Models: From voxels, to fascicles, to brain development and cognition

Jason D. Yeatman, PhD
Assistant Professor
Institute for Learning & Brain Sciences
Department of Speech and Hearing Sciences
University of Washington
http://BrainAndEducation.com
jyeatman@uw.edu
Cognition and the neuron doctrine

Cognitive function can be attributed to localized neural activity

Hubel and Wiesel (1959 onward)
Developmental changes in behavior occur over much longer time scales

- For example ~10 years to become a skilled reader.
- Learning to read requires brain circuits to modify their structure in response to years of training (Wandell & Yeatman, 2013).

Portilla & Simoncelli, 2000
Cognitive development depends on tissue changes that occur over correspondingly long time-scales

- Understanding development requires measurements that are sensitive to changes in glia, axons, myelin and vasculature.

MRI can be used to quantify brain tissue properties and model the interplay between the development of brain circuits and cognitive functions.

But how do we go from MR signals to models of development?

(Allen & Barres (2009))

(Kettenmann (2012))

(Allen & Barres (2009))

(Ture (2000))

(Upuzo (1998))

(LaMantia & Rakic, 1990)
Outline

1. From diffusion to fascicles: Models of an individual’s white matter.
2. Quantitative MRI measurements of tissue volume and composition.
3. Combining multiple measurements to dissociate developmental processes.
   – Testing models of development.
Outline

1. From diffusion to fascicles: Segmenting an individual’s white matter.

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Building a wiring diagram with dMfRI

Choose the model that is the best fit to the data

Fit diffusion model

Optimize model

Dataset 2

ADC (μm/ms²)

Angle (θ)

Tractography

Linear Fascicle Evaluation (LiFE) https://github.com/pestilli
Pestilli, Yeatman, Rokem, Kay & Wandell (2014), Nature Methods
Fitting a tensor model to diffusion measurements

Diffusion signal measured in different directions

Diffusion tensor model: Predicts Gaussian diffusion in three dimensions

Visualization of tensor model: Ellipsoid

Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), *PLoS ONE*
Fitting a tensor model to diffusion measurements

Diffusion signal measured in different directions

Predict diffusion measures from tensor model

$\begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix}$

Diffusion tensor model: Predicts Gaussian diffusion in three dimensions

Visualization of tensor model: Ellipsoid

Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), PLoS ONE
Evaluating the tensor model

Data 1

Test-retest reliability

Cross-validation

Fit

Data 2

Model

Predict

\[
\begin{pmatrix}
\sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\
\sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\
\sigma_{zx} & \sigma_{zy} & \sigma_{zz}
\end{pmatrix}
\]
Evaluating tensor model with cross validation

Data $\Rightarrow$ data

Model $\Rightarrow$ data

Relative RMSE =

If $r$RMSE < 1

Good model

Slide courtesy of Ariel Rokem
Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), PLoS ONE
The tensor model is a good fit through much of the brain

Any idea what is going on here?

Rokem, Yeatman, Pestilli, Kay, Mezer, Van der Walt and Wandell, (2014), PLoS ONE
http://nipy.org/dipy/examples_built/kfold_xval.html#example-kfold-xval
Linear Fascicle Evaluation (LiFE): Validating tractography

Voxel signal = Fascicle 1 + Fascicle 2 + Fascicle 3 + Fascicle 4

Slides courtesy of Franco Pestilli
Linear Fascicle Evaluation (LiFE): Validating tractography

Validation: Eliminate fascicles with zero weight

\[ \text{Diffusion signal, } S(\theta) \begin{bmatrix} \text{v}_1 \\ \text{v}_2 \\ \vdots \\ \text{v}_n \end{bmatrix} = \begin{bmatrix} f_1 & f_2 & \cdots & f_n \end{bmatrix} \begin{bmatrix} W_1 \\ W_2 \\ \vdots \\ W_n \end{bmatrix} \]

One weight per fascicle

Linear Fascicle Evaluation (LiFE) https://github.com/pestilli
Pestilli, Yeatman, Rokem, Kay & Wandell (2014), *Nature Methods*
Automated fiber tract quantification: Segmenting an individual’s white matter

The goal of all this modeling is to generate accurate estimates of an individual’s white matter connections

Yeatman et al. (2012), PLoS ONE -- Software available at: https://github.com/YeatmanLab/AFQ
Automated fiber tract quantification: Segmenting an individual’s white matter

Yeatman et al. (2012), PLoS ONE -- Software available at: https://github.com/YeatmanLab/AFQ
So with all this work, how well do we do?

