An introduction to processing diffusion weighted images

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Overview

- What are the neuroscience issues
- Diffusion: Within the voxel
- Diffusion: Across voxels (tractography)
- Applications
Goals

• Why study the human brain
• Why study axons and glia
• Neuroscience for society
The human brain

Image adapted from J. Horton

human
macaque
mouse
0.5 g 100 g 1500 g
Human brain characteristics

- Neuron cell bodies in cortex
- Long-range axons in white matter
- A system with active wires that develop and whose properties correlate with visual skills (e.g., sight word efficiency)

Courtesy Professor Ugur Ture
MYELIN FORMATION

Long axons insulated with myelin carry signals between neurons faster than unmyelinated axons. Oligodendrocyte cells manufacture the fatty membrane and wrap the axon with 10 to 150 layers. Different factors can stimulate the myelination process; often astrocyte cells "listen in" on the signals traveling along axons and relay chemical messages to the oligodendrocytes. Below, a microscope shows axons in red being wrapped.
An oligodendrocyte in the white matter

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

Note the scale bar
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
Wake, et al. Trends in Neurosciences
Volume 36, Issue 4, April 2013
Neuroscience is broadening its view

Bullock, Bennett, Johnston, Josephson, Marder, Fields
Science, 2005

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 functionally distinct cell body, rather than a simple all-or-nothing electrical switch as previously believed. The synaptic cleft was long thought to be a barrier between nerve cells, but it is now known that it is actually a dynamic interface that plays a crucial role in the regulation of neural activity.

Synaptic activity is now recognized as a key player in information processing and neural computation. The discovery of new forms of synaptic plasticity, such as long-term potentiation and depression, has changed our understanding of how neural circuits are formed and modified by experience. These processes are thought to underlie learning and memory, as well as many other aspects of brain function.

Today, the Neuron Doctrine is undergoing a renaissance as we continue to uncover the complexity and diversity of neuronal interactions. The field of neuroscience is expanding its horizons, and we are beginning to appreciate the intricate web of connections that forms the basis of the nervous system. The study of the Neuron Doctrine has led to a deeper understanding of the brain and its role in shaping behavior and cognition.
Diffusion imaging is providing new understanding


Abstract

Using diffusion tensor imaging (DTI), an MRI-based framework, we examined subjects before and after a spatial learning and memory task. Microstructural changes (as reflected by DTI measures) of limbic system structures (hippocampus and parahippocampus) were significant after only 2 hr of training. This observation was also found in a supporting rat study. We conclude that cellular rearrangement of neural tissue can be detected by DTI, and that this modality may allow neuroplasticity to be localized over short timescales.
Neuroscience for Society
Wandell and Yeatman, CONB, 2013

- Some behaviors, such as psychological tests of performance during brief trials, may be best understood by measuring synaptic activity or spikes.

- Other important behaviors - learning to read or to regulate emotions - take place over longer time periods. These skills may depend on biological processes such as cell development, growth and pruning of dendritic arbors, the proliferation and activity of glia.

- Scientists need to account for the entire range of processes to understand circuit function in health and disease.
White matter reading tracts
(Wandell and Yeatman, Annual Review, 2013)
Diffusion weighted terminology

- Apparent diffusion coefficients
- Parallel and perpendicular diffusivity
- Diffusion images
Diffusion probes brain microscopic structure

Parallel diffusivity ($\mu m^2/ms$)

Given a b-value and gradient direction, we measure **Apparent Diffusion Coefficient (ADC)**

Along the principal direction of axons, within the cytoskeleton, water displacement is large and signal is low

Equivalent names
- Parallel, axial, longitudinal, principal diffusion direction (PDD)

5 um

Optic nerve fibres
George Bartzokis
Diffusion probes brain microscopic structure

Perpendicular diffusivity (μm²/ms)

Perpendicular to the principal direction of axons, bi-lipid membranes limit water displacement so the signal is higher

Other names
- Perpendicular, radial, transverse

Optic nerve fibres
George Bartzokis

5 um
Non-diffusion MR image

Dark means large signal attenuation
High ADC
Diffusion weighting: Directions

Dark means large signal attenuation
High ADC

b = 800
Diffusion weighting: Directions

Dark means large signal attenuation
High ADC
Diffusion-weighting:
b-values

$b=1000$
Diffusion-weighting: 
b-values

b=2000
Diffusion-weighting: $b=4000$

$b$-values
Modeling the diffusion signal

- The diffusion signal data in 3-space
- The diffusion tensor model (DTM)
- The ball-and-stick model (SFM)
Diffusion data analysis

