrightarrow E^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} E$$

DWIs

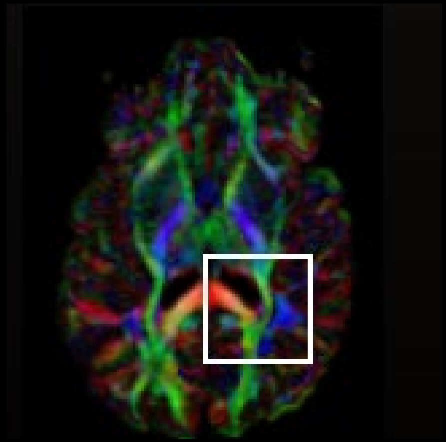
Solve for D

Eigen Decomposition

Eigenvectors

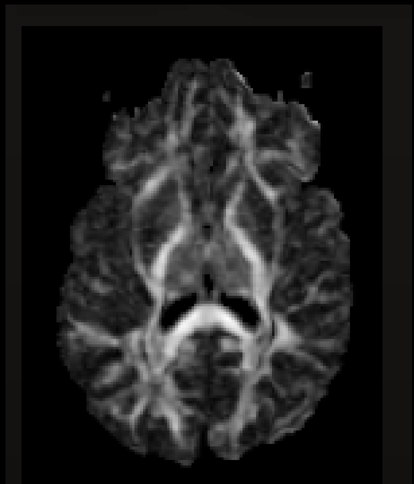
$$E = \begin{bmatrix} e_{1x} & e_{2y} & e_{3z} \\ e_{1x} & e_{2y} & e_{3z} \\ e_{1x} & e_{2y} & e_{3z} \end{bmatrix}$$

Assign Color-code to the Eigen vectors



Anisotropy : Major axis of the ellipsoid

For every voxel



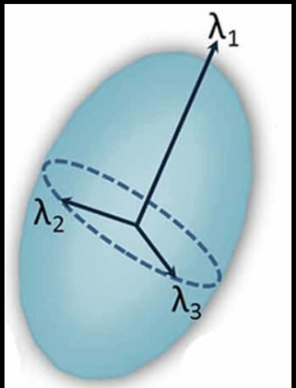
DWIs

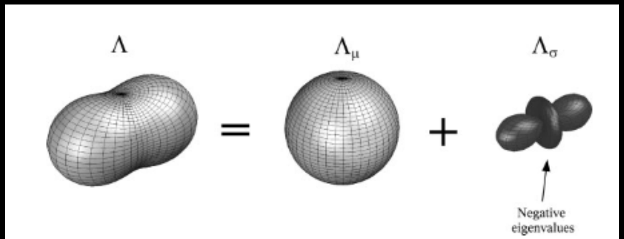
$$\underline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

Solve for D

$$E^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} E$$

Eigen Decomposition





$$\mathrm{FA} = \sqrt{\frac{3}{2}}\frac{\sqrt{\Lambda_\sigma : \Lambda_\sigma}}{\sqrt{\Lambda : \Lambda}}$$

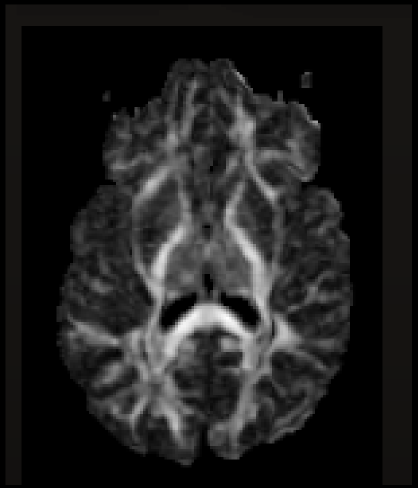
Fractional Anisotropy Map

$$\mathrm{FA} = \sqrt{\frac{1}{2}} \cdot \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{(\lambda_1)^2 + (\lambda_2)^2 + (\lambda_3)^2}}$$

Ranges from values : 0 ->1

1 : high anisotropy, 0: low anisotropy

Anisotropy : Major axis of the ellipsoid



DWIs

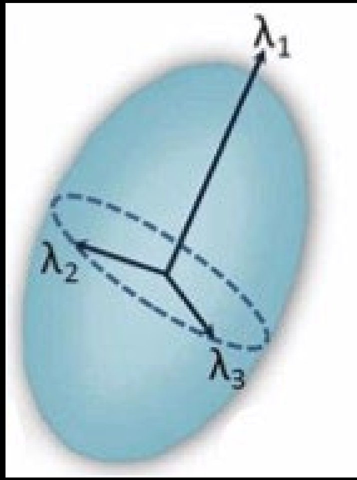
For every voxel

$$\underline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

→ Solve for D

$$E^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} E$$

→ Eigen Decomposition



Axial Diffusivity: λ_1

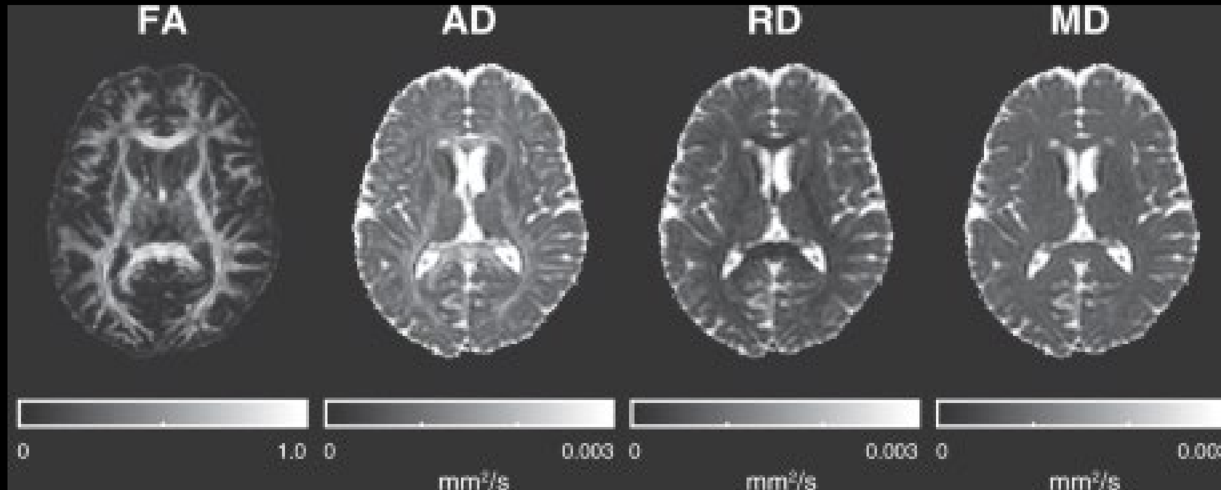
Radial Diffusivity: $\frac{\lambda_2 + \lambda_3}{2}$

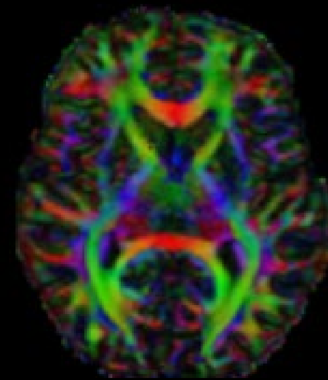
Mean Diffusivity: $\frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$

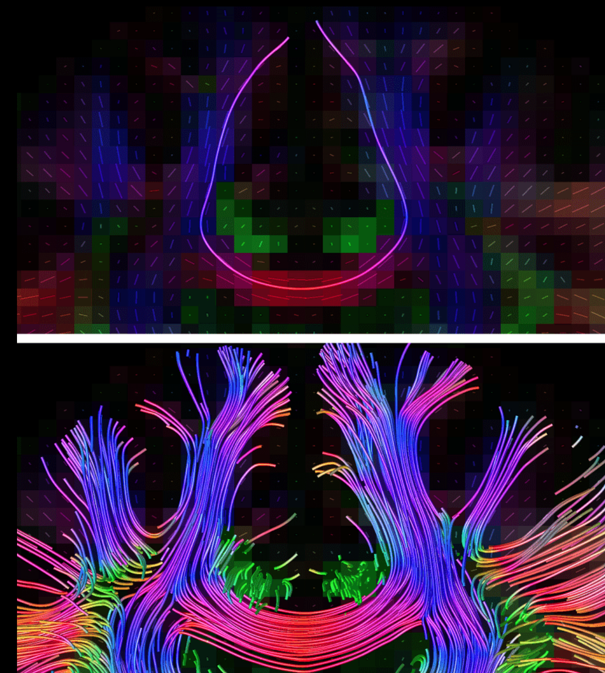
Range: 0 - .003 mm^2/sec

Diffusion Tensor Imaging

- With 6 measurements, diffusion in 3D space is characterized







Enables studies of brain disorders

Is there change of white matter integrity ?

