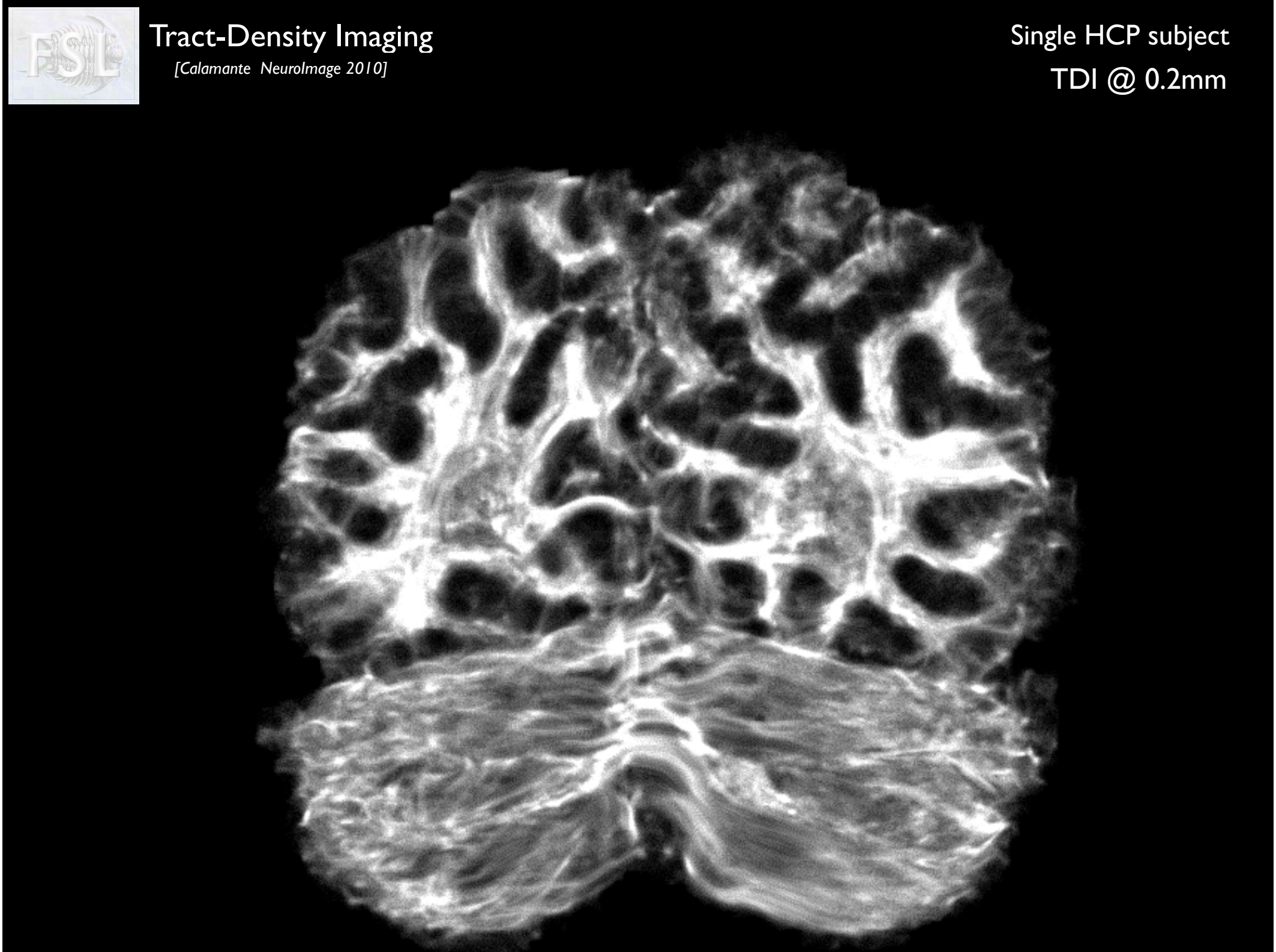
Tract-Density Imaging

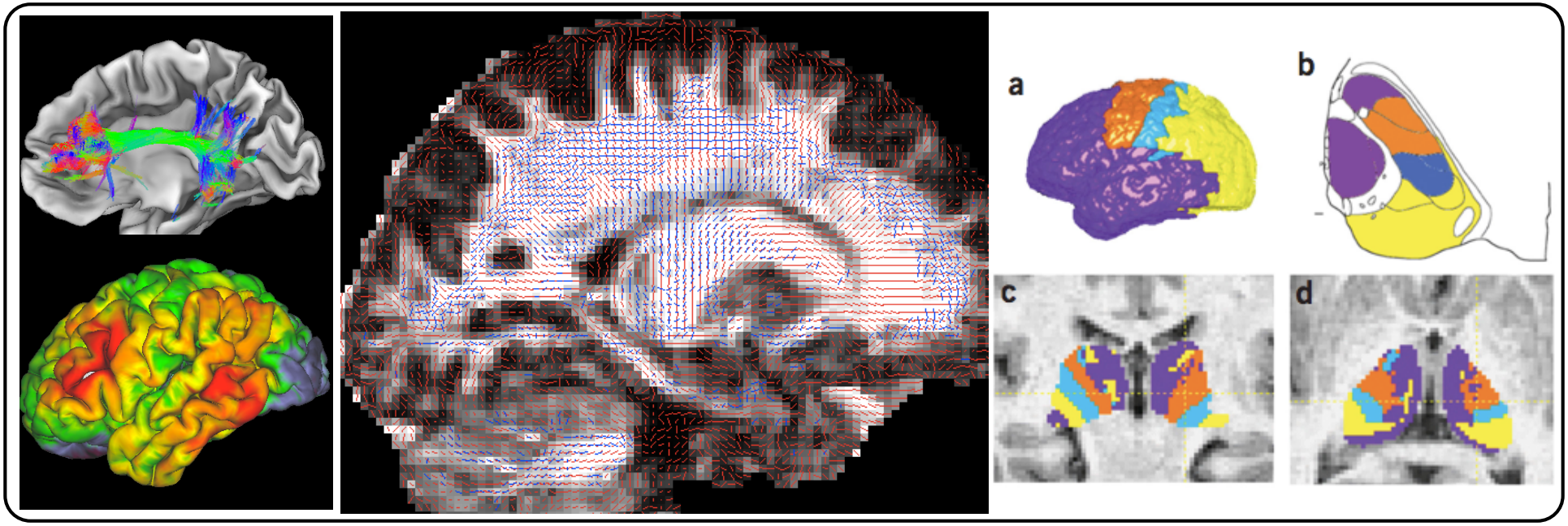
