Mathematical and physical foundations of DTI

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White-matter imaging

- Axons measure ~µm in width
- They group together in bundles that form 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 Gray's Anatomy: IX. Neurology
From the National Institute on Aging
Diffusion in brain tissue

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

  - Gray matter: Diffusion is unrestricted ⇒ isotropic

  - White matter: Diffusion is restricted ⇒ 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” mathematically is by a tensor $D$
- A tensor is a 3x3 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 3x3 $\Rightarrow$ It has 6 unique elements
- Suffices to estimate the upper (lower) triangular part

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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 $e_1$, $e_2$, $e_3$.

\[ D = \lambda_1 e_1 \cdot e_1' + \lambda_2 e_2 \cdot e_2' + \lambda_3 e_3 \cdot e_3' \]

\[ e_1 = \begin{bmatrix} e_{1x} \\ e_{1y} \\ e_{1z} \end{bmatrix} \]
Physical interpretation

- Eigenvectors express diffusion direction
- Eigenvalues express diffusion magnitude

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

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

Image:
An intensity value at each voxel

Tensor map:
A tensor at each voxel

Direction of eigenvector corresponding to greatest eigenvalue
Diffusion tensor imaging

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
Scalar diffusion measures

Mean diffusivity (MD): Mean of the 3 eigenvalues

\[ \text{MD}(j) = \frac{\lambda_1(j) + \lambda_2(j) + \lambda_3(j)}{3} \]

Fractional anisotropy (FA): Variance of the 3 eigenvalues, normalized so that \(0 \leq \text{FA} \leq 1\)

\[ \text{FA}(j)^2 = \frac{3}{2} \left( \frac{\left(\lambda_1(j) - \text{MD}(j)\right)^2 + \left(\lambda_2(j) - \text{MD}(j)\right)^2 + \left(\lambda_3(j) - \text{MD}(j)\right)^2}{\lambda_1(j)^2 + \lambda_2(j)^2 + \lambda_3(j)^2} \right) \]
More summary measures

- **Axial diffusivity:** Greatest eigenvalue
  \[
  AD(j) = \lambda_1(j)
  \]

- **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 primary eigenvector at some voxel and the primary 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)
  - A mixture of the usual ("rank-2") tensors [Tuch’02]
  - A tensor of rank > 2 [Frank’02, Özarslan’03]
  - An orientation distribution function [Tuch’04]
  - A diffusion spectrum (DSI) [Wedeen’05]

- More parameters at each voxel ⇒ More data needed
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 a small number of 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

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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
Spin-echo MRI

- Use a 180° pulse to refocus spins:

- Apply a field gradient $G_y$ for location encoding

Measure transverse magnetization at each location -- depends on tissue properties ($T_1, T_2$)
**Diffusion-weighted MRI**

- Apply two gradient pulses:

  $90^\circ \quad G_y \quad 180^\circ \quad G_y \quad \text{acquisition}$

- **Case 1:** If spins are not diffusing

  $y = y_1, y_2 \quad \Rightarrow \quad y = y_1, y_2$

  $90^\circ \quad G_y \quad 180^\circ \quad G_y$

  No displacement in $y \Rightarrow$
  No dephasing $\Rightarrow$
  No net signal change

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Diffusion-weighted MRI

- Apply two gradient pulses:

\[ y = y_1, y_2 \rightarrow y = y_1 + \Delta y_1, y_2 + \Delta y_2 \]

- Case 2: If spins are diffusing

Displacement in \( y \) ⇒ Dephasing ⇒ Signal attenuation
Choice 1: Directions

- Diffusion direction || Applied gradient direction
  $\Rightarrow$ Maximum signal

- Diffusion direction $\perp$ Applied gradient direction
  $\Rightarrow$ No signal

- To capture all diffusion directions well, gradient directions should cover 3D space uniformly
How many directions?

- Acquiring more directions leads to:
  - More reliable estimation of tensors
  - 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 \cite{Jones2004}

- 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 between 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 tensors 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 same acquisition several times and average to increase signal-to-noise ratio
Looking at diffusion 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 $g_1, g_2, ...$ and b-value $> 0$
- The diffusion-weighted images have lower intensity values
From image to tensor

- $f_j^{b,g} = f_j^0 e^{-b\cdot D_j \cdot g}$
  where the $D_j$ the diffusion tensor at voxel $j$

- Design acquisition:
  - $b$ the diffusion-weighting factor
  - $g$ the diffusion-encoding gradient direction

- Reconstruct images from acquired data:
  - $f_j^{b,g}$ image acquired with diffusion-weighting factor $b$ and diffusion-encoding gradient direction $g$
  - $f_j^0$ “baseline” image acquired without diffusion-weighting ($b=0$)

- Estimate unknown diffusion tensor $D_j$
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
Eddy currents

- 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
- Results: geometric distortions

From Le Bihan et al., Artifacts and pitfalls in diffusion MRI, JMRI 2006
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