Overview

- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- Tractography Applications
Why do we need modelling?

Micro-connectome

Macro-connectome

Ohno et al. 2013

Iowa Virtual hospital
DTI Estimates of Principle Fibre Orientation in WM

Assumption:

Direction of maximum diffusivity (in anisotropic voxels) is an **estimate** of the major fibre orientation.
But is WM always coherently organised within a voxel?

Unfortunately not, complex fibre patterns (e.g. crossings) are very common at the voxel scale.
Predictions from the tensor model
no crossing fibres

One orientation

Measured Signal Shape

Predicted Signal Shape

DTI Ellipsoid

Prediction & Measurements in 2D
Predictions from the tensor model
crossing fibres

Two orientations

Measured Signal Shape

Predicted Signal Shape

DTI Ellipsoid

Prediction & Measurements in 2D
Predictions from the tensor model crossing fibres

Three Orientations

Measured Signal Shape

Predicted Signal Shape

Prediction & Measurements in 2D

DTI Ellipsoid
How good is the DTI Model in regions with crossing fibres?

- In voxels containing two crossing bundles, the tensor ellipsoid is pancake-shaped (oblate, planar tensor).
- In voxels containing three crossing bundles, the tensor ellipsoid is spherical.

- In these areas, DTI $v_1$ is meaningless.
Uncertainty on DTI Fibre Orientation Estimates

Repeat an acquisition many times and obtain the variability in $v_1$ from the different datasets.

Uncertainty Sources
- Modelling errors
- Noise

Cones of uncertainty on DTI $v_1$

Jones, 2002
Do we have to use the DTI model to estimate orientations? Not really, many models exist.

DTI model (dtifit)  Ball & sticks model (bedpostx)

\[ s_j = s_0 \left[ (1-f) \exp(-b_j d) + f \exp(-b_j d(x_j^T v)^2) \right] \]

- Measured Signal for Gradient \( j \)
- b-value for gradient \( j \) (known)
- Unit vector representing the direction of gradient \( j \) (known)
- Anisotropic Volume Fraction (unknown)
- Diffusivity (unknown)
- Fibre Orientation (unknown)
Ball & Sticks Model
Unlike the DT model, it can represent many orientations

- Anisotropic tensors (sticks) with isotropic background (ball)
- Fibre Orientations modelled explicitly and separated from isotropic partial volumes

\[ s_j = s_0 \left[ (1 - \Sigma f_n) \exp(-b_j d) + \Sigma f_n \exp(-b_j d(x_j^T v_n)^2) \right] \]

- Measured Signal for Gradient \( j \)
- b-value for gradient \( j \) (known)
- Unit vector representing the direction of gradient \( j \) (known)
- Anisotropic Volume Fractions (unknown)
- Diffusivity (unknown)
- Max number of sticks (user-defined)
- Fibre Orientation (unknown)
Predictions from the ball and sticks model crossing fibres
How can we estimate uncertainty?

- Remember ... a long time ago in the world of fMRI ...

- We estimated two things:
  - A cope file (the parameters)
  - A varcope file (uncertainty in these parameters)

- We estimated our parameters, and their uncertainty from a single dataset.

- Can we do a similar thing with parameters estimated for the ball & sticks model?
  - In the context of GLM, we have analytic formulas
  - For diffusion (especially orientations) we don’t
Quantifying Uncertainty
Bayesian Modelling (FDT BedpostX)

- Uncertainty can be quantified from a single data set
- Instead of a single orientation estimate, infer a distribution of orientations in each voxel.

<table>
<thead>
<tr>
<th>WM</th>
<th>GM/CSF</th>
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<tbody>
<tr>
<td><a href="#">DTI ellipsoid</a></td>
<td><a href="#">Orientation Distribution</a></td>
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<td><a href="#">DTI ellipsoid</a></td>
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</table>
samples from parameters’ posterior distribution

\[ P(f, d, v | Data) = \frac{P(Data | f, d, v)P(f, d, v)}{P(Data)} \]

Bayesian Inference

Model Parameters \( \Omega \) → Data \( \gamma \)

model

angular plot

Markov Chain - Monte Carlo (MCMC) Sampling

Model Predicted Signal

Measured Signal

5000 iterations per voxel

Output samples
Output in Each voxel = Distributions of Parameters

\[ \phi \quad \Theta \]

WM
GM/CSF

DTI ellipsoid
Orientation Distribution

Orientation Distribution
• Model selection problem: One, two or more fibres within a voxel?

