FMRIB Diffusion Toolbox

- DTI model fit
- Eddy current correction
- Voxel-Based diffusion analysis (TBSS)
- BEDPOSTX modelling crossing fibres
- PROBTRACKX propagating uncertainty in tractography
Diffusion Tensor Imaging - basic principles

- Diffusion in brain tissues
- Apparent Diffusion Coefficient
- Diffusion Tensor model
- Tensor-derived measures
Brownian motion

Molecules are in constant motion

Robert Brown (1773-1858)
Brownian motion

Molecules are in constant motion

Robert Brown (1773-1858)

Adolf Fick (1829-1901)

\[
J = -D \nabla \phi.
\]

\[
\frac{\partial \phi}{\partial t} = D \frac{\partial^2 \phi}{\partial x^2}
\]
Brownian motion

Molecules are in constant motion

Robert Brown (1773-1858)

\[ J = -D \nabla \phi. \]

\[ \frac{\partial \phi}{\partial t} = D \frac{\partial^2 \phi}{\partial x^2} \]

Adolf Fick (1829-1901)

Albert Einstein (1879-1955)

\[ \langle x^2 \rangle = 2nDt \]
Diffusion in tissues

Free Diffusion

Restricted Diffusion
Diffusion in tissues

“Looks” like free diffusion
Diffusion in tissues

Free Diffusion

Restricted Diffusion

“Looks” like free diffusion

“Doesn’t look” like free diffusion
Diffusion in tissues

“Looks” like free diffusion

“Apparent” diffusion coefficient (ADC) depends on the diffusion experiment!
Measuring diffusion with MRI

Diffusion contrast is modulated by:

- Gradient strength
- Gradient orientation
- Diffusion time
Apparent diffusion coefficient

Remember:
$q \sim \text{gradient strength}$

$D_{app} / 10^{-3} \text{mm}^2/\text{s}$

$\sqrt{\text{diffusion time} / \text{ms}}$

$q$ value

Pfeuffer et al, NMR Biomed 1998
Apparent diffusion coefficient

Remember:
q ~ gradient strength

“intrinsic” diffusion coefficient

Pfeuffer et al, NMR Biomed 1998
Apparent diffusion coefficient

Remember:
$q \sim$ gradient strength

Typical experiment (50-100 ms)

"intrinsic" diffusion coefficient

"apparent" diffusion coefficient

Pfeuffer et al, NMR Biomed 1998
Orientation contrast in Diffusion MR
Anisotropy of the Apparent diffusion coefficient

Beaulieu, NMR Biomed 2002
Diffusion tensor model

Iso-probability contour

\[ N(0, 2\tau D) \]

mean squared displacement
Diffusion tensor model

diffusion MRI signal

ADC profile (mm$^2$/s)

Iso-probability contour

$\exp(-bx^T Dx)$

$x^T Dx$

$\mathcal{N}(0, 2\tau D)$

signal attenuation

mean squared displacement
Diffusion tensor model

\[ \exp(-bx^T Dx) \]
Diffusion tensor model
Estimation
Diffusion tensor model eigenspectrum

\[ L_1 = \text{ADC}_{\text{max}} \]
\[ L_3 = \text{ADC}_{\text{min}} \]
\[ L_1 + L_2 + L_3 = 3 \times (\text{average ADC}) \]
Tensor-derived measures

variance ADC (FA)

average ADC (MD)

Longitudinal ADC (L1)

Transverse ADC ((L2+L3)/2)

biophysical properties

generic properties

axon, axonal membrane, myelin, neurofilament

D(1)
TBSS: Tract-Based Spatial Statistics

- Need: robust “voxelwise” cross-subject stats on DTI
- Problem: alignment issues confound valid local stats
- TBSS: solve alignment using alignment-invariant features:
  - Compare FA taken from tract centres (via skeletonisation)
TBSS: Tract-Based Spatial Statistics

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Tensor-derived parameters: Fractional Anisotropy

- FA encodes how strongly directional diffusion is
  - (derived from diffusion tensor eigenvalues)
- Hence good marker for WM integrity
  - i.e., good marker for disease, development, etc.

\[ FA = \sqrt{\frac{3}{2} \left( \frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right) } \]

FA=0  \quad FA=0.8
Orthogonal Tensor Invariants (Kindlmann, TMI 2007)

• Nice to have 3 orthogonal (independent) tensor-derived measures: MD, FA & “Mode”
• Mode: is the tensor tubular (one strong fibre) or flat-cylindrical (two strong fibres)?
At “normal” resolutions, tracts appear thinner than they really are primarily because of the interference between orthogonal anisotropy in GM and WM.

