Understanding functional connectivity of the brain: Diffusion tensor magnetic resonance imaging

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Introduction

• The MRI experiment
• Diffusion weighted/tensor imaging
• Fiber orientation mapping and fiber tracking
• Applications at Cornell Medical College
• White matter fiber tracking in inferior brain regions and cervical spinal cord
• Fiber crossings and non-Gaussian diffusion
The MRI experiment
“There is nothing that nuclear spins will not do for you, as long as you treat them as human beings”

(Erwin L. Hahn 1949)
Larmor equation

\[ \omega_0 = \gamma B_0 \]
Constant gradients in object:

$$\omega \ (x,y,z) = \gamma \ (B_0 + \text{grad } B \ * \ (x,y,z))$$
Diffusion weighted imaging (DWI)
Bipolar pulse field gradient method

RF

90°

180°

Echo

te

Diffusion Gradients

G

Gz

δ

Δ

R. Watts 2004
Theory

- Rigorous approach:
  Add diffusion term to Bloch equations:
  Bloch-Torrey equation

- More convenient approach:
  Start with probability distribution of spins
  and use diffusion equation
1-D approach to keep the math simple:

\[ \delta = \text{length of diffusion gradients} \]

\[ \Delta = \text{duration of diffusion gradients} \]

\[ P(z) = \text{probability distribution} \]

\[ P(z_2, z_1, \Delta) = \text{propagator: probability that after a time } \Delta \text{ the spins are at } z_2 \text{ when they were at } z_1 \text{ before} \]
Assume $\delta \ll \Delta$, then

First gradient: dephasing \[ \Phi_1 = \gamma \int_0^\delta Gz_1 dt = \gamma Gz_1 \delta \]

2nd gradient: dephasing \[ \Phi_2 = \gamma \int_\Delta^{\Delta+\delta} Gz_2 dt = \gamma Gz_2 \delta \]

Net dephasing \[ \Phi_2 - \Phi_1 = \gamma G \delta (z_2 - z_1) \]

Taking into account the conditional probability (propagator) that after a time $\Delta$ the spins are at $z_2$ when they were at $z_1$ before, the signal is

\[ S = S_0 \int dz_1 P(z_1) \int \exp(i \gamma \delta G(z_2 - z_1)) P(z_2, z_1, \Delta) dz_2 \quad (*) \]
Isotropic diffusion process:

\[ \frac{\partial P(z_2, z_1, t)}{\partial t} = D \Delta P(z_2, z_1, t) \] 

\( P \) is Gaussian at \( t=\Delta \):

\[ P(z_2, z_1, \Delta) = \left(4\pi\Delta D\right)^{-1/2} \exp\left(-\frac{(z_2 - z_1)^2}{4\Delta D}\right) \]

[Can be checked by re-insertion into (**), homework]

Combining this with (*), and using Einstein’s law \(<z^2>=2Dt\), we obtain

\[ S \propto \exp\left(-\left(\gamma \delta G \right)^2 \Delta D\right) = \exp\left(-\left(\gamma \delta G \right)^2 <z^2> / 2\right) \]

[requires integration in the complex domain, not trivial, refer to integral table]
We only consider lumped parameter model

\[ S = S_0 \exp(-bD), \]

where \( b \) is the \( b \)-value, fixed in experiment by

- Stejskal-Tanner equation: \( b = (g\gamma\delta)^2(\Delta-\delta/3) \)

- Example:
  \[ b = 1000 \text{ s/mm}^2, \]
  \[ D = 0.003 \text{ mm}^2/\text{s in water at } 37^\circ \text{C}: \]
  Signal drops about 95% as compared with the
  \[ b = 0 \text{ (T2-weighted) image} \]
Diffusion tensor imaging
Anisotropic attenuation

