The AFNI-based Functional and Anatomical Connectivity Platform (including SUMA + FATCAT)

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With SUMA: complement volume info.

- Surface/volume Intersection
- Shell/volume Intersection
SUMA: Surface Mapping
SUMA: why use the surface?

Geometry and Topology

- **Geometry**: Spatial location
  - X, Y, Z coordinates of brain structures

- **Topology**: Spatial connectivity
  - Relative positions of brain structures along the surface

- Geometric proximity does not imply topological proximity
  - If you care about the topology of activation, you should transfer FMRI data onto the surface before spatial manipulations of the data
With SUMA: surface representations

SmoothWm

Inflated

Pial

Spherical

Inflated, Occipital cut

Overlay of anatomically correct Pial and SmoothWm surfaces over anatomical volume

Flattened, Occipital cut
With SUMA: graph + matrix + tract + anatomy ...

Simultaneous linked rendering in graph and matrix modes
3D matrices supported (e.g. time varying correlation matrix)
Outline

+ Why Function + Structure
+ DWI and DTI (→ local structures)
  - Brief diffusion imaging basics and parameters
  - Role of noise → DTI parameter uncertainty
+ Using tractography (→ estimate extended structures)
  - goals of tracking.
  - algorithms/properties
  - final thoughts on interpretation
FMRI: GM Networks

Functional connectivity networks of distinct GM regions, from BOLD time series during task or rest/no task.

+ Quantify GM properties: ALFF, fALFF, RSFA, $\sigma$, ReHo, GMV, etc.

+ Quantify network props: seedbased correlation, ICA, graph theoretical measures, etc.
Functional connectivity: networks

For {RS- | TB-}FMRI: correlation matrices

+ 3dNetCorr: calculated post-processing, input time series data + network maps
  - can be multi-brick maps, 1 network per brick
  - calculate average time series per ROI, correlation among network ROIs
  - outputs correlation matrix/matrices, (can also do Fisher-Z transform output)

++ Can also calculate ReHo, ALFF, fALFF, etc. in FATCAT/AFNI.
DTI-based parameters characterize some local structural properties and also show the presence of spatially-extended WM structures.

Can quantify structural (esp. WM) properties using:
FA, MD, RD, L1, etc.

Can investigate (and Quantify?) network relations with:
tractography
Structural connections in the brain

The (schematic) structure of neurons

Extended white matter fibers, often organized in bundles
Structure + Function

Simple example:

GM ROIs network:

- Somatomotor
- Dorsal attention
- Control
- Default mode

Raichle (2010, TICS)
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Associated WM ROIs

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Structure + Function

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Associated WM ROIs

Our goal for tractography->
estimate likely/probable locations of WM associated with GM, and relate ROI quantities with functional/GM properties
AFNI tools for combining FC and SC:

Combining functional and tractographic connectivity will require:
+ determining networks from FMRI (or other) data;
+ finding correlations and local properties of functional networks;
+ turning GM ROIs into targets for tractography;
+ doing reasonable tractography to find WM ROIs;
+ estimating stats on WM ROIs...

**FATCAT:** Functional And Tractographic Connectivity Analysis Toolbox (Taylor & Saad, 2013), available in AFNI with demo data+scripts.

*picture from google search, not from/of either author*
What is diffusion tensor imaging?

DTI is a particular kind of magnetic resonance imaging (MRI)
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**Diffusion:** random motion of particles, tending to spread out
→ here, hydrogen atoms in aqueous brain tissue
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**Tensor:** a mathematical object (a matrix) to store information
→ here, quantifying particle spread in all directions

\[
D = \begin{pmatrix}
D_{11} & D_{12} & D_{13} \\
D_{21} & D_{22} & D_{23} \\
D_{31} & D_{32} & D_{33}
\end{pmatrix}
\]
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→ here, hydrogen atoms in aqueous brain tissue

