Rethinking tractography

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We can achieve a large-scale, quantified, human connectome in the next few years

• Quantitative white matter measurements in the living human brain
• What we can achieve now
  • Tractography generation
  • In vivo tractography evaluation
  • Tissue quantification
Gray and white matter varies across species

Macaque

Marmoset

Human

Mouse

www.brainmuseum.org
White-matter matters more in humans

1 cm

Macaque

Marmoset

Mouse

www.brainmuseum.org
Why fascicles (tracts) matter

• 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
White matter quantitative assessment

- The tissue properties in these pathways influence many aspects of human health, cognition, and emotion

- Neurodegenerative diseases and traumatic brain injury damage these tracts

Example reviews


**Cognition:** Fields, Trends Neurosci, (2008)

**Reading:** Wandell, Ann. Rev. Psych (2012)

**TBI:** Shenton, Brain Imaging and Behavior (2012)
Basic tractography is successful
(Yeatman et al., Nature Communications, 2014)

Lifespan maturation and degeneration of human brain white matter
An example of what we might achieve

- 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
An example of what we might achieve

• Measure the subject’s visual white matter

• Secure the data!

• Use validated computational tools for quality assurance and tissue estimation
Project on Scientific Transparency (PoST)
Project on Scientific Transparency (PoST)

Fractional anisotropy

Control ±2SD

Control

LHON

LGN Location V1

Leber’s hereditary optical neuropathy
Project on Scientific Transparency (PoST)

Leber’s hereditary optical neuropathy
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

$b = 800$
Diffusion signals in different directions

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

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

E. O. Stejskal and J. E. Tanner (1965)
Diffusion signals in different directions

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Big signal, small ADC

Small signal, large ADC

ADC – apparent diffusion coefficient
Tractography

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

Diffusion data are surfaces
Tractography
Estimate fascicles from diffusion data
White matter fascicles are generated by step-wise sampling of local diffusion information.

150 Directions, 2 mm$^3$, B=2000 projected on a 1 mm$^3$ T1 anatomical image.
Different tractography methods and parameters make different predictions.
Which connectomes should we study?
Which connectomes should we study?
Linear Fascicle Evaluation (LiFE)

Compare how well different models and algorithms do in predicting the original data

Pestilli et al., *Nature Methods*, 2014
1. Stages of LiFE
Use tractography to generate a candidate connectome

First data set → Candidate connectome

Many many fascicles
2. Stages of LiFE

Set up diffusion predictions for each voxel

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

Use the standard fascicle diffusion model to predict the diffusion signal in each voxel
3. Stages of Life
Solve for the fascicle weights

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

\[
\begin{bmatrix}
  v_1 \\
  v_2 \\
  \vdots \\
  v_N
\end{bmatrix}
\begin{pmatrix}
  w_{f_1} \\
  w_{f_2} \\
  \vdots \\
  w_{f_{10^7 \times 10^6}}
\end{pmatrix}
\]

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

Solve for a non-negative weight for each fascicle
(least-squares)
3. Stages of Life
Solve for the fascicle weights

Diffusion signal, $S(\theta)$

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

Depending on voxel size, number of directions, and so forth, about 80% of the fascicle 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
The optimized connectome predicts diffusion data better than test-retest reliability (b=2000 data shown)

White matter volume (%)

150 directions (N=3)

96 directions (N=6)

Model better

79%

85%

$R_{rmse}$ = Ratio of model error to reliability error
Statistical inference
Which connectomes is supported by the data?

To date, we generally find that probabilistic models predict the data more accurately.
Which connectomes should we study?

Deterministic

Probabilistic

✓
Which connectomes should we study?

Deterministic

Probabilistic

Franco Pestilli 2014 - Stanford University
Quantitative MRI of the fascicle tissue
(Mezer et al., *Nature Medicine*, 2013)

• What tissue properties change?
• T1, Macromolecular tissue volume (MTV), and Surface interaction rate (SIR)
• Single patient diagnosis

Aviv Mezer  Jason Yeatman
There are multiple types of MR mechanisms

- **Low energy**: Anti-parallel spins give up energy to macromolecules (lattice) and return to lower parallel state (T1).

- **High energy**: The spins dephase (T2*) and move (diffusion).

*Time 200 ms*
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)

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)
Modeling and calibration of the MRI signal yields quantitative measures of tissue

Mezer et al., Nature Medicine (2013)

Quantitative biophysical modeling

Non
water

Interactions

Water

Macromolecule tissue volume (MTV)

Surface interaction ratio (SIR)
Single subject measures and multiple sclerosis

Control distribution

Cortical spinal track

Macromolecule tissue volume

Core fiber node

0.31
0.27
0.23
0.19
Single subject measures (MS)

Cortical spinal track

Macromolecule tissue volume

Individual A

Individual B
Tissue development from 7-85 years
(Yeatman, Wandell, Mezer, 2014, *Nature Communications*)

(N=120), Technology development
Conclusions

- Diffusion-weighted imaging, tractography, AFQ, and LiFE identify the major tracts in individual subjects.

- These methods provide means of testing hypotheses about fascicles and their tissue properties on datasets from individual subjects.
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