- Remember: One dimensional lumped parameter model: \( S = S_0 \exp (-bD) \)
- Now: Directionality dependence
  \[ S = S_0 \exp (-b \mathbf{g}^T D \mathbf{g}), \]
  where \( \mathbf{g} \) is a vector containing the diffusion gradient direction,
  and \( D \) is the diffusion tensor
\[
\begin{align*}
S_0 & \quad S_1 & \quad S_2 & \quad S_3 & \quad S_4 & \quad S_5 & \quad S_6 \\
g_0 &= \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} & g_1 &= \begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix} & g_2 &= \begin{pmatrix} 0 \\ 1 \\ 1 \end{pmatrix} & g_3 &= \begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix} & g_4 &= \begin{pmatrix} 0 \\ 1 \\ -1 \end{pmatrix} & g_5 &= \begin{pmatrix} 1 \\ -1 \\ 0 \end{pmatrix} & g_6 &= \begin{pmatrix} -1 \\ 0 \\ 1 \end{pmatrix}
\end{align*}
\]
The diffusion tensor

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

Tensor derived from directional diffusivities (ADC’s)

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

Eigenvalues

Matrix of 3 eigenvectors

Jellison 2004
What is measured?

Restricted, permeable barrier, hindered diffusion?

D. Le Bihan 1995
How many measurements?

- One needs to measure the symmetric diffusion tensor and a $b=0$ weighted image
- $6+1=7$ measurements
- It has been shown that more = better: 6 icosahedral directions are not rotationally invariant (precision matrix contains 15 indep. parameters and depends on tensor itself)
Fiber orientation mapping
Some invariants (not depending on angle of coordinate system):

Mean diffusivity = $\frac{tr(D)}{3} = \frac{D_{xx} + D_{yy} + D_{zz}}{3}$

Fractional anisotropy = $\left[ \frac{3(\lambda_1 - \Lambda)^2 + (\lambda_2 - \Lambda)^2 + (\lambda_3 - \Lambda)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)} \right]^{1/2}$

with $\Lambda = (\lambda_1 + \lambda_2 + \lambda_3)/3$
Interpreting Diffusivity and FA

Diffusivity and FA help determine the number, size and myelination of fibers, whereas only FA gives information about directionality.

**Number of fibers**
- High Diffusivity, Low FA
- High FA, Low Diffusivity

**Myelination of fibers**
- High Diffusivity, Low FA
- High FA, Low Diffusivity

**Size of fibers**
- High Diffusivity, Low FA
- High FA, Low Diffusivity

**Directionality of Fibers**
- Low FA, Same Diffusivity
- High FA, Same Diffusivity
Directionality maps of normal brain and brain with tumor
White matter fiber tractography
Direction of greatest diffusion

R. Watts 2004, Mori et al, 1999
Fig 14. Corpus callosum, axial view.

A–D, Illustration (A), gross dissection (B), directional map (C), and tractogram (D). The largest WM fiber bundle, the corpus callosum connects corresponding areas of cortex between the hemispheres. Close to the midline, its fibers are primarily left-right oriented, resulting in its red appearance on this DTI map. However, callosal fibers fan out more laterally and intermingle with projection and association tracts, resulting in more complex color patterns.
Applications at WMC

- Presurgical planning in epilepsy/tumor patients (Neurosurgery / Radiology)
- Quantification of white matter lesions in traumatic brain injury (Brain Trauma Foundation / Sackler Institute for Developmental Psychobiology)
- Case studies with the Department of Neurology and Neuroscience
Presurgical planning

Neurosurgery/Radiology at NYPH (tumor & epileptic surgery) and CBIC

Patient with tumor infiltrating brain tissue, block design rhyming paradigm, ca 100 repetitions a 2s, 0.63 < R < 0.73, overlaid onto anatomical image
Fiber tracking in inferior brain regions and cervical spine

Geometric distortions

\[ y_+ = y^+ \Delta y \]

\[ y_- = y^- \Delta y \]

Phase direction
Intensity distortions

\[ \int_{0}^{y_+} I_+(y) \, dy_+ = \int_{0}^{y_-} I_-(y) \, dy_- \]
Correction:
Acquire both gradient directions and merge images

Geometry: \( y = (y_+ + y_-)/2 \)
Intensity: \( I = 2I_+I_-/(I_+ + I_-) \)