• Automatic Relevance Determination: Only estimate complexity that is supported by the data
Automatic Relevance Determination (A.R.D.)

- No benefit from including a 2nd fibre
  => 2nd volume fraction goes to zero

Model with one stick  Model with two sticks

- Measured Signal
  - Model Predicted Signal

Signal for one fibre configuration
- After running BedpostX all voxels will have estimated parameters for the maximum number of sticks requested.

- But due to ARD, the sticks that are not supported in a voxel will have an almost zero volume fraction.

- We use a threshold (e.g. >5%) to exclude sticks with tiny volume fraction.
Ball & Sticks Orientations

All sticks, with secondary ones thresholded ($f_n > 5\%$)

Orientations RGB-colour coded
DTI vs Ball & Sticks Orientations
A large portion of the WM supports crossing fibres

Coherence in orientations shows that we are not over-fitting (the ARD works)
Multi-Shell Diffusion Acquisitions
Why bother?

One Orientation

Two Orientations

Three Orientations

Signal at different $b$ values (s/mm$^2$)

Higher $b$ value gives us more angular contrast!!!

😊
Multi-Shell Diffusion Acquisitions

Why bother?

One Orientation

Two Orientations

Three Orientations

Signal at different b values (s/mm^2)

b = 1000

b = 2000

b = 3000

b = 4000

b = 5000

But SNR goes down very quickly with b… 😞
Generalised Ball & sticks Model
Gets best of both worlds

- Multi-shell model (or model=2) in Bedpostx options.
- Allows representation of multiple diffusivities within a voxel (rather than just one).
- More accurate model for multi-shell data & partial volume effects.

Human Connectome Project Data

*Jbabdi, Sotiropoulos et al, MRM 2012
*Sotiropoulos, Jbabdi et al, NeuroImage 2013
Overview

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Connectivity - Why do we care?

- White matter (dys)connectivity is thought to form the substrate for many different neurological and psychiatric disorders.

Catani and Ffytche 2005
Connectivity - Why do we care?

- Tractography provides non-invasive localisation and semi-quantitative biomarkers
Connectivity - Why do we care?

- Connections constrain function

- Different regions have distinct connectivity fingerprints

Passingham et al. 2002
Anatomy tools

<table>
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<tr>
<th>Invasive</th>
<th>Non-invasive</th>
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<tr>
<td><img src="image1.png" alt="Dissection" /></td>
<td><img src="image2.png" alt="Tractography" /></td>
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<tr>
<td><img src="image3.png" alt="Lesions" /></td>
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<tr>
<td><img src="image4.png" alt="Tracers" /></td>
<td><img src="image5.png" alt="Tractography" /></td>
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</tbody>
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- **Invasive**: Dissection, Lesions, tracers (only in non-humans)
- **Non-invasive**: Tractography
What is Tractography?

Tractography
The post-imaging reconstruction of fibre bundles/anatomical connections in the brain using a set of DW images.
(in-vivo virtual dissection)

Post-mortem dissection of some white matter fibre bundles (tracts)
What does tractography offer?

+ non-invasive
+ in-vivo
+ whole brain
+ can address new questions

...But
- low resolution (large bundles)
- indirect (diffusion paths)
- error prone (MRI is noisy)
- difficult to interpret quantitatively
Formally, we solve numerically the differential equation:

\[
\frac{dr(s)}{ds} = v_1(r(s)), \quad r(0) = r_0
\]
But When to Stop?
Heuristics to avoid error propagation.
+ Knowledge of the anatomy

**Curvature Change Threshold:** To avoid crossings of boundaries and very bended trajectories, impose a smoothness criterion.

**Anisotropy Threshold:** To avoid propagating in regions where \( v_1 \) is meaningless.

**Anatomical criteria** (e.g. reach grey matter)
Streamline tractography can dissect major bundles

- Arcuate fasciculus
- Cingulum bundle
- Inferior longitudinal fasciculus
- Corpus callosum
- Inferior fronto-occipital
- Fornix
- Uncinate fasciculus
- Corona radiata
- Cerebellar tracts

Catani and Thiebaut de Schotten 2008
DTI Streamline Tractography Summary

- Use the major axis of the DTI ellipsoid as a fibre orientation estimate.

- Propagate curves within this vector field until empirical thresholds are exceeded.

- Major fibre bundles can be reconstructed.
Streamlining reproducibility

Repeat an acquisition many times and repeat streamline tracking.

Due to uncertainty in $v_1$, curves will not perfectly overlap.