High-resolution ex-vivo diffusion data:
McNab & Miller (FMRIB)

Computation resources:
Jones, Stathakis & Wise (CUBRIC cluster)
VBM-style Analysis of FA

- VBM [Ashburner 2000, Good 2001]
- Align all subjects’ data to standard space
- Segment -> grey matter segmentation
- Smooth GM
- Do voxelwise stats (e.g. controls-patients)

- Like VBM but no segmentation needed
VBM-style Analysis of FA

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- Like VBM but no segmentation needed
**VBM-style Analysis of FA**

- **Strengths**
  - Fully automated & quick
  - Investigates whole brain

- **Problems** [Bookstein 2001, Davatzikos 2004, Jones 2005]
  - Alignment difficult; smallest systematic shifts between groups can be incorrectly interpreted as FA change
  - Needs smoothing to help with registration problems
  - No objective way to choose smoothing extent
Hand-placed voxel/ROI-based FA Comparison

labour-intensive, subjective, potentially inaccurate, doesn’t investigate whole brain
Tractography-Based FA Comparison

  - Define a given tract in all subjects
  - Parameterise FA along tract
  - Compare between subjects
- Strength: correspondence issue hopefully resolved
- Problems
  - Currently requires manual intervention to specify tract
  - Hence doesn’t investigate whole brain
  - Projection of FA onto tract needs careful thought
Tractography-Based FA Comparison

Gong 2005
TBSS: Tract-Based Spatial Statistics

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TBSS: Tract-Based Spatial Statistics

- Need: robust “voxelwise” cross-subject stats on DTI
- Problem: alignment issues confound valid local stats
- TBSS: solve alignment using alignment-invariant features:
  - Compare FA taken from tract centres (via skeletonisation)
1. Use medium-DoF nonlinear reg to pre-align all subjects’ FA
   (nonlinear reg: FNIRT)
1. Use medium-DoF nonlinear reg to pre-align all subjects’ FA (nonlinear reg: FNIRT)

2. Create mean FA image  (no smoothing)
2. “Skeletonise” Mean FA
2. “Skeletonise” Mean FA
3. Threshold Mean FA Skeleton

giving “objective” tract map
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giving “objective” tract map
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giving “objective” tract map
4. For each subject’s warped FA, fill each point on the mean-space skeleton with nearest maximum FA value (i.e., from the centre of the subject’s nearby tract)
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one skeleton voxel’s data vector (to be fed into GLM)
5. Do cross-subject voxelwise stats on skeleton-projected FA
5. Do cross-subject voxelwise stats on skeleton-projected FA 
6. Threshold, (e.g., permutation testing, including multiple comparison correction)
Testing for Gaussianity

- 36 controls & 33 schizophrenics (Mackay)
- Test each voxel across subjects for Gaussianity using Lilliefors at 5%
- No smoothing with any preprocessing method

![Graph showing % voxels non-Gaussian for controls and schizophrenics across VBM, TBSS skeleton-masked, and TBSS skeleton-projected methods. The graph indicates expected failure rate with thresholds.](image-url)
Repeatability Tests

- 8 controls scanned twice each
- Measure %CoV across sessions & subjects
- Test hand-placed points and global mode & median
Differences in healthy controls

Normal variation in bimanual co-ordination skill

- Inter-individual variation in FA along a specific motor pathway is related to variation in motor skill
- Experience-dependent structural changes?
Differences in healthy controls

Normal variation in bimanual co-ordination skill

- Inter-individual variation in FA along a specific motor pathway is related to variation in motor skill
- Experience-dependent structural changes?

Johansen-Berg et al, OHBM, 2006
Schizophrenia (Mackay)

TBSS & VBM show reduced FA in corpus callosum & fornix. VBM shows spurious result in thalamus due to increased ventricles in schiz.
TFCE for TBSS

controls > schizophrenics
p<0.05 corrected for multiple comparisons across space, using randomise

TFCE
Multiple Sclerosis (Cader, Johansen-Berg & Matthews)

- 15 MS patients

- **Yellow** = -ve corr. FA vs EDSS
- **Blue** = group lesion probability (50%)
- **Red** = -ve corr. FA vs lesion volume
  
  Note reduced FA away from lesions
Multiple Sclerosis (Cader, Johansen-Berg & Matthews)

A. CC area
B. Lesions
C. EDSS

FA

Ax

Ra
Lower FA in Stutterers in ventral-premotor (Watkins)
Lower FA in Stutterers in ventral-premotor (Watkins)
TBSS & FSL-VBM in adolescent-onset schizophrenia
Douaud & James, Brain 2007

FA reduction
GM reduction
• Attempting to solve correspondence/smothing problems
• Less ambiguity of interpretation / spurious results than VBM
• Easier to test whole brain than ROI / tractography

• Limitations & Dangers
  • Interpretation of partial volume tracts still an issue
  • Crossing tracts?