High angular resolution diffusion imaging (HARDI)

MRI diffusion signal

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

The measured diffusion signal in a direction, \( \theta \), is related to the apparent diffusion coefficient in that direction, \( D(\theta) \).
Diffusion data analysis
High angular resolution diffusion imaging (HARDI)

MRI diffusion signal

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

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

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

Model the diffusion term using a quadratic form

\[ D(\theta) = \theta^t Q \theta \]
\[ Q = A^t A \]

Stejskal-Tanner

Basser, Pierpaoli

One way to model the signal is state a formula for diffusion in different directions (Gaussian)
Diffusion tensor model

Signal re: $b=0$
The ball and stick model

Predicts the **voxel diffusion signal** with a model of the sum of fascicles plus isotropic diffusion

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

Larry Frank (2002)
Tim Behrens (2003)
The ball and stick model

Predicts the **voxel diffusion signal** with a model of the sum of fascicles plus isotropic diffusion
Sparse fascicle model (SFM)

Ariel Rokem and I call it this because
- BS model seemed like a bad idea
- We estimate the fascicles using a linear method with a sparseness constraint

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

Same idea as in spherical deconvolution; different estimation method
Summary

• DTM is a phenomenological description of the diffusion signal (like spherical harmonics)

• The ball and stick model (SFM) uses concepts that are evoke biological structures
References

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
Evaluating diffusion models within the voxel

- How do you evaluate the fit?
- Comparing DTM and SFM
Diffusion tensor model (DTM)

Predicts the **voxel diffusion signal** with a **phenomenological** equation, motivated by **Gaussian** diffusion.
Cross-validation assessment

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

Best possible = $\frac{1}{\sqrt{2}}$
DTM errors are localized in a few regions \((b = 4000)\)

Centrum semiovale

Optic radiation
SFM outperforms DTM in these regions \((b = 4000)\)

- **Centrum semiovale**
- **Optic radiation**

**Model**
- Better
- Worse
Summary

- We have excellent quantitative models of the diffusion signal within a voxel
- The model fits are more reliable predictors of independent measurements than the data; use them for tractography
- People should stop whining about diffusion data.
References


Recent directions

• Integrating data from multiple b-values (Diffusion spectrum imaging)

• Estimating properties of axons

• Much more in the pipeline
Summary diffusion measures

• Once you have a model, it is natural to produce summary measures

• For the DTM, the Principal diffusion direction (PDD) and fractional anisotropy (comparing eigenvalues) have been convenient

BEWARE

• For the SFM (ball and stick), no standard has emerged but Dell’Aqua et al. (2007) have proposed useful univariate measures
Models and data replication

DTM  Data 1  Data 2  SFM

Low b-value

\[ b=1000 \]
Models and data replication

DTM  Data 1  Data 2  SFM

$b=1000$

Higher $b$-value

$b=2000$
Once you think about varying b-level, go nuts people. Ask yourself: What are the implications of varying diffusion time and b-level?

Assaf and colleagues fit a model based on assumptions about the intra-axonal diffusion of water.
Tractography tools

• Tract generation
  • Deterministic and DTM
  • Probabilistic and ball/stick
• Tract scoring
• Tract labeling
Tract generation and visualization packages

MRI studio - http://www.mristudio.org

FMRIB
- PROBTRACK
  http://users.fmrib.ox.ac.uk/~behrens/fdt_docs/fdt_probtrack.html
- Tract Based Spatial Statistics
  http://users.fmrib.ox.ac.uk/fsl/fslwiki/TBSS

TrackVis - http://www.trackvis.org

DSI studio - http://dsi-studio.labsolver.org/


Exploredti - http://www.exploredti.com/

Camino - http://cmic.cs.ucl.ac.uk/camino/

http://www.nitrc.org/
Central source
Early deterministic tractography

- Summarize each voxel with a DTM
- Follow voxels (bi-directional) in PDD direction
- Stopping rule (e.g., tensor becomes round)
- Rinse and repeat
- Significant implementation differences
Tracking fibers in the human brain (Mori et al., 1999; Conturo et al, 1999)

- Summarize each voxel with a DTM
- Follow voxels (bi-directional) in PDD direction
- Stopping rule (e.g., tensor becomes round)
- Rinse and repeat
- Significant implementation differences
Limitations of deterministic methods