Create a map that shows the degree of overlap across the trials.

- Streamlines from a single dataset
- Map that shows where results across datasets overlap

Path Probability Map

Low Reproducibility  High Reproducibility
- We normally have one dataset per subject, not many.

- Probabilistic Tractography as a two-step process:
  a) Use DWI data and a model to infer a fibre orientation and its uncertainty in each voxel.

  b) Use the estimates and the uncertainty to build a path probability map to a seed.
Probabilistic tractography

• But now, we no longer have a single direction at each voxel. How can we do tractography?

'Streamlining'

Probabilistic tractography
- Propagate N streamlines from a seed, but for each propagation step choose randomly an orientation from the underlying distribution.

- Build a spatial distribution of curves that mimics the overlapped results from multiple deterministic tracking on multiple scans
Define the degree of overlap at each location B, as:

\[ P_{AB} = \frac{M}{N} \]

- \( M \) : number of streamlines that go through B
- \( N \) : total streamlines generated from A

This is the probability of a curve starting at A and going through B.
- Can now propagate through isotropic regions (e.g. GM).

- Do not need to stop when anisotropy is low, as in deterministic tracking.

- The high uncertainty will be reflected in the probability map.

- Still impose a curvature threshold to avoid swirled trajectories.
Probabilistic Tractography in Multi-Fibre Fields

When multiple fibre orientations exist in a voxel, choose the one that is most compatible with the incoming trajectory.


Cortico-spinal tracts.
9 subjects
Behrens et al, 2007

* If one fibre is modelled and we track through a crossing, a) we may not make it through the crossing, b) if we make it, the connectivity index will be relatively low.
Probabilistic Tractography in Multi-Fibre Fields
Examples

Acoustic radiations.
9 subjects
Behrens et al, 2007
Path Probability Map

- Recall that it assesses how reproducible results are

- Often called “connection probability”, “connectivity index”, “connectivity strength”. But it does not quantify how strong a connection is...

- Rather, how robust it is against noise/uncertainty
What is a quantitative measure of connectivity?

- Number of axons connecting 2 areas?
- Proportion of axons from a seed that reach a target?
- “Integrity” of the connecting white matter ... 
  - Effective conductivity?
  - Degree of myelination?
  - Packing density?
- What are we measuring?
  - The probability that the **dominant** path through the **diffusion field** passes through this region.
Connection Probabilities

- They may reflect “Connection Strength”

- But they do also reflect other uninteresting factors, such as:

  * **Connection length**: Longer connections have smaller probability than shorter ones

  * **Geometric complexity**: Probabilities of connections that go through regions of complex structure will be smaller than connections than go through more coherent regions

  * **Resolution of the spatial grid**: Probabilities change if we change the size of “bins” for displaying the spatial histogram
Dependence on Spatial Resolution

- Probability maps are spatial histograms. The spatial resolution of the grid on which we compute these probabilities defines how many bins and how small the bin size is.

- E.g. displaying the results in native diffusion space vs displaying results in standard MNI space of different resolution.

- Normally we would use the spatial grid of our data (i.e. the inherent data resolution).

- But we don’t have to. We could use a higher resolution grid.
Dependence on Spatial Resolution

- Probability maps are spatial histograms. The spatial resolution of the grid on which we compute these probabilities defines how many bins and how small the bin size is.

Let’s see a simple 1D example. Obtain random samples from a Normal distribution and get their 1D histogram. Sample Counts (vertical axis) in each bin change with resolution!
Tract-Density Imaging
[Calamante NeuroImage 2010]

Single HCP subject
TDI @ 0.2mm
• Because of the uncertainty propagation, the spatial distribution of paths is often very wide.
• Once a seed is specified, prior anatomical knowledge can be imposed to assist the dissection of a specific tract.

• Waypoint ROI
  If a curve does not go through, it is discarded.

• Exclusion ROI
  If a curve goes through, it is discarded.

• Termination ROI
  If a curve goes through, it is terminated.
Adding Prior Knowledge to Tractography

Cortico-spinal tract

Seed: M1, hand area

No ROIs
Adding Prior Knowledge to Tractography

Cortico-spinal tract

Seed: M1, hand area

Exclusion: Mid-Sagittal plane
Adding Prior Knowledge to Tractography

Cortico-spinal tract

Seed: M1, hand area

Waypoint: Internal Capsule
Adding Prior Knowledge to Tractography

Corpus Callosum

Seed: dorsal PMC

No ROIs
Adding Prior Knowledge to Tractography

Corpus Callosum

Seed: dorsal PMC

Waypoint: Corpus Callosum
- Needs apart from orientation estimates, an estimate of their uncertainty. Does not need to be the ball and stick model, the DTI model can be used instead!