• Future work
  • Use full tensor (for registration and test statistic)
  • Use other test statistics (MD, PDD, width)
  • Multivariate stats (across voxels and/or different diffusion measures) & discriminant (ICA, SVM)
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Connectivity - Why do we care?

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

  Evangelou et al. 2000

  E.g. axonal degeneration/demyelination in MS.

  - Diffusion tractography allows in-vivo measurements specific to different connections.
Different regions have distinct connectivity fingerprints.
Basic Science - Connections constrain function

Different regions have distinct connectivity fingerprints

Understanding regional connectivity will be essential for our understanding of systems neuroscience.

Passingham et al, NNR, 2003
Investigating connectivity
Investigating connectivity

- Tracer studies in non-human animals

- In human
  - Post-mortem dissection reveals large tracts
  - Post-mortem histology shows degeneration after remote lesions

Rouiller et al, 1998
Investigating human brain connectivity
Investigating human brain connectivity

Diffusion-weighted MR imaging
- Fractional anisotropy
- Principal diffusion direction
Investigating human brain connectivity

Diffusion-weighted MR imaging
- Fractional anisotropy
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Investigating human brain connectivity

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Diffusion-weighted MR imaging
- Fractional anisotropy
- Principal diffusion direction
Investigating human brain connectivity

Diffusion-weighted MR imaging
- Fractional anisotropy
- Principal diffusion direction
Streamline tractography can dissect major bundles
But elsewhere...Uncertainty in fibre orientation.

Derek Jones

Measured from repeated datasets
But elsewhere... Uncertainty in fibre orientation.
So what can we do?
So what can we do?

• Remember ... a long time ago in the world of fMRI ...
So what can we do?

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• We estimated two things:
  • A cope file (the parameters)
  • A varcope file (uncertainty in these parameters)
So what can we do?

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

- We estimated two things:
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- We estimated our parameters, and their uncertainty from a single dataset.
So what can we do?

• 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 Diffusion parameters?
FDT tractography uses a simple model of local diffusion:
- A single anisotropic direction with isotropic background diffusion.

Reasons:
- No ambiguity between ADC profile and uncertainty.
- Avoid errors due to sorting eigenvectors in DTI.
- Simplifies extensions to multiple fibre orientations.
Modelling complex architecture
Modelling complex architecture

- Form testable hypotheses.
- Ask questions about parameters of interest
Modelling complex architecture

- Form testable hypotheses.
- Ask questions about parameters of interest
- Extra sensitivity gained from assumptions
Modelling complex architecture

- Form testable hypotheses.
- Ask questions about parameters of interest
- Extra sensitivity gained from assumptions
- Only estimate complexity that is supported by the data
Uncertainty from a single dataset

Empirical

Bayesian

White Matter Voxel

CSF Voxel
Modelling complex architecture

- Form testable hypotheses.
  - Ask questions about parameters of interest

- Extra sensitivity gained from assumptions

- Only estimate complexity that is supported by the data
Probabilistic tractography

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

‘Streamlining’

Probabilistic tractography
Probabilistic tractography

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

'Streamlining'

Probabilistic tractography
Probabilistic Tractography

• Allows you to track into regions of low anisotropy, e.g., grey matter

• Provides quantitative (see later) probability of connection from A to B

Behrens et al, MRM, 2003
Thalamic connections with cortex

MD -> PFC

VL -> M1
Connectivity-based classification of thalamic voxels produces clusters.

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Connectivity-based classification of thalamic voxels produces clusters

Functional validation: meta-analysis of FMRI activations within thalamus

Johansen-Berg et al, Cerebral Cortex, 2005

- Executive tasks
- Motor tasks
Correspondence between functional activations and connectivity-defined volumes: motor tasks
Correspondence between functional activations and connectivity-defined volumes: executive tasks
Parieto-premotor connections

Behrens and Rushworth
Parieto-premotor connections

Posterior PL <-> Anterior PMC

Behrens and Rushworth
Parieto-premotor connections

Posterior PL <-> Anterior PMC
Anterior PL <-> Posterior PMC

Behrens and Rushworth
Parieto-premotor connections

Posterior PL <-> Anterior PMC
Anterior PL <-> Posterior PMC
Lateral PL <-> Frontal Eye Fields

Behrens and Rushworth
Parieto-premotor connections

Posterior PL <-> Anterior PMC
Anterior PL <-> Posterior PMC
Lateral PL <-> Frontal Eye Fields

Behrens and Rushworth
But....