- Measures of white matter microstructure are **highly** reliable.

Arcuate Fasciculus – dMRI acquisition: 32 directions $b=800$; 64 directions $b=2000$

Yeatman et al. (2012), *PLoS ONE* -- Software available at: [https://github.com/YeatmanLab/AFQ](https://github.com/YeatmanLab/AFQ)
How might we select the optimal tractography algorithm to use with AFQ?

• Consider two use cases:
  – Clinical data collected on children with traumatic brain injury versus Human Connectome Project data.

• What might be the pros and cons to using a tensor model with deterministic tractography versus spherical deconvolution with probabilistic tractography?
The choice of algorithm has a substantial impact on the results.

Spherical Deconvolution
Probabilistic tractography

Tensor Model
Deterministic Tractography
The choice of algorithm has a substantial impact on the results

Spherical Deconvolution
Probabilistic tractography

Tensor Model
Deterministic Tractography
The core of the fascicle is consistent but the cortical endpoints differ

- Select the appropriate algorithm based on the goals of the study.
- Test the fit of the fascicles to the diffusion measurements.
  - Remember that tractography is a model
Summary: From diffusion to fascicles

• Based on diffusion measurements we can fit a model of the fascicles that pass through a voxel and quantify the fit of the model with cross-validation.
  – http://nipy.org/dipy/examples_built/kfold_xval.html#example-kfold-xval

• Inferences about brain connectivity depend on selecting the appropriate diffusion model and tractography algorithm for your research question.
  – Fascicles are themselves a model and we should use cross-validation to test how well they predict the data.
  – https://github.com/pestilli
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Inferring tissue biology from diffusion

- Diffusion is very sensitive to tissue changes and can help generate hypotheses about potential biological processes.

High Mean Diffusivity (MD)  
Low Mean Diffusivity (MD)

Wandell & Yeatman (2013); Stikov et al., (2011); Assaf & Pasternak (2008); Beaulieu (2002)
Diffusion is affected by many tissue properties

- It’s amazing that water diffusion correlates with behavior (e.g., Klingberg et al., 2000).
- The relationship between water diffusion and tissue biology is not straightforward (Beaulieu, 2002; Jones, Knosche & Turner 2013).
- Additional measurements modalities will be help constrain our models.

Quantitative MRI measurements of tissue volume and composition

Mezer, Yeatman et al. (2013), Nature Medicine

Aviv Mezer
In vivo histology with quantitative MRI

Aviv Mezer
Hebrew University

In vivo histology with quantitative MRI

- MR signals (T1) from water protons change when the protons interact with membranes.
- T1 image intensity depends on the **amount** and **composition** of tissue in each voxel as well as scanner biases.

Macromolecule tissue volume (MTV)

In vivo histology with quantitative MRI

- MR signals (T1) from water protons change when the protons interact with membranes.
- T1 image intensity depends on the **amount** and **composition** of tissue in each voxel as well as scanner biases.

\[ \text{Image intensity} = f(\text{coil gain}, \text{scan parameters}, \text{tissue properties}) \]

In the white matter T1 relaxation rate is principally driven by myelin content (Stuber et al., 2014).

What does “quantitative MRI” mean?

- **T1 (s)** - The T1 relaxation rate is a physical property of water protons in a magnetic field, has units, and does not depend on scanner hardware/pulse sequence.
What does “quantitative MRI” mean?

- **T1 (s)** - The T1 relaxation rate is a physical property of water protons in a magnetic field, has units, and does not depend on scanner hardware/pulse sequence.

\[
S = b e^{-\frac{TR}{T1}} + c
\]

\[
S = b \sin(a) \frac{1 - \exp\left(-\frac{TR}{T1}\right)}{1 - \cos(a) \exp\left(-\frac{TR}{T1}\right)}
\]
From images to quantitative tissue maps

Image intensity = \( f(g, \alpha, T1, MTV) \)

Mezer, Yeatman et al. (2013), Nature Medicine
Quantitative MRI measures are independent of scanner hardware

Yeatman, Wandell & Mezer, (2014). *Nature Communications*
Summary: Quantitative MRI

• MRI can be used to quantify many important properties of the tissue.
  – Volume of tissue macromolecules (MTV).
  – $T_1$ relaxation rate is sensitive to myelin (Stuber et al., 2014).