Is there change in connectivity patterns?

Myth about FA

❌ Lower FA means loss of WM integrity (and vice versa)

✅ Lower FA can result from increased WM integrity also (and vice versa)

Myth about DTI

- ✗ DTI provides measures of WM only
- ☑ All DTI maps are valid in both WM and GM
- ☑ Changes in FA are more frequently "tried" to be interpreted in WM
- ☑ DTI can detect changes in GM also

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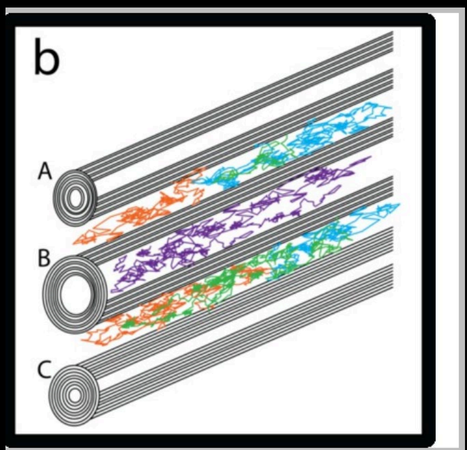
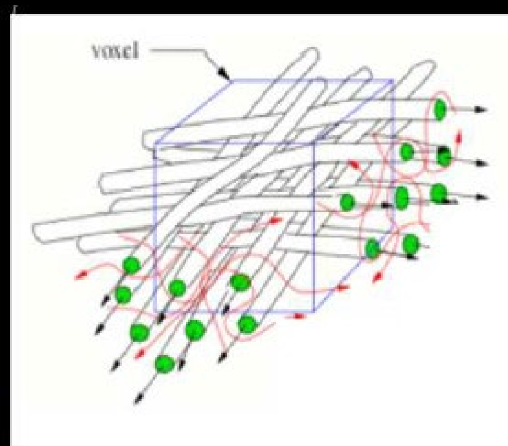
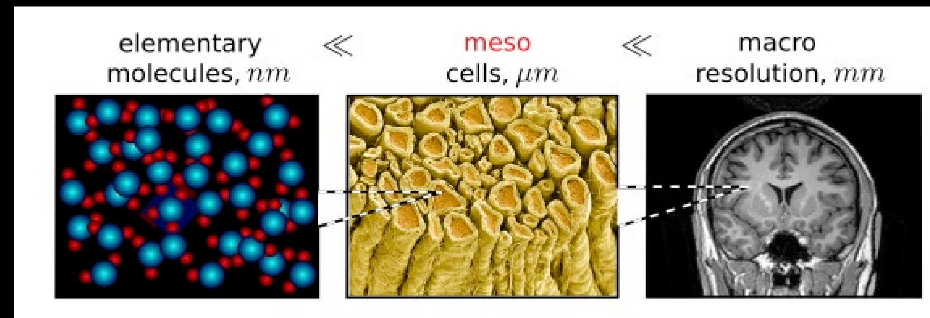
Pitfalls of DTI (ellipsoid) model

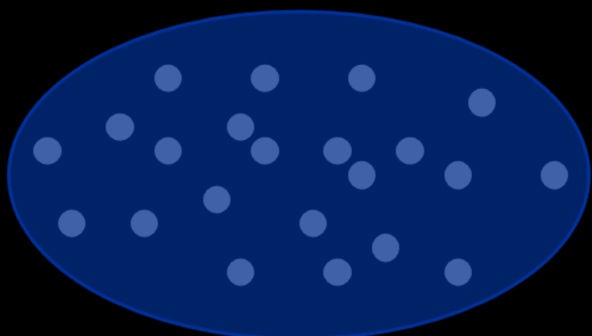
- Diffusion Tensor is a over-simplistic model for brain studies
  - With unparalleled sensitivity





Most MRI voxels are > 8mL





??

Axons are orders of magnitude smaller structures

Anisotropic Diffusion

Key word: “change”

Pitfalls of DTI (ellipsoid) model

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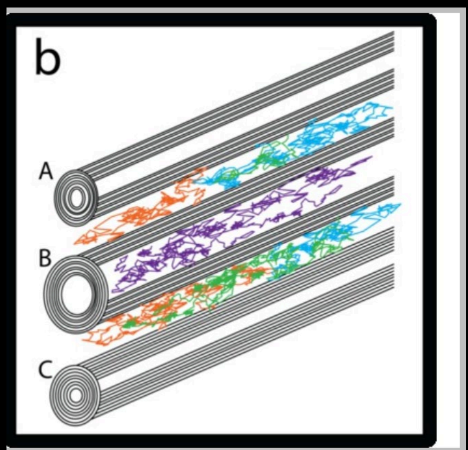
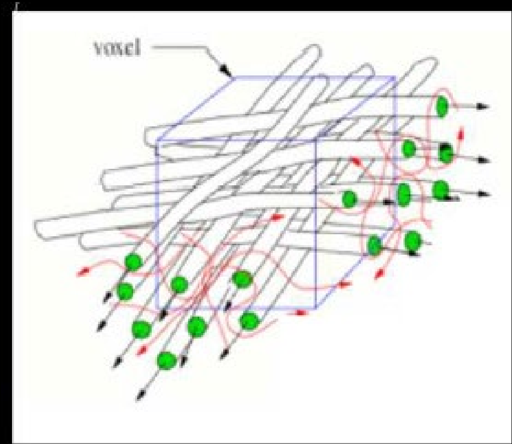
    - With unparalleled sensitivity





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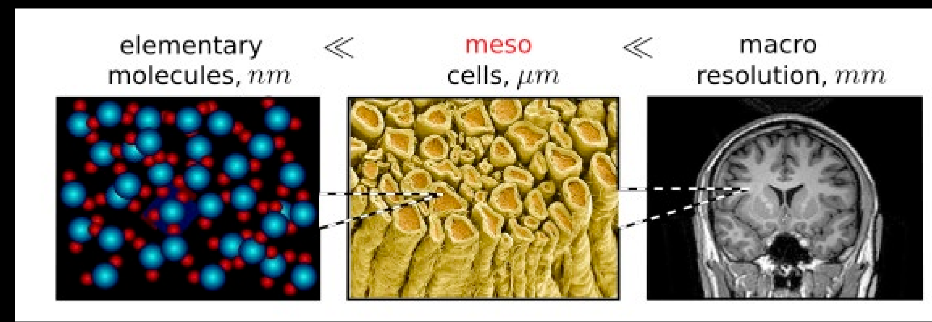
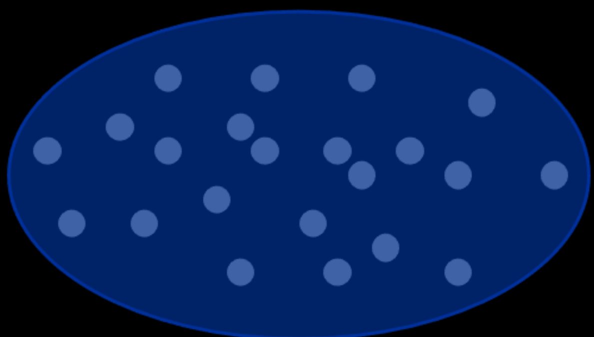
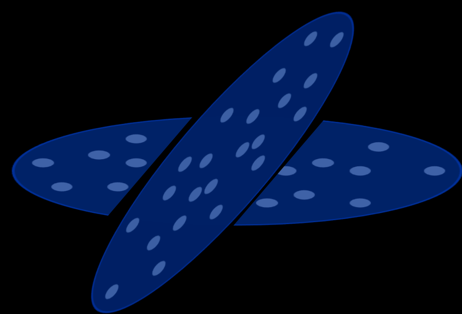