Tracking Parietal -> Medial premotor regions in 9 subjects
Tracking Parietal -> Medial premotor regions in 9 subjects
But....

Tracking Parietal -> Medial premotor regions in 9 subjects
Using multi-fibre modelling.
Using multi-fibre modelling.
Using multi-fibre modelling.
Topography of premotor connections in parietal lobe.

Average of 9 subjects.

Tracking from parietal To:

- Anterior Premotor
- Posterior Premotor
- Frontal Eye Fields

Behrens and Rushworth
Topography of premotor connections in parietal lobe.

Average of 9 subjects. Tracking from parietal To: Anterior Premotor Posterior Premotor Frontal Eye Fields

Behrens and Rushworth
Connectivity of prefrontal cortex

Hayashi T et al. Society for Neuroscience, Atlanta 2006

Probability (%)

Caudate

Thalamus

Pallidum

Midbrain peduncle

BA9

DWI                                Mn

24h  48h  72h  96h  168h

3                       100

40                          120

X= -4.0mm

z= 5.5mm

z= 1.0mm

z= -8.5mm
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.
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BEDPOSTX

GUI options

data.nii.gz
nodif_brain_mask.nii.gz
bvecs
bvals

Data

Model parameters
BEDPOSTX

Results

- Sample orientations
  - merged_th1samples.nii.gz
  - merged_ph1samples.nii.gz
  - merged_th2samples.nii.gz
  - merged_ph2samples.nii.gz

- Sample fractional volumes
  - merged_f1samples.nii.gz
  - merged_f2samples.nii.gz

- Mean orientation
  - dyads1.nii.gz
  - dyads2.nii.gz

- Mean fractional volumes
  - mean_f1samples.nii.gz
  - mean_f2samples.nii.gz
BEDPOSTX

Results

- Mean orientation

(dyads1.nii.gz)
(dyads2.nii.gz)
BEDPOSTX

Results

• Mean fractional volumes
BEDPOSTX

Results

- Mean orientation
BEDPOSTX
Modelling crossing fibres

- Large portion of the white matter voxels has two fibres
- Crossing fibres form coherent bundles
BEDPOSTX

Modelling crossing fibres

1 fibre

2 fibres
PROBTRACKX
Seed specification

- Different ways of specifying seeds
- Allow seed specification in a different space
Seed specification

- single voxel
- single mask
- multiple masks
• Different seed spaces

Diffusion space  Structural space  Standard space
PROBTRACK\textsuperscript{X} (optional) Targets specification

- Waypoints
- Exclusion
- Termination
- Classification

- Dissecting specific tracts
- Quantification of connectivity
PROBTRACKX
(optional) Targets specification

- Waypoints
- Exclusion
- Termination
- Classification

Dissecting specific tracts

Quantification of connectivity

ALL THE TARGETS IN THE SAME SPACE AS THE SEEDS
PROBTRACKX
(optional) Targets specification

- Waypoints
- Exclusion
- Termination
- Classification
PROBTRACKX
Dissecting a specific tract
Cortico-spinal tract

Seed: M1, hand area
No targets
PROBTRACKX

Dissecting a specific tract
Cortico-spinal tract

Seed: M1, hand area

Exclusion: Mid-Sagittal plane
PROBTRACKX

Dissecting a specific tract
Cortico-spinal tract

Seed: M1, hand area
Waypoint: Internal Capsule
PROBTRACKX

Dissecting a specific tract
Cortico-spinal tract

Seed: dorsal PMC

No targets
PROBTRACKX

Dissecting a specific tract

Cortico-spinal tract

Seed: dorsal PMC

Waypoint: Corpus Callosum
PROBTRACKX
Dissecting a specific tract
Cortico-cerebellar projections

Seed: M1 hand

Waypoint: Thalamus

Termination: Thalamus
PROBTRACKX

Connectivity-based seed classification

• Quantify the connectivity of seed regions to target regions

• e.g. thalamic voxels can be classified according to their probability of connection to specific cortical targets
PROBTRACKX

Connectivity-based seed classification
Thalamic segmentation
Discussion

What are we (not) measuring?

• Distribution of a fibre orientation rather than distribution of fibre orientations

• Thresholding tract distribution is tricky

• Bins (voxels) are arbitrary

• Favour seed classification for quantitative analysis (masks are meaningful)
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