- Don’t account for noise and uncertainty

- Greedy: Uses the local (voxel) diffusion measurements to estimate global white matter tracts; never measures the whole solution

- Validation
• Use the ball and stick model for local diffusion
• Repeatedly trace a path, choosing directions at each step from a probability distribution of angles determined by local diffusion data
• Stopping rule: No strong direction in local data

(Fig 1a)
• Given a seed in region A, evaluate connection strength to region B as

The number of fibers between the regions A and B divided by the total number of fibers from A

See Sherbondy et al., 2008A for a discussion of the implications of this rule for symmetry and independence

(Fig 1a)
Separating tract discovery and evaluation
(Contrack, Sherbondy et al., 2008A,B)
Tract identification

Reproducibility of quantitative tractography methods applied to cerebral white matter

Setsu Wakana, Arvind Caprihan, Martina M. Panzenboeck, James H. Fallon, Michele Perry, Randy L. Gollub, Kegang Hua, Jiangyang Zhang, Hangyi Jiang, Prachi Dubey, Ari Blitz, Peter van Zijl, and Susumu Mori

Dougherty et al., 2007, PNAS
Tract segmentation and identification

Automated Fiber Quantification
Yeatman et al., 2012

TRACULA
Yendiki A et al., 2011

https://github.com/jyeatman/AFQ
https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula
Summary

• There are high quality tools for tract generation

• Visualization is important for understanding the tracts

• The tool set is evolving and expanding to include segmentation, and measurements along tracts (tractometry)
Tractography validation
(Pestilli et al., under review)

Linear iterative fascicle evaluation
(LIFE)
Tractography algorithms differ
Mrtrix, L=2, deterministic
Tractography algorithms differ
Mrtrix, L=2, deterministic
Mrtrix, L=8, probabilistic
Validation principles

- Evaluates data at hand; these subjects and this instrument
- Measures individual tracts in individual subjects
- Specifies strength of evidence, not probability of existence
- Compares connectome solutions
Tractography
Estimate fascicles from diffusion data
Tractography validation
Linear iterative fascicle evaluation (LIFE, Pestilli et al.)

Compare how well different models and algorithms do
Fascicle contributions

- Each fascicle makes a contribution to the diffusion signal for each voxel it passes through.

- The contribution depends on the fascicle orientation.

- The fascicles contributions are weighted (size, length).

\[ S(\theta) = w_0 D_0 + \sum_{f} w_f D_f (\theta) \]

In each voxel, the fascicles are the sticks.
Set up the non-negative LS equations

• The system of linear equations is biggish
  rows - 100 directions x 100,000 voxels
  cols - 1,000,000 fascicles

Each column is the prediction of a fascicle

Each matrix entry is the contribution from a voxel in a direction

Diffusion signal, $S(\theta)$

Weight for each fascicle

Or

(smoothly varying weights along the length)
Compare measurements and connectome predictions

First data set  Connectome

Solving a big system of linear equations (non-negative least-squares)
Compare independent measurements with connectome predictions

Connectome

Prediction

Big matrix multiplication
Compare independent measurements with connectome predictions.

Subtraction and root mean square error.
Scatter density histogram comparing two MRtrix parameters
On average, the connectome predicts an independent data set a little better than replication.
Summary

• Validation methods should enable us to test hypotheses about human tracts using the internal validation of the data at hand
Neuroscience applications

• The visual map hierarchy
• Learning to see words
Vertical occipital fasciculus (Yeatman et al., 2012)

Image courtesy Pestilli and Takemura
Visual field maps in humans

Wandell and Winawer (2011) Vision Res
Macaque field map organization

Felleman and Van Essen (1991), Annotated by Wallish and Movshon (2008)

Human diagram

V3 is much bigger (75% of V2) V3A is accompanied by V3B hV4 position

What about dorsal-ventral segregation
Dorsal VOF endpoints
Ventral VOF endpoints
Rethinking the human wiring diagram

DiCarlo and Cox, 2007
Some behaviors, such as psychological tests of performance during brief trials, may be best understood by measuring synaptic activity or spikes.

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Scientists need to account for the entire range of processes to understand circuit function in health and disease.
Predicting reading scores from white matter maturity
(Yeatman et al., PNAS, 2012)

- With very simple models based on diffusion data, we predict reading skill
- The predictions are statistically significant, but not yet useful

See work by Gabrieli and Hoeft groups
Thank you!

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