Hard to solve mathematically



Anisotropic Diffusion



Multiple ellipsoids

Fact about DTI

- ✓ DTI can be used to study brain changes
- ✓ DTI is not a good model for anisotropy detection in most brain voxels
- ✓ Because of fiber orientation heterogeneity

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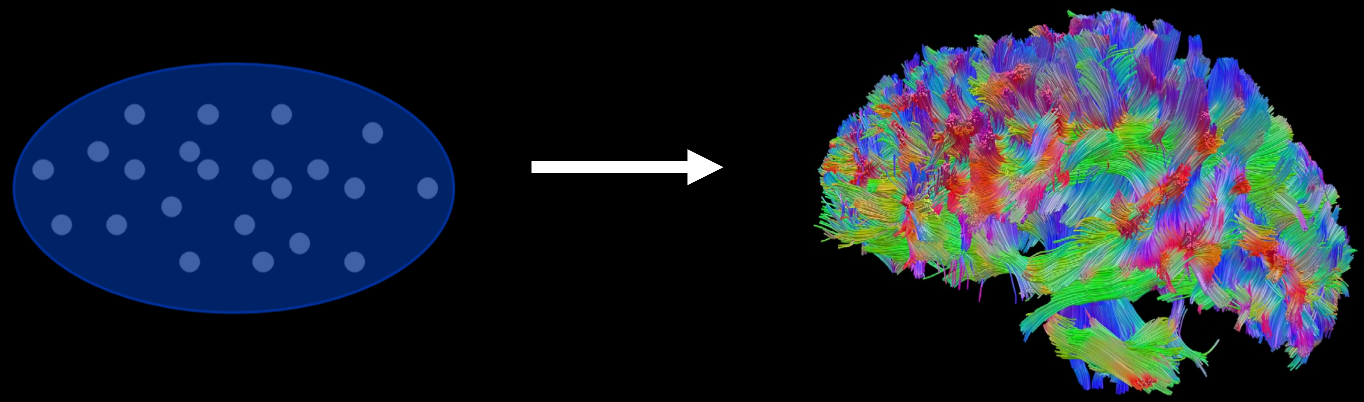
Fiber Tracking Using Diffusion data

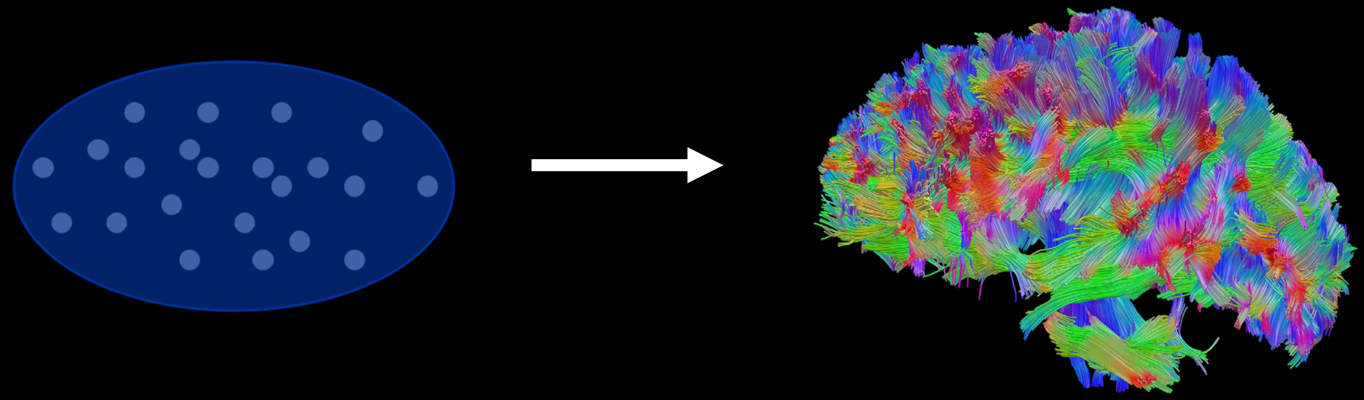
- If the ellipsoid model is not good, how can you do fiber tracking ??



- Modern day fiber tracking is not performed using ellipsoids
- Makes use of a method called spherical deconvolution

Fiber Tracking Using SD

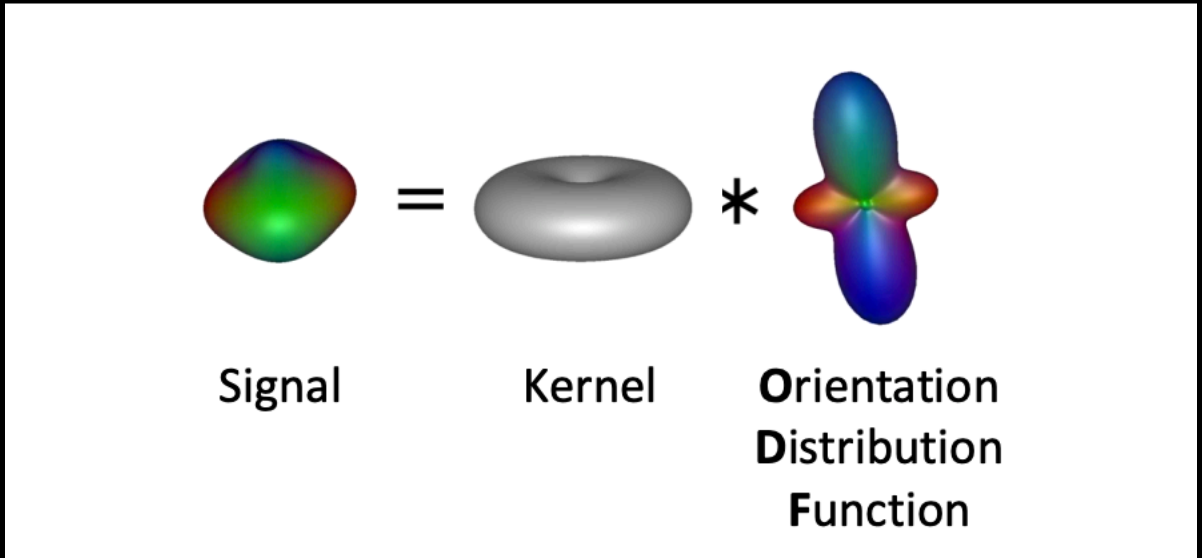
- If the ellipsoid model is not good, how can you do fiber tracking ??