**Tensor:** a mathematical object (a matrix) to store information
→ here, quantifying particle spread in all directions

**Imaging:** quantifying brain properties
→ here, esp. for white matter
The DTI model:
Assumptions and relation to WM properties
Diffusion as environmental marker

Diffusion: random (Brownian) motion of particles \( \rightarrow \) mixing or spreading

Ex: unstirred, steeping tea (in a large cup):
Diffusion as environmental marker

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Ex: un stirred, steeping tea (in a large cup):

Empty cup, no structure:
Atoms have equal probability of movement any direction
→ spherical spread of concentration
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$\rightarrow$ Diffusion shape tells of structure presence and spatial orientation
Local Structure via Diffusion MRI

(In brief)

1) Random motion of molecules affected by local structures
Local Structure via Diffusion MRI

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2) Statistical motion measured using diffusion weighted MRI
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3) Bulk features of local structure approximated with various reconstruction models, mainly grouped by number of major structure directions/voxel:

   + one direction:
     DTI (Diffusion Tensor Imaging)
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(In brief)

1) Random motion of molecules affected by local structures

2) Statistical motion measured using diffusion weighted MRI

3) Bulk features of local structure approximated with various reconstruction models, mainly grouped by number of major structure directions/voxel:

+ one direction:
  DTI (Diffusion Tensor Imaging)

+ >=1 direction:
  HARDI (High Angular Resolution Diffusion Imaging)
  Qball, DSI, ODFs, ball-and-stick, multi-tensor, CSD, ...
Diffusion in MRI

Mathematical properties of the matrix/tensor:

\[ \mathbf{D} = \begin{pmatrix} D_{11} & D_{12} & D_{13} \\ D_{21} & D_{22} & D_{23} \\ D_{31} & D_{32} & D_{33} \end{pmatrix} \]

Having: 3 eigenvectors: \( \mathbf{e}_i \)

3 eigenvalues: \( \lambda_i \)

- Real-valued
- Positive definite (\( \mathbf{r}^T \mathbf{D} \mathbf{r} > 0 \))
  \[ \mathbf{D} \mathbf{e}_i = \lambda_i \mathbf{e}_i, \quad \lambda_i > 0 \]
- Symmetric (\( D_{12} = D_{21} \), etc),

6 independent values
Diffusion in MRI

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- Real-valued
- Positive definite \((r^T Dr > 0)\)
- Symmetric \((D_{12} = D_{21}, \text{ etc})\)
- 6 independent values

Having: 3 eigenvectors: \(e_i\)

3 eigenvalues: \(\lambda_i\)

Geometrically, this describes an ellipsoid surface:

\[
C = D_{11}x^2 + D_{22}y^2 + D_{33}z^2 + 2(D_{12}xy + D_{13}xz + D_{23}yz)
\]

**Isotropic case**

\(\lambda_1 = \lambda_2 = \lambda_3\)

**Anisotropic case**

\(\lambda_1 > \lambda_2 > \lambda_3\)
DTI: ellipsoids

Important mathematical properties of the diffusion tensor:

+ Help to picture diffusion model:
  tensor $D \rightarrow$ **ellipsoid surface**
  eigenvectors $\rightarrow$ orientation in space
  eigenvalues $\rightarrow$ 'pointiness' + 'size'
DTI: ellipsoids

Important mathematical properties of the diffusion tensor:

+ Help to picture diffusion model:
  tensor $D \rightarrow \text{ellipsoid surface}$
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+ Determine the minimum number of
  DWIs measures needed (6 + baseline)
DTI: ellipsoids

Important mathematical properties of the diffusion tensor:

+ Help to picture diffusion model:
  tensor $\mathbf{D} \rightarrow$ ellipsoid surface
  eigenvectors $\rightarrow$ orientation in space
  eigenvalues $\rightarrow$ 'pointiness' + 'size'

+ Determine the minimum number of DWIs measures needed (6 + baseline)

