Introduction to diffusion MRI
White-matter imaging

- Axons measure $\sim \mu m$ in width
- They group together in bundles that traverse the white matter
- We cannot image individual axons but we can image bundles with diffusion MRI
- Useful in studying neurodegenerative diseases, stroke, aging, development...

From the National Institute on Aging
From Gray's Anatomy: IX. Neurology
Diffusion in brain tissue

- Differentiate between tissues based on the diffusion (random motion) of water molecules within them

- Gray matter: Diffusion is unrestricted $\Rightarrow$ isotropic

- White matter: Diffusion is restricted $\Rightarrow$ anisotropic
Diffusion MRI

- Magnetic resonance imaging can provide “diffusion encoding”

- Magnetic field strength is varied by gradients in different directions

- Image intensity is attenuated depending on water diffusion in each direction

- Compare with baseline images to infer on diffusion process
How to represent diffusion

- At every voxel we want to know:
  - Is this in white matter?
  - If yes, what pathway(s) is it part of?
    - What is the orientation of diffusion?
    - What is the magnitude of diffusion?
- A grayscale image cannot capture all this!
Tensors

- One way to express the notion of direction is a tensor $D$

- A tensor is a $3 \times 3$ symmetric, positive-definite matrix:

$$D = \begin{bmatrix}
d_{11} & d_{12} & d_{13} \\
d_{12} & d_{22} & d_{23} \\
d_{13} & d_{23} & d_{33}
\end{bmatrix}$$

- $D$ is symmetric $3 \times 3 \implies$ It has 6 unique elements

- Suffices to estimate the upper (lower) triangular part
Eigenvalues & eigenvectors

- The matrix $D$ is positive-definite $\Rightarrow$
  - It has 3 real, positive eigenvalues $\lambda_1, \lambda_2, \lambda_3 > 0$.
  - It has 3 orthogonal eigenvectors $e_1, e_2, e_3$.

$$D = \lambda_1 e_1 \cdot e_1 + \lambda_2 e_2 \cdot e_2 + \lambda_3 e_3 \cdot e_3$$

$e_i = \begin{bmatrix} e_{ix} \\ e_{iy} \\ e_{iz} \end{bmatrix}$
Physical interpretation

- Eigenvectors express diffusion direction
- Eigenvalues express diffusion magnitude

Isotropic diffusion:
\[ \lambda_1 \approx \lambda_2 \approx \lambda_3 \]

Anisotropic diffusion:
\[ \lambda_1 \gg \lambda_2 \approx \lambda_3 \]

- One such ellipsoid at each voxel: Likelihood of water molecule displacements at that voxel
Diffusion tensor imaging (DTI)

**Image:**
An *intensity value* at each voxel

**Tensor map:**
A *tensor* at each voxel

Direction of eigenvector corresponding to greatest eigenvalue
Diffusion tensor imaging (DTI)

Image:
An intensity value at each voxel

Tensor map:
A tensor at each voxel

Direction of eigenvector corresponding to greatest eigenvalue
Red: L-R, Green: A-P, Blue: I-S
Summary measures

- Mean diffusivity (MD):
  Mean of the 3 eigenvalues
  \[
  MD(j) = \frac{[\lambda_1(j) + \lambda_2(j) + \lambda_3(j)]}{3}
  \]

- Fractional anisotropy (FA):
  Variance of the 3 eigenvalues, normalized so that \(0 \leq FA \leq 1\)
  \[
  FA(j)^2 = \frac{3}{2} \frac{[\lambda_1(j)-MD(j)]^2 + [\lambda_2(j)-MD(j)]^2 + [\lambda_3(j)-MD(j)]^2}{\lambda_1(j)^2 + \lambda_2(j)^2 + \lambda_3(j)^2}
  \]
More summary measures

- Axial diffusivity: Greatest of the 3 eigenvalues
  \[ AD(j) = \lambda_1(j) \]

- Radial diffusivity: Average of 2 lesser eigenvalues
  \[ RD(j) = \frac{\lambda_2(j) + \lambda_3(j)}{2} \]

- Inter-voxel coherence: Average angle b/w the major eigenvector at some voxel and the major eigenvector at the voxels around it
Beyond the tensor

• The tensor is an imperfect model: What if more than one major diffusion direction in the same voxel?