- Modern day fiber tracking is not performed using ellipsoids
- Makes use of a method called spherical deconvolution
- Only pertains to finding the fiber orientations
- Do not provide any information about the diffusivity
- Makes certain assumptions

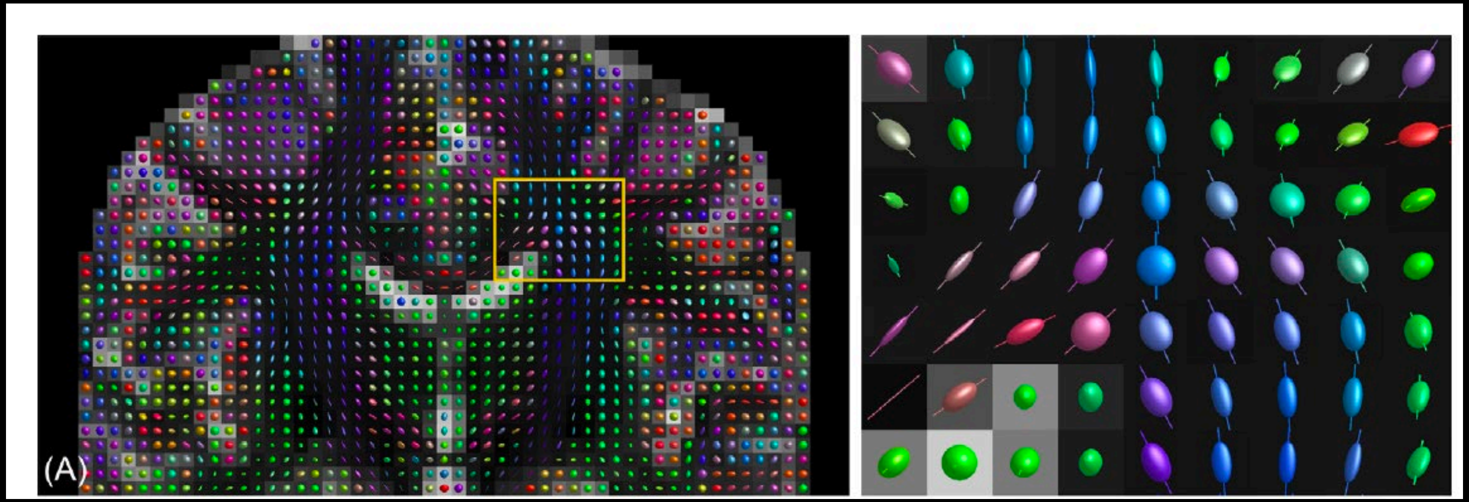
Fiber Tracking Using SD

- SD Model

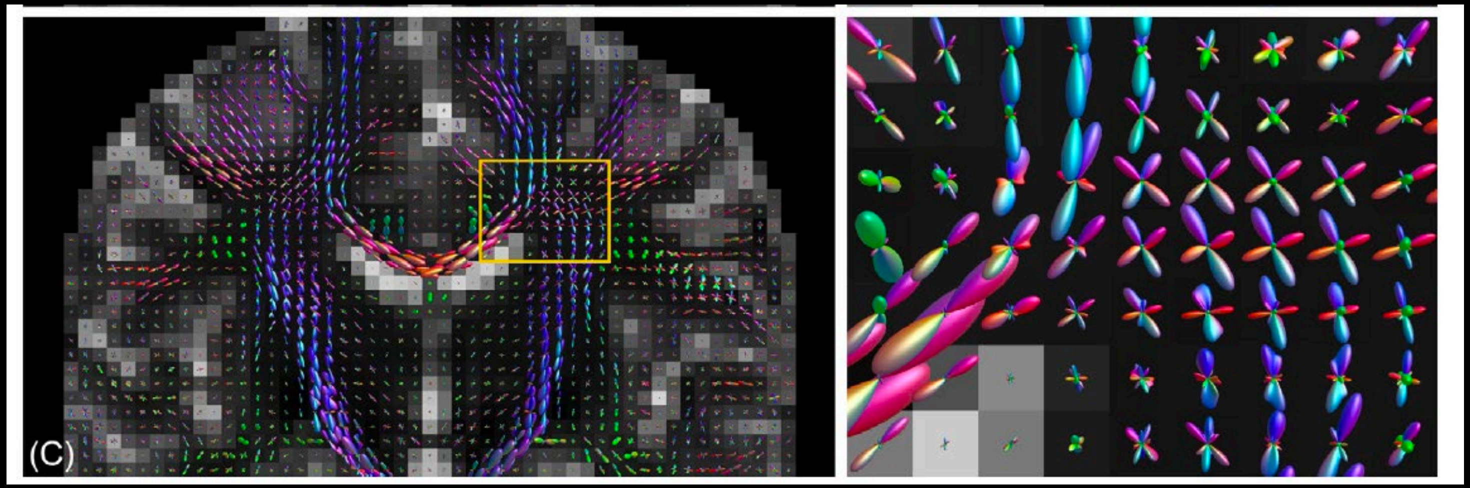


- Measured diffusion signal is a convolution
  - Of a known fiber response kernel
  - With a fiber orientation distribution function (fODF)
- Goal: Given the kernel, find the fiber ODF

