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?

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

- Restricted Medium:
  - Isotropic Diffusion not possible

- Patterns of water diffusion in tissue reflect the microstructure of the medium
What is diffusion and why do we care?

- 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?

- 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

- 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

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)

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

- Each element captures the variance of the diffusion process
Modeling diffusion

- Full diffusion behavior in 3D space

Diffusion Tensor

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

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

\[ S_{u_i} = S_{ref} \exp(-b u_i^T D u_i) \]

- b-value, b-vector

Dataset: 4D

- b-value ≠ 0 b-vector=[0 0 1]
- b-value ≠ 0 b-vector=[0 1 0]
- b-value ≠ 0 b-vector=[1 0 0]
- b-value =0 b-vector=[0 0 0]
Modeling diffusion

\[ S_{u_i} = S_{ref} \exp(-b u_i^T D u_i) \]

b-value, b-vector

\[ S_{ref} \]

\[ S_{u_1} \]

\[ S_{u_2} \]

\[ S_{u_3} \]

\[ \ldots \]

b-vector = 

\[ \begin{bmatrix} u_{x1} & u_{y1} & u_{z1} \end{bmatrix} \]

E.g.: [1 0 0]

b-vector = 

\[ \begin{bmatrix} u_{x2} & u_{y2} & u_{z2} \end{bmatrix} \]

E.g.: [0 1 0]

b-vector = 

\[ \begin{bmatrix} u_{x3} & u_{y3} & u_{z3} \end{bmatrix} \]

E.g.: [0 0 1]
Modeling diffusion

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

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

\[ y_i = u_{xi}u_{xi}D_{xx} + u_{yi}u_{yi}D_{yy} + u_{zi}u_{zi}D_{zz} + 2u_{xi}u_{yi}D_{xy} + 2u_{yi}u_{zi}D_{yz} + 2u_{zi}u_{xi}D_{zx} \]
Modeling diffusion

\[ \begin{align*}
y_1 &= u_{x1} u_{x1} D_{xx} + u_{y1} u_{y1} D_{yy} + u_{z1} u_{z1} D_{zz} + 2 u_{x1} u_{y1} D_{xy} + 2 u_{y1} u_{z1} D_{yz} + 2 u_{z1} u_{x1} D_{zx} \\
y_2 &= u_{x2} u_{x2} D_{xx} + u_{y2} u_{y2} D_{yy} + u_{z2} u_{z2} D_{zz} + 2 u_{x2} u_{y2} D_{xy} + 2 u_{y2} u_{z2} D_{yz} + 2 u_{z2} u_{x2} D_{zx} \\
y_6 &= u_{x6} u_{x6} D_{xx} + u_{y6} u_{y6} D_{yy} + u_{z6} u_{z6} D_{zz} + 2 u_{x6} u_{y6} D_{xy} + 2 u_{y6} u_{z6} D_{yz} + 2 u_{z6} u_{x6} D_{zx} \\
\end{align*} \]

\[
\begin{bmatrix}
y_1 \\
y_2 \\
\vdots \\
y_6
\end{bmatrix} =
\begin{bmatrix}
u_{x1} u_{x1} & u_{y1} u_{y1} & \cdots & 2 u_{z1} u_{x1} \\
u_{x2} u_{x2} & u_{y2} u_{y2} & \cdots & 2 u_{z2} u_{x2} \\
\vdots & \vdots & \ddots & \vdots \\
u_{x6} u_{x6} & u_{y6} u_{y6} & \cdots & 2 u_{z6} u_{x6}
\end{bmatrix}
\begin{bmatrix}
D_{xx} \\
D_{yy} \\
D_{zz}
\end{bmatrix}

\]

\[X = A^{-1} Y\]

Many software programs have built-in tools to perform a DTI fitting
Anisotropy: Major axis of the ellipsoid