• High angular resolution diffusion imaging (HARDI): More complex models to capture more complex microarchitecture
  – Mixture of tensors [Tuch’02]
  – Higher-rank tensor [Frank’02, Özarslan’03]
  – Ball-and-stick [Behrens’03]
  – Orientation distribution function [Tuch’04]
  – Diffusion spectrum [Wedeen’05]
Models of diffusion

Diffusion spectrum (DSI):
Full distribution of orientation and magnitude

Orientation distribution function (Q-ball):
No magnitude info, only orientation

Ball-and-stick:
Orientation and magnitude for up to N anisotropic compartments

Tensor (DTI):
Single orientation and magnitude
Example: DTI vs. DSI

From Wedeen et al., Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging, MRM 2005
Data acquisition

- Remember: A tensor has six unique parameters

\[
D = \begin{bmatrix}
  d_{11} & d_{12} & d_{13} \\
  d_{12} & d_{22} & d_{23} \\
  d_{13} & d_{23} & d_{33}
\end{bmatrix}
\]

- To estimate six parameters at each voxel, must acquire at least six diffusion-weighted images.

- HARDI models have more parameters per voxel, so more images must be acquired.
**Choice 1: Gradient directions**

- True diffusion direction \( \parallel \) Applied gradient direction
  \( \Rightarrow \) Maximum attenuation
  \[ \text{Diffusion-encoding gradient } g \]
  \( \text{Displacement detected} \)

- True diffusion direction \( \perp \) Applied gradient direction
  \( \Rightarrow \) No attenuation
  \[ \text{Diffusion-encoding gradient } g \]
  \( \text{Displacement not detected} \)

- To capture all diffusion directions well, gradient directions should cover 3D space uniformly
  \[ \text{Diffusion-encoding gradient } g \]
  \( \text{Displacement partly detected} \)
How many directions?

- Acquiring data with more gradient directions leads to:
  - More reliable estimation of diffusion measures
  - Increased imaging time $\Rightarrow$ Subject discomfort, more susceptible to artifacts due to motion, respiration, etc.

- DTI:
  - Six directions is the minimum
  - Usually a few 10’s of directions
  - Diminishing returns after a certain number [Jones, 2004]

- HARDI/DSI:
  - Usually a few 100’s of directions
Choice 2: The b-value

- The b-value depends on acquisition parameters:
  \[ b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \]
  
  - \( \gamma \) the gyromagnetic ratio
  - \( G \) the strength of the diffusion-encoding gradient
  - \( \delta \) the duration of each diffusion-encoding pulse
  - \( \Delta \) the interval b/w diffusion-encoding pulses
How high b-value?

- Increasing the b-value leads to:
  - Increased contrast b/w areas of higher and lower diffusivity in principle
  - Decreased signal-to-noise ratio ⇒ Less reliable estimation of diffusion measures in practice

- DTI: $b \sim 1000 \text{ sec/mm}^2$
- HARDI/DSI: $b \sim 10,000 \text{ sec/mm}^2$

- Data can be acquired at multiple b-values for trade-off
- Repeat acquisition and average to increase signal-to-noise ratio
Looking at the data

A diffusion data set consists of:

- A set of non-diffusion-weighted a.k.a “baseline” a.k.a. “low-b” images (b-value = 0)
- A set of diffusion-weighted (DW) images acquired with different gradient directions $g_1, g_2, \ldots$ and b-value $>0$
- The diffusion-weighted images have lower intensity values
Distortions: Field inhomogeneities

• Causes:
  – **Scanner-dependent** (imperfections of main magnetic field)
  – **Subject-dependent** (changes in magnetic susceptibility in tissue/air interfaces)

• Results:
  – Signal loss in interface areas
  – Geometric distortions (warping) of the entire image
Distortions: Eddy currents

- **Cause:** Fast switching of diffusion-encoding gradients induces eddy currents in conducting components.

- **Eddy currents lead to residual gradients that shift the diffusion gradients.**

- **The shifts are direction-dependent, i.e., different for each DW image.**

- **Result:** Geometric distortions.

Data analysis steps

• Pre-process images to reduce distortions
  – Either register distorted DW images to an undistorted (non-DW) image
  – Or use information on distortions from separate scans (field map, residual gradients)

• Fit a diffusion model at every voxel
  – DTI, DSI, Q-ball, ...

• Do tractography to reconstruct pathways and/or

• Compute measures of anisotropy/diffusivity and compare them between populations
  – Voxel-based, ROI-based, or tract-based statistical analysis
Caution!

- The FA map or color map is not enough to check if your gradient table is correct - **display the tensor eigenvectors as lines**
- Corpus callosum on a coronal slice, cingulum on a sagittal slice
Tutorial

- Use `dt_recon` to prepare DWI data for a simple voxel-based analysis:
  - Calculate and display FA/MD/... maps
  - Intra-subject registration (individual DWI to individual T1)
  - Inter-subject registration (individual T1 to common template)
  - Use anatomical segmentation (aparc+aseg) as a brain mask for DWIs
  - Map all FA/MD/... volumes to common template to perform voxel-based group comparison