Spherical Deconvolution

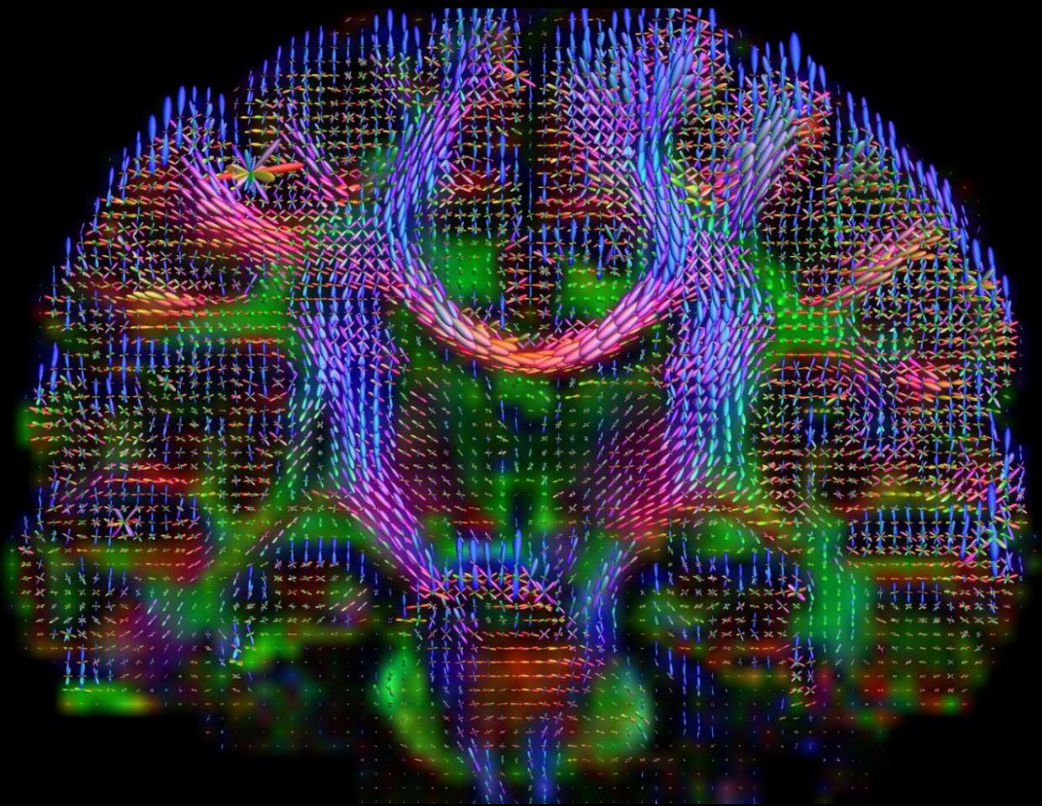


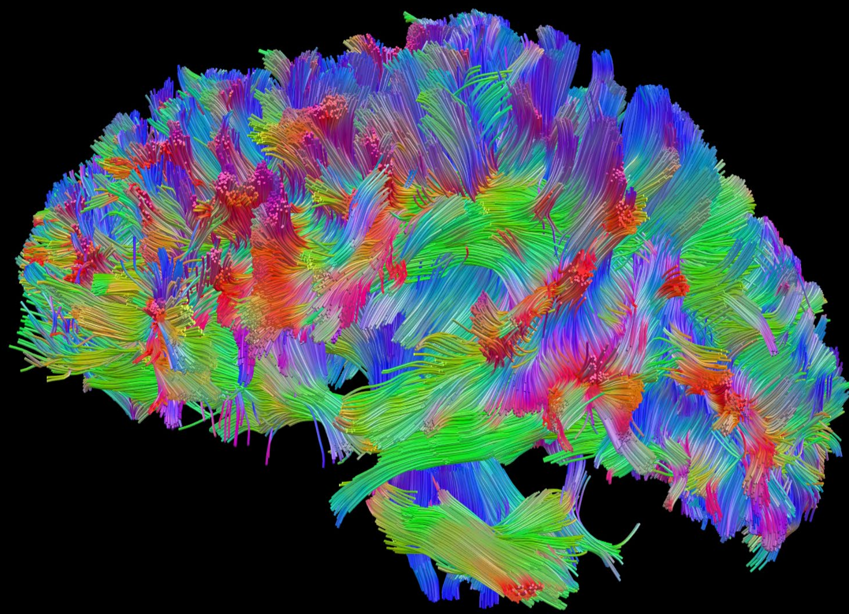
- Tensor fitting



- SD

Fiber Tracking Using Diffusion data





- Implemented in many software packages
  - MrTrix, DIPY

Outline

- What is diffusion and why do we care ?
- How to model diffusion signal?
- What are the pitfalls of modeling ?
- Fiber Tracking using diffusion MRI
- How to pre-process diffusion data?
- How to extract biologically meaningful diffusion measures ?

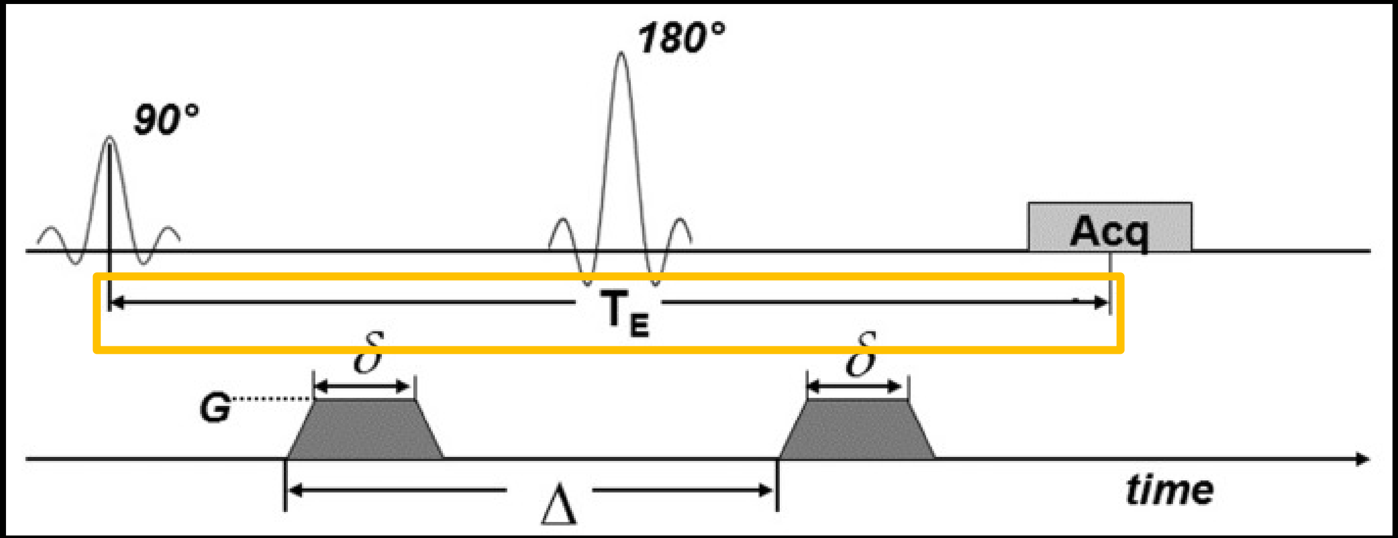
Need for preprocessing

- DW images are affected by noise and by artifacts such as Gibbs ringing and distortions.

Noise in diffusion MRI

- DW images are affected by noise and by artifacts such as Gibbs ringing and distortions.

- Noise: diffusion MRI has very low SNR



  - TE definition

Noise in diffusion MRI

- DW images are affected by noise and by artifacts such as Gibbs ringing and distortions.
- Noise: diffusion MRI has very low SNR
- Acquisition parameters that affect the SNR:
    - b-value (which affects the TE)
    - Spatial resolution (which affects the TE)
    - The scanner itself (G_{max}, $Slew_{max}$)

Denoising

- Many correction methods are available:
  - Local-PCA, Marchenko Pastur PCA
  - Patch2Self
  - Both implemented in DIPY

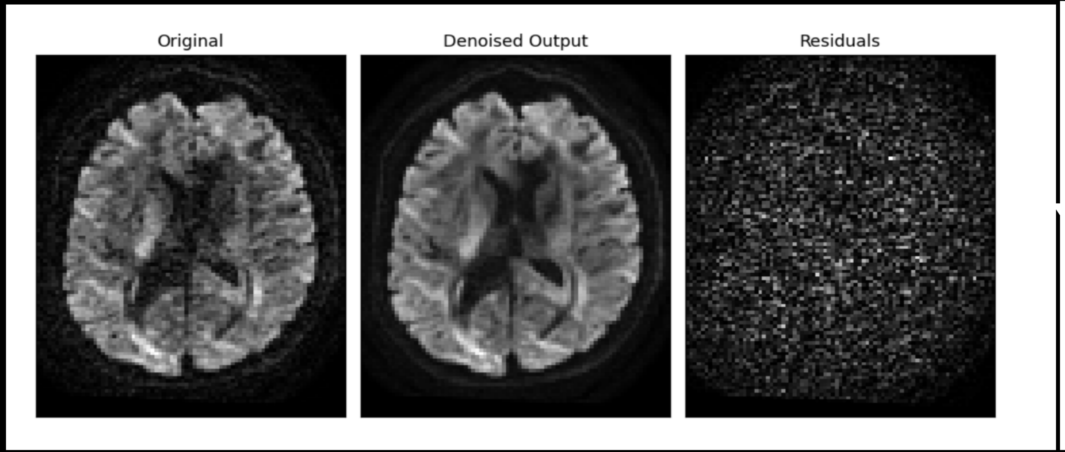
```
denoised_arr = mppca(data, patch_radius=2)
```

```
denoised_arr = patch2self(data, bvals)
```

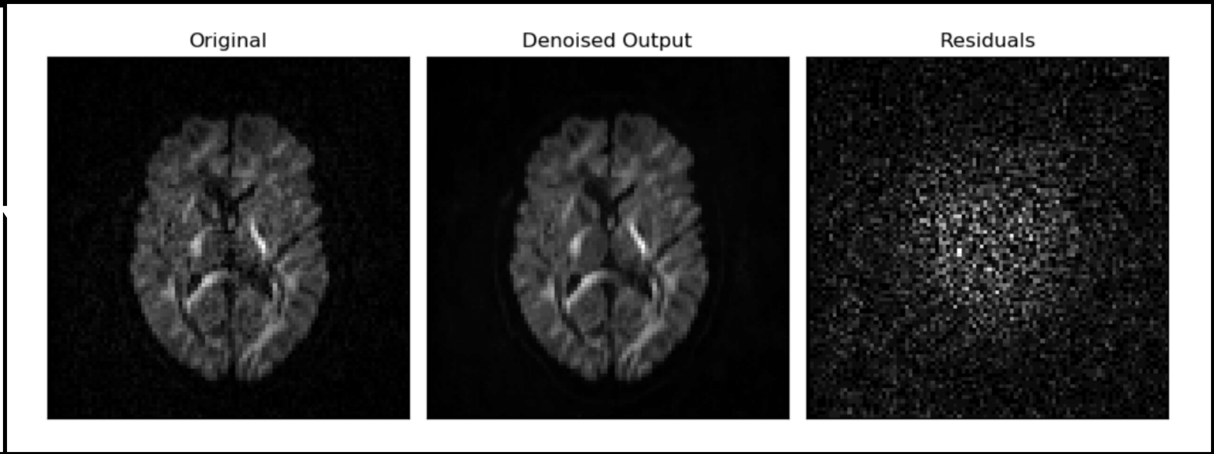
  - NORDIC, qModeL, AIReconDL

Denoising

- Many correction methods are available:
  - Local-PCA, Marchenko Pastur PCA
  - Patch2Self
  - Both implemented in DIPY