• Quantitative MRI measurements are independent of the specific scanner hardware and pulse sequence.
  – Opens up new diagnostic applications.
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In vivo histology:
Combining measures to model brain tissue

• What can we learn about development with qMRI:
  – Do different types of tissue have distinct maturational time-courses (e.g., myelin vs. astrocytes)?
  – Which properties of the white matter are related to behavior?
  – Can we model how properties of the white matter affect cortical computation (i.e., why do white matter measures predict behavior)?
**In vivo histology**: Combining measures to model brain tissue

- T1 map
- 1/R1 map
- MTV map
- Diffusivity

- Secs: 0-4
- Volume fraction: 0-1
- ADC: 0-3

![Brain images with color maps for T1, MTV, and Diffusivity](image-url)
Measuring the creation of new tissue in the developing brain

Yeatman, Wandell & Mezer, (2014). *Nature Communications*
Yeatman, Wandell & Mezer, (2014). *Nature Communications*
Does each qMRI parameter measure the same underlying biological properties? Can we detect multiple developmental processes in the white matter?

Yeatman, Wandell & Mezer, (2014). *Nature Communications*
Does each qMRI parameter measure the same underlying biological properties? Can we detect multiple developmental processes in the white matter?

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Does each qMRI parameter measure the same underlying biological properties? Can we detect multiple developmental processes in the white matter?

- R1 and MTV are sensitive to the same developmental processes.
- Diffusion is sensitive to independent processes.

Yeatman, Wandell & Mezer, (2014). *Nature Communications*
Last-in-first-out hypothesis: Late developing brain regions are more susceptible to degenerative processes.

- Are the last regions to develop, the first to degenerate?
  - Important implications for models of aging and disease.
- How might we test this hypothesis?
  - Implement a model and test the fit to the data.

https://github.com/yeatmanlab/lifespan piecewiseFit.m, piecewiseEval.m
Last-in-first-out hypothesis: Late developing brain regions are more susceptible to degenerative processes.

Prediction 1: Tracts that develop **late** decline **early**

Prediction 2: Tracts that develop **early** decline **late**

Prediction 3: Negative correlation between the two transition points

https://github.com/yeatmanlab/lifespan  piecewiseFit.m, piecewiseEval.m
Last-in-first-out hypothesis: Late developing brain regions are more susceptible to degenerative processes.

- There is no relationship between the age of maturation and the age of degeneration for R1 or diffusivity.
- We can reject the Last-in-first-out hypothesis.

https://github.com/yeatmanlab/lifespan
nc_Figure6.m

https://github.com/yeatmanlab/lifespan
piecewiseFit.m, piecewiseEval.m
Symmetry hypothesis: The amount of growth predicts the amount of decline.

The graphs illustrate the relationship between age and R1 data, showing a second-order polynomial fit for both age 10 and old age. The graphs also highlight the difference in voxel counts between age 10 and old age.


[GitHub Repository](https://github.com/yeatmanlab/lifespan)
Symmetry hypothesis: The amount of growth predicts the amount of decline

1. Testing the prediction of the parabolic model: Lifespan changes should be symmetric.
2. Growth of myelin during development predicts degeneration during aging.

https://github.com/yeatmanlab/lifespan
nc_Figure5.m

Yeatman, Wandell & Mezer, (2014). Nature Communications
Summary

- The time-courses of R1 and diffusion changes demonstrate that multiple biological processes drive changes in the white-matter over the lifespan.
  - qMRI can dissociate different tissue changes.
- There is not a systematic relationship between the age of maturation and degeneration
  - Last-in-first out does not fit the data
- A symmetric model predicts R1 changes over the lifespan.
  - Models provide insight into mechanisms and generate testable predictions.
- We can define, test and interpret models at the level of voxels, tracts and lifespan maturation.
Thank you!
Removing bias and computing MTV

Each coil sees the same underlying MTV value but has its own gain function. Solve for the each coil’s gain function to uncover the true MTV value.

\[ g_i \ast (1 - MTV) \min g_i \left\{ \sum (MTV_i - MTV)^2 \right\} \]

Mezer, Yeatman et al. (2013), *Nature Medicine*