+ Determine much of the processing and noise minimization steps
Cartoon examples: white matter ↔ FA

GM vs WM
Cartoon examples: white matter ↔ FA
Cartoon examples: white matter ↔ FA

GM vs WM

WM bundle organization

FA↑
Cartoon examples: white matter ↔ FA

GM vs WM

WM bundle organization

FA ↑
Cartoon examples: white matter ↔ FA

GM vs WM

WM bundle density

FA↑

FA↑

FA↑

FA↑
Cartoon examples: white matter ↔ FA

GM vs WM

WM bundle density

WM bundle organization

GM     vs     WM

WM maturation (myelination)
Interpreting DTI parameters

General literature:

**FA**: measure of fiber bundle coherence and myelination
  - in adults, FA > 0.2 is proxy for WM

**MD, L1, RD**: local density of structure

**e_1**: orientation of major bundles
Interpreting DTI parameters

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**e₁**: orientation of major bundles

Cautionary notes:

- Degeneracies of structural interpretations
- Changes in myelination may have small effects on FA
- WM bundle diameter << voxel size
  - don't know location/multiplicity of underlying structures
- More to diffusion than structure-- e.g., fluid properties
- Noise, distortions, etc. in measures
Noise in DW signals

→ Leads to errors in surface fit, equivalent to *rotations* and *rescalings* of ellipsoids:

'Un-noisy' vs perturbed/noisy fit
Now discuss using *local* structure information to generate/estimate *nonlocal* structures: WM tractography
Tractography in brief

old, invasive

stain and preserve brain, get some idea of structure... non-ideal:
brain physiology changes postmortem, also `mortem' aspect

new(er), theoretical

(images from Iowa Virtual Hospital and Bammer et al. 2003)
Tractography

Estimate WM structure (fiber tract locations)

- Ellipsoid measures (~smoothing of real structures)
- Some kind of algorithm for connecting

= Estimate spatial extents of WM ‘tracts’ in vivo

(images from Bammer et al. 2003)
Tractography: connecting the brain

(looking at you)

(looking downward)
Importance of being processed (in earnest)

NB words of wisdom from wikipedia GIGO entry:

On two occasions I have been asked, "Pray, Mr. Babbage, if you put into the machine wrong figures, will the right answers come out?" ... I am not able rightly to apprehend the kind of confusion of ideas that could provoke such a question.

—Charles Babbage, Passages from the Life of a Philosopher
Importance of being processed (in earnest)

In addition to the tracking algorithm, the quality of data acquisition and preparation matter quite a bit → see the TORTOISE tool (Pierpaoli et al., 2010)

https://science.nichd.nih.gov/confluence/display/nihpd/TORTOISE

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Importance of being processed (in earnest)

Data from the morning session, same target ROI in brainstem. Consider reach of tracts, symmetry, physiology, etc.
Cinematic side note:

La Belle et la Bête of tractography
Known Challenges for Tracking

- Axon diameters are of order a few micrometers
- MRI voxel size is of order millimeters

*images of Eyewire data via NPR website*
Known Challenges for Tracking

+ Axon diameters are of order a few micrometers
+ MRI voxel size is of order millimeters

+ WM regions are tightly packed, with many connections and potentially complicated sub-voxel scale structure

(images of Eyewire data via NPR website)

+ Crossing/kissing fibers can:
  - Lower FA (stop tracking)
  - Redirect (or not) tracking incorrectly.
Known Challenges for Tracking

+ Comparisons: high res DTI with tracer anatomy

Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited

Cibu Thomas\textsuperscript{a,b,1}, Frank Q. Ye\textsuperscript{c,d}, M. Okan Irfanoglu\textsuperscript{a,b}, Pooja Modi\textsuperscript{a}, Kadharbatcha S. Saleem\textsuperscript{a}, David A. Leopold\textsuperscript{c,d}, and Carlo Pierpaoli\textsuperscript{a,b}