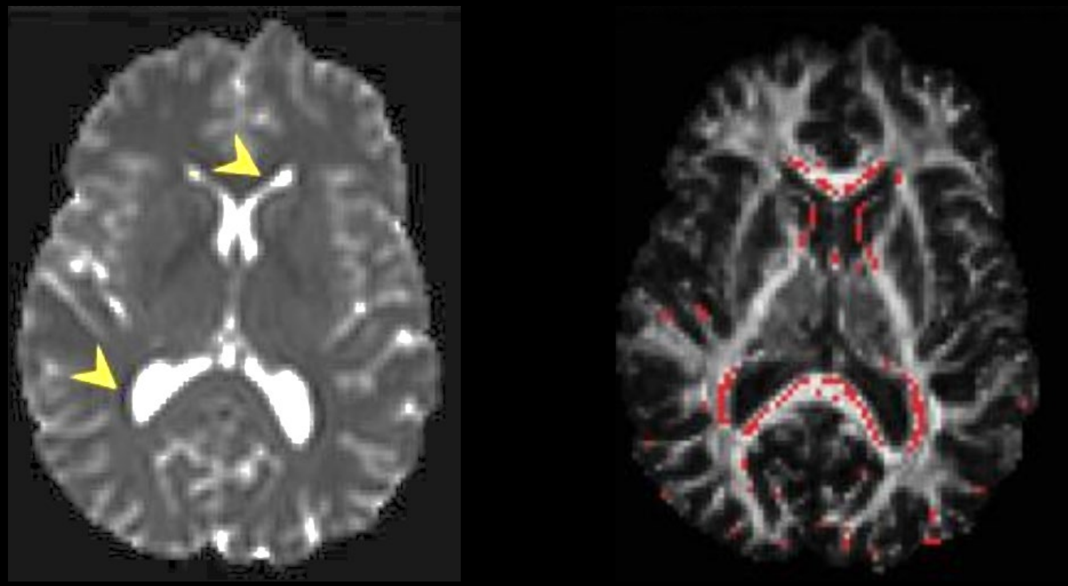

```
denoised_arr = mppca(data, patch_radius=2)
```




```
denoised_arr = patch2self(data, bvals)
```

Gibbs Ringing

- DW images are affected by noise and by artifacts such as Gibbs ringing and distortions.
- Gibbs Ringing



- Caused by truncation of high frequency Fourier co-efficients
- Usually most prominent on the b0 images
- Leads to over-estimation of FA (>1)

Gibbs Ringing

- Correction needed to remove outliers
  - Sub-voxel shift method
    - Implemented in DIPY

To run the Gibbs unringing on the data it suffices to execute the `dipy_gibbs_ringing` command, e.g.:

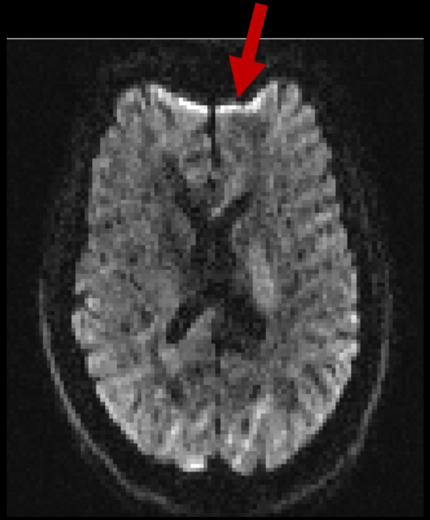
```
dipy_gibbs_ringing data/tissue_data/t1_brain_denoised.nii.gz --num_threads 4 --out_dir "gibbs_ringing_(
```

- Advanced version for partial Fourier acquired data (RPG)
  - Implemented in DESIGNER https://github.com/NYU-DiffusionMRI/DESIGNER

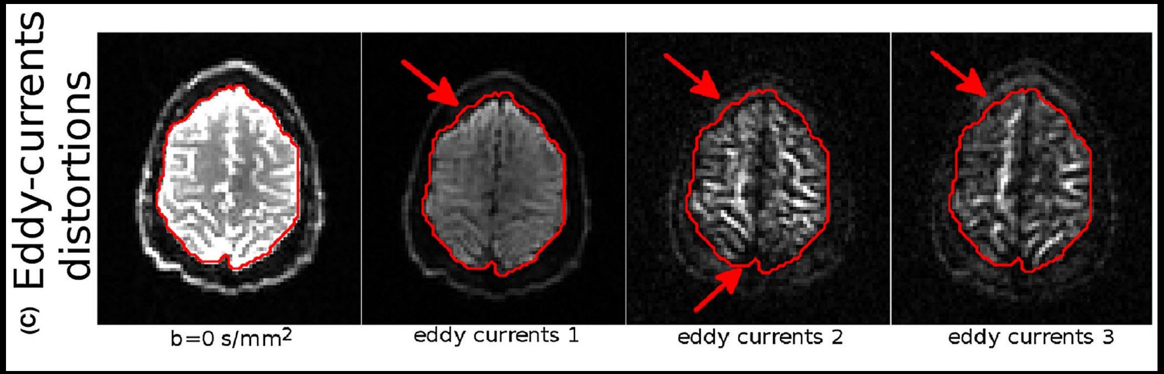
    designer dwi1.nii.gz out_dir -rpg -pf 6/8 -dim 2

Distortion Correction

- DW images are affected by noise and by artifacts such as Gibbs ringing and distortions
- Two sources:
  - B0 field inhomogeneity