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

Eigen Decomposition

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

Isotropic

- spherical
- linear
- planar

$$\lambda_1 = \lambda_2 = \lambda_3$$

Anisotropic

- $\lambda_1 > \lambda_2 > \lambda_3$
- $\lambda_1 > \lambda_2 = \lambda_3$

Eigenvalues

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

Eigenvectors
Anisotropy: Major axis of the ellipsoid

For every voxel

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

Solve for \( D \)

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

Eigen Decomposition

Assign Color-code to the Eigen vectors
Anisotropy: Major axis of the ellipsoid

For every voxel

\[ D = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix} \quad \text{Eigenvectors: } \begin{pmatrix} \lambda_1 & 0 & 0 \\
0 & \lambda_2 & 0 \\
0 & 0 & \lambda_3 \end{pmatrix} \]

Solve for \( D \) via Eigen Decomposition

Fractional Anisotropy Map

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

Ranges from values: 0 -> 1

1: high anisotropy, 0: low anisotropy
Anisotropy: Major axis of the ellipsoid

For every voxel

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

Solve for \( D \)

Eigen Decomposition

Axial Diffusivity: \( \lambda_1 \)

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 an over-simplistic model for brain studies
  - With unparalleled sensitivity

Most MRI voxels are $> 8\text{mL}$

Axons are orders of magnitude smaller structures

Key word: “change”
Pitfalls of DTI (ellipsoid) model

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

- Most MRI voxels are > 8mL

- Anisotropic Diffusion

- Multiple ellipsoids

- Hard to solve mathematically
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
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 ($G_{\text{max}}$, $\text{Slew}_{\text{max}}$)
Many correction methods are available:

- Local-PCA, Marchenko Pastur PCA
- Patch2Self
- Both implemented in DIPY

```python
# Denoising example
import mppca
import patch2self
denoised_arr = mppca(data, patch_radius=2)
denoised_arr = patch2self(data, bvals)
```

- NORDIC, qModeL, AlReconDL
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

- Usually most prominent on the b0 images

- Leads to over-estimation of FA (>1)

- Caused by truncation of high frequency Fourier coefficients
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](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 --datin=acquisition_parameters.txt --config=b02b0.cnf --out=my_output
```
Distortion Correction

- Eddy-current induced: eddy
- Also corrects for head motion, and signal dropout
Magnitude MRI images have a Rician noise distribution

- Creates a bias in parameter estimates
- Major concern at low SNR acquisitions
  - For $b \sim 1000$, 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

- MP-PCA (nonlocal-patch, eigenvalue shrinkage)
- RPG correction for Gibbs
- EPI distortion correction
- Eddy current + motion correction
- Rician bias correction
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- How to measure diffusion data?
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Biologically meaningful diffusion measures

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

\[ S(q) = S_0 \int P(\kappa, \mu) \left[ f_1 e^{-bD_a}g \mu + f_2 e^{-bD_e} - b(D_e^H-D_e^L)g \mu + f_{iso} e^{-bD_{iso}} \right] \]
Biologically meaningful diffusion measures

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

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

- $b$-value = 0, $b$-vector = [0 0 0]
- $b$-value = 1000, 2000, $b$-vector = [0 1 0]
- $b$-value = 1000, 2000, $b$-vector = [1 0 0]
- $b$-value = 0, $b$-vector = [0 0 0]
Biologically meaningful diffusion measures

\[ S(q) = S_0 \int P(\kappa, \mu) \left[ f_1 e^{-bD_{ag}g\mu} + f_2 e^{-bD_{e}^\perp - b(D^\parallel_e - D^\perp_e)g\mu} + f_{iso} e^{-bD_{iso}} \right] \]

- 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

- Large number of biomarkers for neurodegeneration!

\[ S(q) = S_0 \int P(\kappa, \mu) \left[ f_1 e^{-bD_{a\mu}} + f_2 e^{-bD_{\mu} - b(D_{e} - D_{\mu})g} + f_{iso} e^{-bD_{iso}} \right] \]

- Axonal loss
- Axonal Beading
- Demyelination
- Neuroinflammation

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!!