Fig. 2. The specificity and sensitivity of diffusion tractography techniques differ by diffusion model and location of the seed ROI. Specificity and sensitivity for seed ROI-PCG (A) and seed ROI-V4v (B). For all four types of diffusion models tested, the seed ROI was a sphere with a radius of 10 voxels, and the default angular threshold was used for deterministic (45°) and probabilistic (80°) tractography techniques. The Youden index value (J), which summarizes the performance of each tractography technique, is noted.
Achievements of Tracking

- Reproduction of many known pathways
- In vivo vs post-mortem information

(Wakana et al., 2004)

(Bammer et al., 2003)
Achievements of Tracking

+ Helping in planning electrode placement in deep brain stimulation (DBS)

DBS application: Parkinsons disease (Lauro et al., 2015)

DBS application: treatment-resistant depression (Rive-Posse et al., 2014)
Light at the end of the tunnel?

Tractography seems useful and logically consistent as follows:

1) GM ROIs are connected by WM skeleton.
2) We can use tracking to estimate and highlight WM likely to be associated with GM ROIs.
3) One can then use DTI parameters in the tracked 'WM ROIs' for quantitative comparisons (or use ROIs as masks for other data).
4) Tractography can parcellate the WM skeleton based on the subject's own data.
5) Avoid interpreting reconstructed tracks to represent literal, underlying fibers.
Applying tractography
FMRI provides:
maps of (GM) regions working together

GM ROIs network:

Raichle (2010, TiCS)
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Structure + Function

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GM ROIs network:

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and relate ROI quantities with functional/GM properties

Raichle (2010, TiCS)
1) Start with FMRI:
→ threshold to obtain networks of GM ROIs

Example: Tractographic selections of WM
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2) Use DTI-tractography to find likely location of WM associated with these 'targets'

(Deterministic tracking using publicly available AFNI-FATCAT software)
Example: Probabilistic tractography

More robust tracking method (many Monte Carlo iterations)

→ 'most likely' locations of WM

orange = GM ROIs
blue = WM estimates
(via AFNI-FATCAT)
Deterministic vs Probabilistic

+ NB: coverage and connectivity differences between tractography types

+ Deterministic can be useful for initial investigations, but is more susceptible to noise/errors and truncation
3dTrackID: Probabilistic tractography

+ compare with existing algorithms:
  - purple: FSL-probtrackX (and FSL-bedpostX for uncertainty)
  - same parameters: FA>0.2, max angle 60deg, 5000 Monte Carlo iterations; 1 tract direction/voxel
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+ generally similar connections, but FSL bigger blobs
+ FSL took several hours for uncertainty, and then >24 hours for tracking this single network (and had to run 4 for this study)
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+ generally similar connections, but FSL bigger blobs
+ 3dDWUncert took 7min; 3dTrackID took 25mins total for 4 netw.
Mini-Probabilistic Tracking

+ Full probabilistic methods generate voxelwise brain maps without linear track structure
+ 'Mini-probabilistic' tracking performs a few extra iterations of deterministic tracking on uncertainty-perturbed data sets
  - track structure is retained,
  - results generally exhibit more robust tracks and fewer false negatives than deterministic tracking alone
  - false positives tend to be isolated and visually apparent.

A

B

C

Deterministic (AND) with `-mini_prob 7'
Mini-Probabilistic Tracking

Deterministic vs mini-Probabilistic

Through single ROI

AND logic through network, cf with full-prob results
WM (ROI) Quantities

For connected pairs of GM ROIs in a network, have an average WM property (or can map to T1, PD...)

Have produced sets of localized structural/anatomical quantities for comparison with functional values or behavioral scores, genetics, etc.

Can use for group or individual comparisons/regressions.
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3dNetCorr: correlation matrices
Of average time series in ROIs (e.g., uninflated GM ROIs from 3dROIMaker)