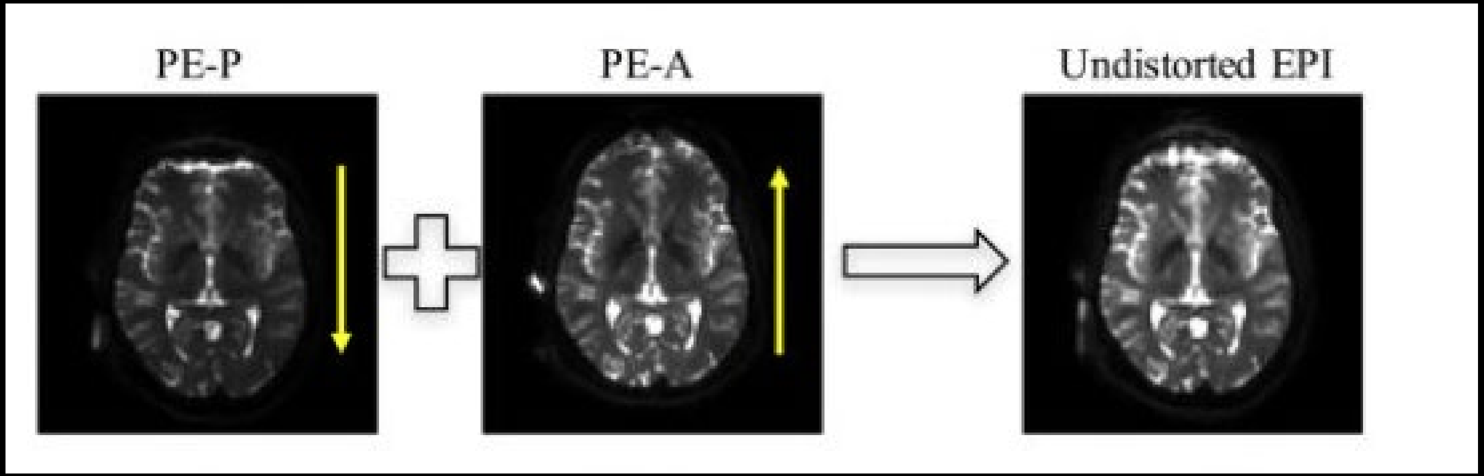


  - Eddy current



Distortion Correction

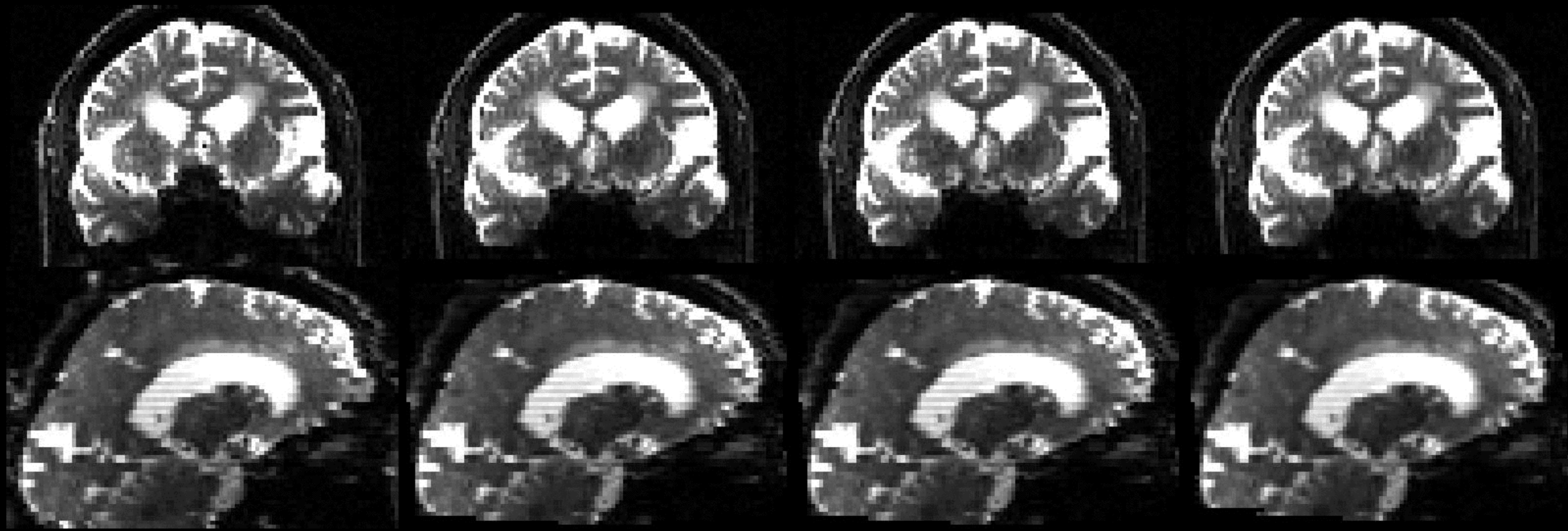
- Susceptibility-induced : top-up
  - Two scans (b0s) acquired with opposite k-space read-out polarity are needed




```
topup --imain=all_my_b0_images.nii --datain=acquisition_parameters.txt --config=b02b0.cnf --out=my_output
```

Distortion Correction

- Eddy-current induced : eddy
  - Also corrects for head motion, and signal dropout

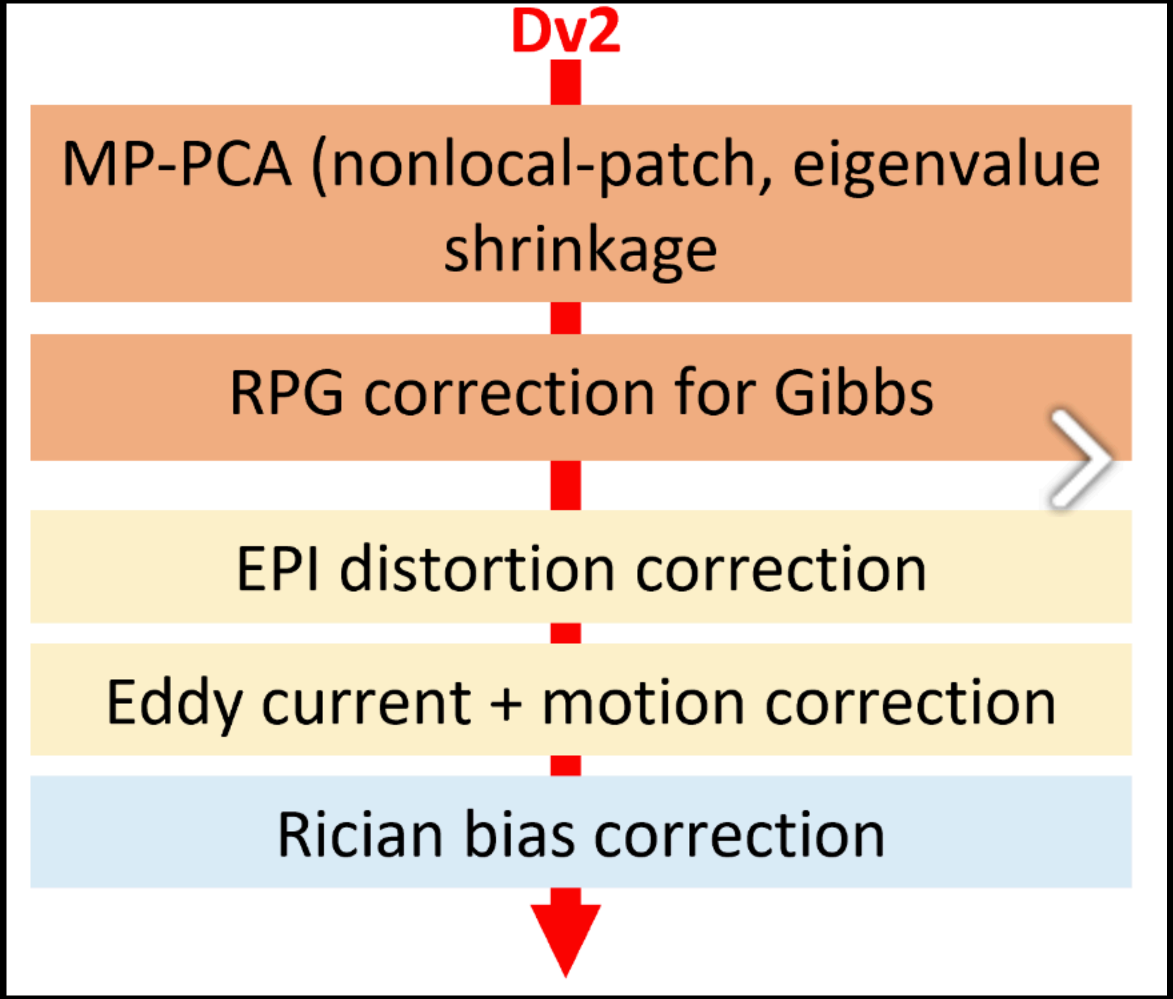


Bias Correction

- Magnitude MRI images have a Rician noise distribution
  - Creates a bias in parameter estimates
  - Major concern at low SNR acquisitions
    - For b~1000, not a big issue
    - For b>1000, needs bias correction
  - Not many toolboxes have this implemented
    - Implemented in DESIGNER https://github.com/NYU-DiffusionMRI/DESIGNER

designer dwi1.nii.gz out_dir –denoise -rician

Diffusion Preprocessing steps



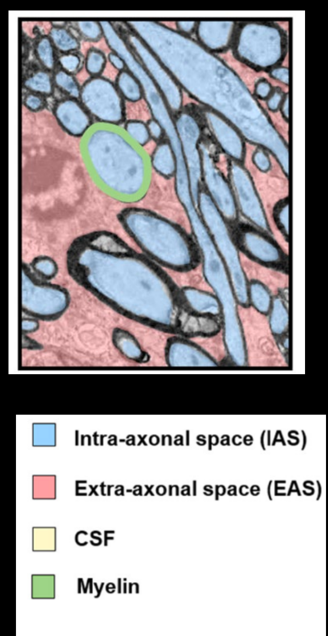
Outline

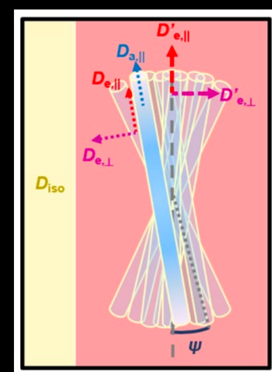
- What is diffusion and why do we care ?
- How to model diffusion ?
- What are the pitfalls of modeling ?
- How to measure diffusion data?
- How to pre-process diffusion data?
- How to extract biologically meaningful diffusion measures ?