Andersson, Skare, Ashburner, Neuroimage 20, 870 (2003)
Morgan et al., JMRI 19, 499 (2004)
Geometric distortions

$I_+$  $I_-$  Corrected  Anatomical reference

(All images scaled to individual full intensity range)
Shift for distortion correction

Factor for intensity correction

Phase direction
DTI with reversed gradients

Example: Cerebellum

- pontine crossing tract
- middle cerebellar peduncle
pontine
crossing tract

middle cerebellar
peduncle
Application to inferior brain regions and spinal cord

$I_+$  $I_-$  Corrected

4 channel phased array torso coil
Fiber crossings and non-Gaussian diffusion
q-space imaging

Resolves intravoxel orientational heterogeneity
(crossing / branching / kissing fibers)
Remember:

\[ S = S_0 \int dz_1 P(z_1) \int \exp(i \gamma \delta G(z_2 - z_1))P(z_2, z_1, \Delta)dz_2 \]

Define \( q = \gamma \delta G \) and \( z = z_2 - z_1 \) to get

\[ S(q, \Delta) = S_0 \int \exp(i q z)P(z, \Delta)dz \]

Therefore, the signal \( S \) is again the Fourier-transform of a density \( P \).

By inversion, one can measure \( P \).

This requires lots of \( q \)-values, i.e., one needs to vary timing \( \delta \) or gradient strength \( G \).
Q-ball imaging

- Drastically reduced scan time
- HARDI-sequence (High angular resolution diffusion imaging)
- Spherically sampled data
- Postprocessing (Funk Radon transform)
The orientation distribution function (ODF)

\[ P(r) = F[S(q)] \quad (r \text{ and } q \text{ are reciprocal vectors}) \]

ODF:
\[ \psi(u) = \frac{1}{Z} \int_0^\infty P(ru)dr \]
Q-Ball imaging: Sample only on a sphere, not on 3D volume:

Funk-Radon transform
= extension of planar Radon transform to the sphere
= transform from sphere to sphere
= line integral along equator of sphere, for each vector on sphere

\[ w = \text{unit direction vector} \]
\[ f(w) = \text{scalar function on sphere} \]
\[ u = \text{direction of interest} \]

\[ G[f(w)](u) = \int f(w) \delta(w'u) dw \]
Extended FRT: Maps from 3D Cartesian space to sphere

\( \mathbf{x} = \) unit direction vector
\( r = \) particular radius at which FRT is evaluated
\( f(\mathbf{x}) = \) scalar function in 3D Cartesian space

\[
G_r = G[f(w)](u, r) = \int f(\mathbf{x}) \delta(\mathbf{x}'u) \delta(|\mathbf{x}| - r) d\mathbf{x}
\]
Theorem (D. S. Tuch):
The extended FRT of the diffusion signal gives a strong
approximation to the ODF, i.e.,

$$\psi(u) \approx \frac{1}{Z} G_r[S(q)]$$  (u and q are reciprocal vectors)

The sum of the diffusion signal over an equator approximately
gives the diffusion probability in the direction normal to the
plane of the equator.
Central element: The diffusion orientation distribution function (ODF)

(a) Diffusion signal sampled on fivefold tessellated icosahedron (m 252). The signal intensity is indicated by the size and color (white yellow red) of the dots on the sphere.
(b) Regridding of diffusion signal onto set of equators around vertices of fivefold tessellated dodecahedron.
(c) Diffusion ODF calculated using FRT.
(d) Color-coded spherical polar plot rendering of ODF.
(e) Min–max normalized ODF. (D. S. Tuch 2004)
ODF map of caudal midbrain

cp, cerebral peduncle;
ctt, central tegmental tract;
fp, frontopontine tract;
rst, reticulospinal tract;
scp, superior cerebellar peduncle;
sn, substantia nigra;
xscp, crossing of the superior cerebellar peduncle.
Mathematical/statistical problems

- How to reduce # of measurements?
- How to smooth tensor fields? (bias-variance optimum?)
- Can one learn more about tissue properties than fiber directions from ODF?
- Global fiber tracking algorithms?
- Do proper bootstrapping?