Mostly diffusion and tractography

Professor Brian Wandell
Center for Cognitive and Neurobiological Imaging (CNI)
Neurosciences Institute
Department of Psychology
Stanford University
NEUROSCIENCE

The Neuron Doctrine, Redux

Theodore H. Bullock, Michael V. L. Bennett, Daniel Johnston, Robert Josephson, Eve Marder, R. Douglas Fields

After a century, neuroscientists are rethinking the Neuron Doctrine, the fundamental principle of neuroscience. This proposition, developed primarily by the great Spanish anatomist and Nobel laureate Santiago Ramón y Cajal, holds that a neuron is an anatomically and synaptic switch regulating information flow through neural circuits. The synaptic cleft went unseen until a half-century later, when in 1954 the electron microscope provided convincing evidence that essentially refuted the earlier “reticular” view of a nerve fiber web (1).
Human fascicles (tracts)

- There are many long-range connections
- These connections are not passive – they change their properties in response to use
- A system with active wires
Human fascicles (tracts)

- There are many long-range connections
- These connections are not passive – they change their properties in response to use
- A system with active wires

Courtesy Professor Ugur Ture
**Types of Glia**

**Microglia** (20%) scavenging for infections, plaques, damaged neurons; regulating healthy neurons

**Astrocytes** bring nutrients to neurons as well as surround and regulate synapses. (50%)

**Oligodendrocytes** produce myelin that insulates axons.

**Schwann cells** perform myelination duties in the body’s peripheral nervous system.

Image from
An oligodendrocyte in the white matter

Electron micrograph showing the myelin sheath from an oligodendrocyte wrapping a single axons (cross-section)

Note the scale bar
Motor skill learning requires active central myelination

Ian A. McKenzie,¹* David Ohayon,¹* Huiliang Li,¹ Joana Paes de Faria,¹† Ben Emery,² Koujiro Tohyama,³ William D. Richardson¹‡

Myelin-forming oligodendrocytes (OLs) are formed continuously in the healthy adult brain. In this work, we study the function of these late-forming cells and the myelin they produce. Learning a new motor skill (such as juggling) alters the structure of the brain’s white matter, which contains many OLs, suggesting that late-born OLs might contribute to motor learning. Consistent with this idea, we show that production of newly formed OLs is briefly accelerated in mice that learn a new skill (running on a “complex wheel” with irregularly spaced rungs). By genetically manipulating the transcription factor myelin regulatory factor in OL precursors, we blocked production of new OLs during adulthood without affecting preexisting OLs or myelin. This prevented the mice from mastering the complex wheel. Thus, generation of new OLs and myelin is important for learning motor skills.
Free induction decay
The free induction decay experiment

Beaker of water in a perfectly uniform magnetic field
The free induction decay experiment

Beaker of water in a perfectly uniform magnetic field

RF signal excites spins

Coil

Bloch

Purcell
The free induction decay experiment

Beaker of water in a perfectly uniform magnetic field

RF signal excites spins

Coil

Measured voltage signal

Bloch

Purcell
The FID signal depends on the B1 duration

How can we explain this?
Source of the MR signal
Hydrogen nuclei (spins, protons)

An average person who weighs 150 lbs. contains approximately $5 \times 10^{27}$ hydrogen nuclei (spins);
The FID signal: quantal description

In the presence of the Bo field, the spins generally align with the field (Z-direction)

But they occupy one of two states: Parallel and anti-parallel

(mrTutMR explains how to calculate the percentage in each state)
The **bulk magnetization** is the sum of the spins.

There are lots of spins in each voxel, and we measure the sum of these.

There is no xy-plane direction preference.

There is a z-direction preference because of the Bo field.
Precession

When excited by an RF pulse, the bulk magnetization is modeled as spinning around the z-axis, like a top.

It has spin rate (frequency), an angle and a vector length.
FID: The bulk (net) magnetization metaphor

An RF receive-coil measures the precessing bulk magnetization.