Biologically meaningful diffusion measures

IOWA

- Involve biophysical modeling
  - Split a voxel into multiple compartments
  - Measure diffusion properties associated with each compartment





$$S(q) = S_0 \int P(\kappa,\mu)\ [\ f_1 e^{-bD_a g.\mu} + f_2 e^{-bD_e^{\perp}\ -b(D_e^{\parallel} - D_e^{\perp}) g.\mu} + f_{iso} e^{-bD_{iso}}]$$

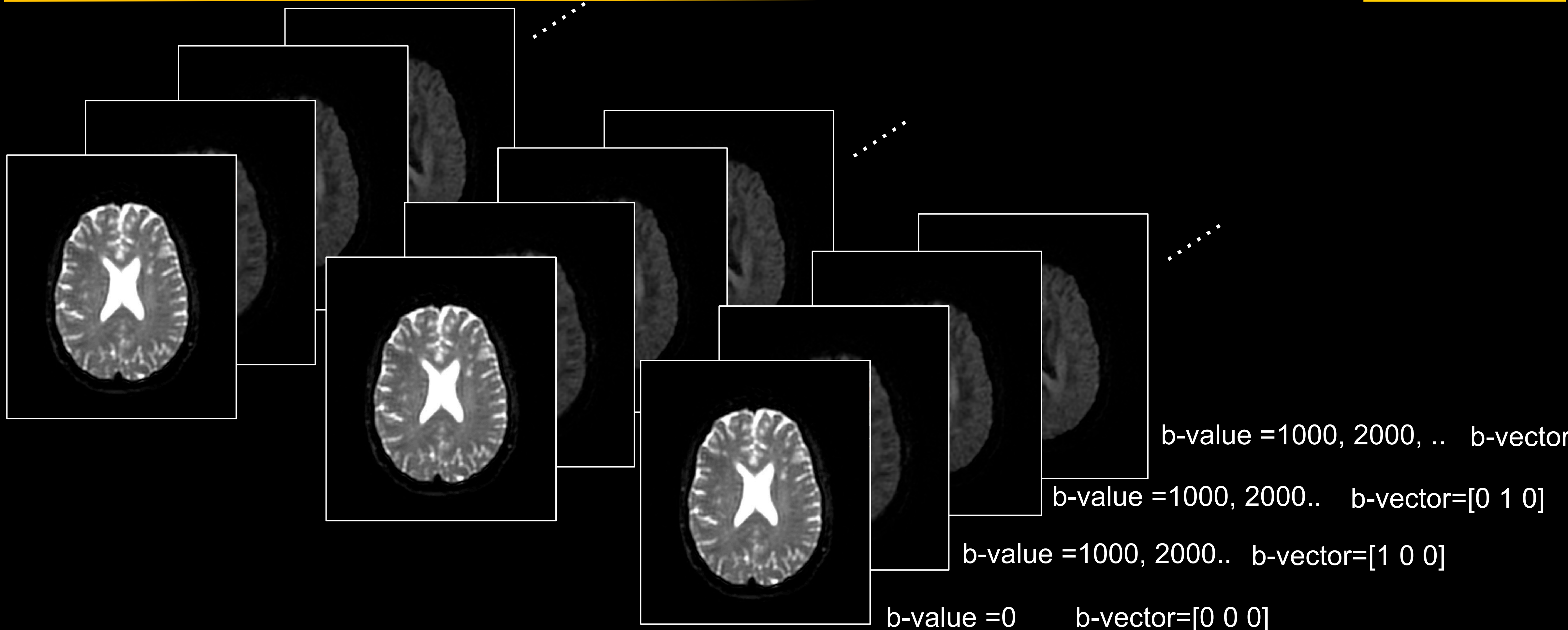
FODF | Intra-axonal compartment | Extra-axonal compartment | Isotropic compartment

Biologically meaningful diffusion measures

$$S(q) = S_0 \int \underbrace{P(\kappa,\mu)}_{\text{FODF}} \left[\underbrace{f_1 e^{-bD_a g.\mu}}_{\text{Intra-axonal compartment}} + \underbrace{f_2 e^{-bD_e^{\perp} - b(D_e^{\parallel} - D_e^{\perp}) g.\mu}}_{\text{Extra-axonal compartment}} + \underbrace{f_{iso} e^{-bD_{iso}}}_{\text{Isotropic compartment}} \right]$$

- Large number of unknowns
- Requires multi-shell sampling
- Requires special MRI scanners
- HCP study was a big leap

➢Multi-shell acquisition



Biologically meaningful diffusion measures

IOWA

$$S(q) = S_0 \int P(\kappa, \mu) \left[f_1 e^{-bD_a g.\mu} + f_2 e^{-bD_e^{\perp} - b(D_e^{\parallel} - D_e^{\perp}) g.\mu} + f_{iso} e^{-bD_{iso}} \right]$$

FODF

Intra-axonal compartment

Extra-axonal compartment

Isotropic compartment

- Large number of unknowns
- Requires multi-shell sampling
- Requires special MRI scanners
- New dedicated scanner are now available for such studies
- MAGUS scanner installed at UIOWA in Dec 2022 !!

Biologically meaningful diffusion measures

IOWA

- Large number of biomarkers for neurodegeneration!

Axonal loss — AxonalBeading — Demyelination — Neuroinflammation

$$S(q) = S_0 \int P(\kappa,\mu) \left[f_1 e^{-bD_a g.\mu} + f_2 e^{-bD_e^{\perp} - b(D_e^{\parallel} - D_e^{\perp}) g.\mu} + f_{iso} e^{-bD_{iso}} \right]$$

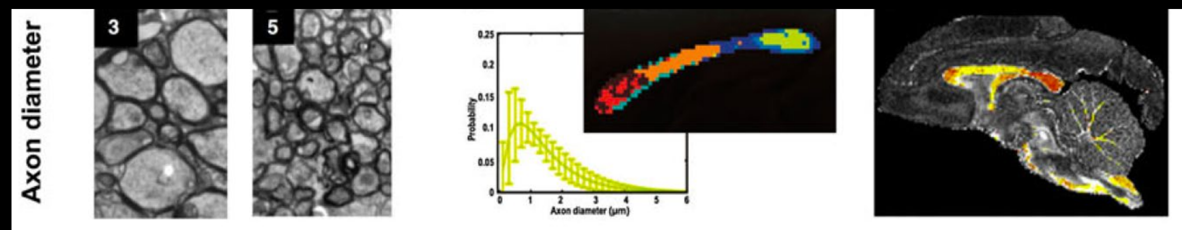
FODF

Intra-axonal compartment

Extra-axonal compartment

Isotropic compartment

- Axon diameter mapping



Summary

- Diffusion measures are highly sensitive
- DTI is a useful tool that exploits the high sensitivity
- DTI studies do not facilitate biological interpretation
- Biophysical models do facilitate biological interpretation
- Always collect multi-shell data when planning diffusion studies
- Requires dedicated scanner
- Hawkeyes can be proud to own the rarest scanner yet!
- Many tools are already available for testing on argon!
- Please plan to make use of it !!