- Propagate streamlines repeatedly from a seed, but the orientation field is no longer deterministic. In each propagation step choose randomly an orientation from the underlying distribution.

- A connection probability value $\geq 0$ can be obtained from a seed A to any voxel in the brain B. This assesses the **reproducibility of the path from A to B**, along which water molecules preferably diffuse.
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Connectional “contrast”

no contrast on conventional MRI

VL $\rightarrow$ M1

MD $\rightarrow$ PFC

Behrens et al, 2003
(probabilistic tractography)

Rouiller et al, 1998
(BDA anterograde tracing)
Connectional “contrast” in the thalamus

Behrens et al. Nat Neuro 2003
Johansen-Berg et al. Cereb Ctx 2005
Correspondence between functional activations and connectivity-defined volumes

Executive Tasks

Motor Tasks
DBS for treatment of tremor in Parkinson's

Pouratian et al. JNS 2011
Distinguishing cortical areas in humans

Ongur and Price, J. Comp Neurol. 2003

Mackey and Petrides (EJN, 2010)

Vogt (2009, Cingulate Neurobiology and Disease)
Relation of folds to cytoarchitecture.

Amunts, Zilles, Fischl e.g. Cerebral cortex 2008
Changes in connectivity profiles
Medial Frontal Cortex

Medial area 6 contains two distinct regions with very different connectivity:
SMA and Pre-SMA

Can we define a border based on a change in connectivity profile?
Changes in connectivity profiles
Medial Frontal Cortex

Seed voxels

Rest of brain

Rest of brain

Seed voxels
Changes in connectivity profiles
Medial Frontal Cortex

Seed voxels

Rest of brain

Cross-correlation matrix

clustering algorithm
Clusters in the re-ordered matrix represent seed voxels with similar connectivity.

Breaks between clusters represent where connectivity patterns change.
Finding homologies across species
Finding homologies across species

Mars et al. PNAS 2013
Rushworth et al. Cereb Ctx 2006
Tractography defines distinct regions of human PPC

Paths from superior colliculus

Paths from parahippocampal

Paths from premotor cortex

≈ macaque LIP?

superior colliculus

parahippocampal

≈ macaque 7a?

≈ macaque AIP?
human → macaque

Mars et al. PNAS 2013
Lack of homologies
How have brain connections changed in evolution?

Rilling, Glasser, Preuss, Ma, Zhao, Hu, Behrens
Nature Neuroscience 2008
Quantitative analysis
Comparative anatomy

9 humans

2 macaques

Behrens et al, ISMRM 2006
Using tractography to test generic rules from tracing

Tracing

Tractography

Macaques

Humans

CC z-position

vPFC x-position

 GCC
Can we trust tractography?

Is the direction of least hindrance to diffusion a good proxy for fibre orientation?

mapping between axon geometry and diffusion profile can be ambiguous
What’s in a voxel?

White matter?

bad

good
White matter organisation can be surprising

Whole mouse brain Electron Microscopy!
Mikula Binding Denk, Nature Methods 2012
Can we trust tractography?

In the white matter: jumping between tracts

Near the cortex ambiguities/biases
Many false positives in tractography

25 synthetic WM tracts (based on real data) Simulated diffusion data

Bundle detection

Maier-Hein et al. (Nat. Comm., 2017)
Validation: comparison with classical chemical tracing

CC

SLF III

dorsal

ventral

IC

point of entry within the CB

CB
Functional validation: meta-analysis of FMRI activations within thalamus

Johansen-Berg et al, Cerebral Cortex, 2005
The Human Connectome Project
www.humanconnectome.org

Functional Connectivity

Predominant Structural Connections from a Certain Point (dot)

Structural Connectivity

Negative
Positive
Low
High
Different techniques, same pathways

Macaques
(Vincent et. al Nature 2007)

Humans
(HCP data)

RFMRI correlations

TFMRI coactivation

Diffusion tractography

Spontaneous correlation pattern
Evoked response pattern
Anatomical connectivity pattern

FEF
IPS3

3/4
4/4
Conjunction

P < 0.05
P < 10^{-4}

Light
Strong Density

MT/MST
LIP
CeS
SF
STS
AS
cerebellum
how different methods can fail in different ways

textbook connections
 Left
 RFMRI connectivity
 Right
 tractography
That's all folks