The receive coil can be the same or different as the transmit (excite) coil.
MR signals

Spin-lattice interactions (T1)
Spin-spin interactions (T2)
There are multiple mechanisms that can influence the bulk magnetization.

- **High energy**

- **Low energy**

Anti-parallel spins give up energy to macromolecules (lattice) and return to lower parallel state ($T_1$).

The spins dephase ($T_{2*}$).

The spins move (diffusion).
The bulk magnetization is the sum of two components

Precessing spin = Longitudinal component + Transverse component
Longitudinal relaxation (T1)

Suppose we apply a pulse that flips the bulk magnetization 180 deg. The longitudinal recovery follows an exponential time course, with a constant called T1.

\[ M_z = M_0 \left(1 - e^{-\frac{t}{T_1}}\right) \]
Longitudinal relaxation rate depends on your neighborhood

The T1 values of water located in different brain tissue vary. At 1.5T a good time to measure for contrast is around 0.8-1.2 sec following the RF pulse.

\[ M_z = M_0 \left(1 - e^{-\frac{t}{T_1}}\right) \]

Gray (T1,G): 0.88 s
White (T1,W): 0.65 s
Analyzing spin-lattice exchange (T1)

Energy from anti-parallel spins is absorbed by the macromolecules in the environment (lattice)

How efficient is this energy exchange?

I am glad you asked.
Analyzing spin-lattice exchange (T1) (Mezer et al., 2014)

Spin-lattice energy exchange rate (T1) depends on

- How many macromolecules are in the lattice
- The type of macromolecules

If you could measure this in the brain, these are pretty good things to know (noninvasively)
The T1-contrast distinguishes gray and white matter.

T1-weighted images are typically used for understanding gray matter atrophy, or ventricular enlargement.
The $T_2^*$ signal and functional MRI
Blood Oxygen Level Dependent (BOLD) signals
Transverse magnetization

Field-free space  B0 field  Following RF Pulse

RF pulse
Transverse relaxation: $T_2$ (and $T_2^*$)

Bulk transverse magnetization follows an exponential recovery with a time constant called $T_2$

\[ M_{xy} = M_0 e^{-\frac{t}{T_2}} \]

Red arrows denote individual spins

200 ms
The T2 time constant is much shorter than T1. Consider the practical aspects.

The equation for transverse magnetization decay is:

$$M_{xy} = M_0 e^{-\frac{t}{T_2}}$$

Selection of delay for T2 contrast
(After Huettel et al., Functional Magnetic Resonance Imaging)
Blood oxygenation effects $T_2$ but not $T_1$
Blood oxygenation increase is localized

Control state

Heart lung

Arterial: 1
Venous: 60 → 40
OEF: 0.4

Active state

Heart lung

Arterial: 1.3
Venous: 63 → 37
OEF: 0.4/1.2

Sokolow Raichle Fox
Human eccentricity mapping with fMRI
(Engel et al., 1994, 1997; Sereno; DeYoe; Others)
More than twenty visual field maps

Wandell, Dumoulin, Brewer (2007) *Neuron*

Wandell and Winawer (2011) *Vision Research*

Wang et al. (2014) *Cerebral Cortex*

- Tile the occipital lobe
- Extend into IPS and VOT
- Response properties differ
Diffusion weighted imaging tutorial

- Measuring the diffusion signal

Bob Dougherty
Non-diffusion MR image

Dark means large signal attenuation
High ADC

$b = 0$
Diffusion weighting: Directions

Dark means large signal attenuation
High ADC

$b = 800$
Diffusion weighting: Directions

Dark means large signal attenuation
High ADC

$b = 800$
Protons Precessing in Phase
Diffusion Weighting: First Pulse

Gradient over space

- Slower (local field is lower)
- Faster (local field is higher)
Diffusion Weighting: Second Pulse

Gradient over space

Faster
(local field is higher)

Slower
(local field is lower)
Reduced signal from spin dephasing

E. O. Stejskal and J. E. Tanner (1965)

Signal attenuation = \( \exp(-b \times \text{ADC}) \)

Signal from spins that diffused is lower because the spins are not aligned (incoherent)
Pulse sequences for diffusion-weighted imaging
(Huettel et al.)
Diffusion orientation distribution function (ODF)

\[ S(\theta) = S_0 \ e^{-bD(\theta)} \]

The measured diffusion signal in a direction, \( \theta \), is related to the apparent diffusion coefficient in that direction, \( D(\theta) \).
Modeling the diffusion signal

- The diffusion tensor model (DTM)
- The ball-and-stick model (SFM)
Diffusion tensor model (DTM)

Predicts the **voxel diffusion signal** with a phenomenological equation, motivated by Gaussian diffusion (Basser, Pierpaoli, 1996)

\[
S(\theta) = S_0 \ e^{-bD(\theta)} \quad \leftarrow \quad D(\theta) = \theta^t Q \theta
\]

\[
Q = A^t A
\]
Diffusion tensor model fits

Signal re: b=0
**Summary measures of the DTM**
(Basser & Pierpaoli, 1996)

- **Axial diffusivity (AD)**
  \[ \lambda_1 \]

- **Radial diffusivity (RD)**
  \[ \frac{\lambda_2 + \lambda_3}{2} \]

- **Mean diffusivity (MD)**
  \[ \bar{\lambda} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \]

- **Fractional anisotropy**
  \[ \sqrt{\frac{3}{2}} \frac{1}{\lambda_1} \sqrt{\left(\lambda_1 - \bar{\lambda}\right)^2 + \left(\lambda_2 - \bar{\lambda}\right)^2 + \left(\lambda_3 - \bar{\lambda}\right)^2} \]
  \[ \frac{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \]
DTI analyzes white matter structure

Mean Diffusivity

Anisotropy

Principal Direction

MD (um^2/ms)

Fractional anisotropy
The sparse fascicle model (SFM)  
Frank (2002), Behrens et al. (2003)

Predicts the diffusion signal with an isotropic diffusion term \textbf{(ball)} plus a weighted sum of anisotropic terms \textbf{(sticks)} that are meant to summarize oriented fibers.

\[ S(\theta) = w_0 D_0 + \sum_f w_f e^{-bD_f(\theta)} \]

- \textbf{Ball} \quad \text{isotropic}
- \textbf{Sticks} \quad \text{weights}

\textbf{fascicles}
From diffusion data to fiber orientations

Orientation distribution function (ODF)

Fiber orientation distribution (FOD)

ARD/Probtrackx (Behrens et al., 2007)

Constrained spherical deconvolution (CSD) (Tournier et al., 2007)

Sparse Fascicle Model (Rokem, 2015)

Others
Sparse fascicle model (SFM) (Rokem et al. 2015)

SFM uses a sparseness constraint on the sticks (fascicles). Related to mrTrix, but no intermediate spherical harmonics.

Signal attenuation

0.75
0.5
0.25
Evaluating models using cross-validation (Rokem et al., 2015)
Evaluating models using cross-validation (Rokem et al., 2015)

Low b-value

DTM  Data 1  Data 2  SFM

$b=1000$
Evaluating models using cross-validation (Rokem et al., 2015)
Evaluating models using cross-validation (Rokem et al., 2015)

Two data sets, one b-value, many directions, same session

Fit the model to these data

Data set 1

Measure prediction error with these data

Data set 2

(In the old days, we used to call this testing the model on an independent data set)
DTM predicts the independent data more accurately than assuming replication.
The SFM is slightly better (whole brain analysis)

Both are very good, and just short of best possible performance

\[ \text{Best possible} = \frac{1}{\sqrt{2}} \]
SFM outperforms DTM in ~10% of the voxels (b = 4000)
In a few regions, the SFM outperforms DTM ~10% of the voxels ($b = 4000$).

**Centrum semiovale**

**Optic radiation**

SFM
Summary

If your goal is to provide a mathematical model of the diffusion signal in each voxel then:

• DTM and SFM are both excellent descriptions of the diffusion data; much better than test-retest reliability

• The summary statistics of the DTM (e.g., FA, RD, AD, MD) are useful for voxel-wise experimental comparisons

• In a few brain regions the SFM is better

• **BUT:** The principal diffusion direction of the DTM is not a good estimate of local axonal direction
Moseley, Cohen et al. 1990 Radiology
Origins of white matter diffusion

Le Bihan, Mangin, Poupon et al. 2001 Journal of Magnetic Resonance Imaging
A nice early review

Basser et al., 1994 – Biophysical Journal
Good opening sentence: “This paper describes a new NMR imaging modality-MR diffusion tensor imaging.”

Basser and Pierpaoli – 1996,
Journal of Magnetic Resonance Imaging
Introduces FA and univariate statistics for DTM

Klingberg et al., 2000, Neuron
First application to human cognition
Linear Fascicle Evaluation

- Tractography
- Linear Fascicle Evaluation (LiFE)

Franco Pestilli
Hiromasa Takemura
Jason Yeatman
Tractography

Use the local (voxel) diffusion measurements to estimate white matter tracts

Diffusion data are surfaces
Tractography limitations
Estimate fascicles from diffusion data
Different tractography methods and parameters make different predictions.
Linear Fascicle Evaluation (LiFE)
Predict diffusion data from fascicles

Compare how well different models and algorithms do
2. Stages of LiFE
Set up diffusion predictions for each voxel

\[ S(\theta) = w_0 D_0 + \sum_f w_f e^{-bD_f(\theta)} \]

In each voxel use the conventional fascicle diffusion model to predict the diffusion signal from the candidate connectome.
3. Stages of Life

Solve for the fascicle weights

Diffusion signal, \( S(\theta) \)

\[
\begin{pmatrix}
  v_1 \\
  v_2 \\
  \vdots \\
  v_N
\end{pmatrix}
\]

Each column is the prediction of a fascicle

Each entry is the fascicle contribution for a voxel in a direction

\( w_f \)

Solve for a non-negative weight for each fascicle (least-squares)

\( 10^7 \times 10^6 \)
3. Stages of Life
Solve for the fascicle weights

Diffusion signal, $S(\theta)$

\[
\begin{bmatrix}
S(\theta) \\
v1 \\
v2 \\
vN
\end{bmatrix}
=\begin{bmatrix}
w_f
\end{bmatrix}
\]

Depending on voxel size, number of directions, and so forth, about 80% of typical tractography weights are zero.

Each column is the prediction of a fascicle
Each entry is the fascicle contribution for a voxel in a direction

$10^7 \times 10^6$
4. Stages of LiFE
Eliminate zero weight fibers (false alarms)

Candidate connectome: Many many fascicles

Optimized connectome

Solving a system of linear equations
(non-negative least-squares)
5. Stages of LiFE
Predict diffusion signal

Optimized connectome and weights

Prediction

Big matrix multiplication
6. Stages of LiFE
Cross-validation error between predicted and 2\textsuperscript{nd} data set

Prediction

Second data set

Subtraction and root mean square error
The optimized connectome predicts diffusion data slightly better than test-retest reliability (b=2000 data shown)

White matter volume (%)

150 directions (N=3)

96 directions (N=6)

$R_{\text{rmse}} = \text{Ratio of model error to reliability error}$
Methods for hypothesis testing
Path-neighborhood (Wedeen)
Earth Mover’s Distance on error distribution (Guibas)
### Partial list of tractography and visualization software

<table>
<thead>
<tr>
<th>Software</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI studio</td>
<td><a href="http://www.mristudio.org">http://www.mristudio.org</a></td>
</tr>
<tr>
<td>FiberTools</td>
<td>(Reisert)</td>
</tr>
<tr>
<td>FMRIB</td>
<td></td>
</tr>
<tr>
<td>PROBTRACK</td>
<td><a href="http://users.fmrib.ox.ac.uk/~behrens/fdt_docs/fdt_probtrack.html">http://users.fmrib.ox.ac.uk/~behrens/fdt_docs/fdt_probtrack.html</a></td>
</tr>
<tr>
<td>Tract Based Spatial Statistics</td>
<td><a href="http://users.fmrib.ox.ac.uk/fsl/fslwiki/TBSS">http://users.fmrib.ox.ac.uk/fsl/fslwiki/TBSS</a></td>
</tr>
<tr>
<td>TrackVis</td>
<td><a href="http://www.trackvis.org">http://www.trackvis.org</a></td>
</tr>
<tr>
<td>Camino</td>
<td><a href="http://cmic.cs.ucl.ac.uk/camino/">http://cmic.cs.ucl.ac.uk/camino/</a></td>
</tr>
<tr>
<td>mrDiffusion</td>
<td><a href="https://github.com/vistalab/vistasoft">https://github.com/vistalab/vistasoft</a></td>
</tr>
</tbody>
</table>

Central source: [http://www.nitrc.org/](http://www.nitrc.org/)
Building a model of the circuit for seeing words

- White matter tissue properties predict how well children can quickly recognize words

Michal Ben-Shachar  Jason Yeatman  Andreas Rauschecker
Locating reading circuits and maps

VWFA - essential for reading, but not unique to reading
The cortical reading network

Learning to See Words
Seeing the white matter reading tracts
(Yeatman et al., 2011)
Intermediate summary

- Reading requires quickly and accurately identifying forms (seeing words)

- The cortex learns to do this using the VWFA, a region located in ventral temporal cortex, amidst a set of visual field maps

- White matter development (arcuate, ILF) predicts reading development
Data management for reproducible research

Prof. Brian Wandell

Director
Stanford Center for Cognitive and Neurobiological Imaging (CNI)

Deputy Director
Stanford Neurosciences Institute (SNI)

Disclosure: Flywheel.io
Replication is often impractical

- Neuroscience has entered an era of 'big science' in which replication is impractical

  - **Example 1:** Analyses of 320 subjects with autism, each measured using MRI, at 3 time points over four years
  - **Example 2:** Structural MRI of 50 illiterate adults flown in from the Amazon rain forest
Reproducible research is within reach

**Replication** means obtaining the data again, usually by independent investigators using similar methods, equipment and protocols.

Many big science experiments are too expensive and time-consuming to replicate.

**Reproducible** means that starting with the data gathered by the scientists, we can confirm the derived results (e.g., statistics, summary curves and images, numerical relationships).

Proper tools enable scientists to achieve reproducibility much more often.
Computational reproducibility is not an afterthought—it is something that must be designed into a project from the beginning. **One does need to develop a whole set of programming and research disciplines** with the end result in mind and stick with them.
Scientific data management tools

• Reproducible research requires scientific data management tools Disclosure: Flywheel.io

• These should be an expected part of any important scientific experiment

• For reproducible research the tools should simplify both
  - Data sharing
  - Computational sharing
Personalized neuroscience

An opportunity that derives from a combination of data management and the quest for reproducible research
A motivating example

- A subject or patient with a retinal eye disease comes to the lab
- We want to know the consequences of retinal degeneration on cortical structures
A motivation example

- Measure the subject’s visual white matter and secure the data!

- Use validated computational tools for quality assurance

- Use open-source software for tract identification, tissue estimation and comparison with other populations
Use databases to find controls

The expectation based on data acquired and stored in the SDM
Compare your subject with the distribution and think

**Control ±2SD**

**LHON**
Leber’s hereditary optical neuropathy

This subject compared to the expectation
Each subject with the disease has some variation and we would like to know, and track each one over time.
We are building computational tools that automate the comparison of individual patients with groups of matched controls.
The Project on Scientific Transparency [PoST] is a multi-site collaborative effort that aims to revolutionize the way that neuroscience imaging research is done. By developing simple tools that permit investigators – from many disciplines and institutions – to share data and analytical methods we hope to increase scientific transparency and data exchange.
• Maps and models

• White matter methods

• Reading

Thanks to NIH, NSF, Simons, Weston-Havens, Wallenberg Foundation