[Calamante NeuroImage 2010]

Single HCP subject

TDI @ 0.2mm

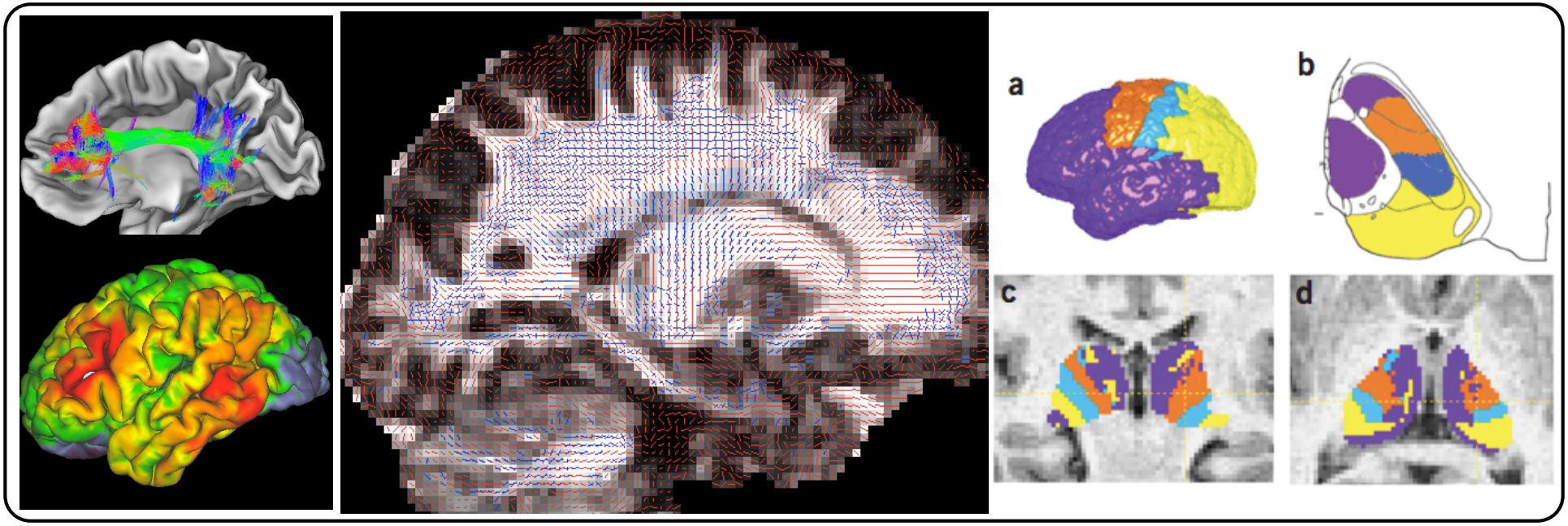


Diffusion Tractography



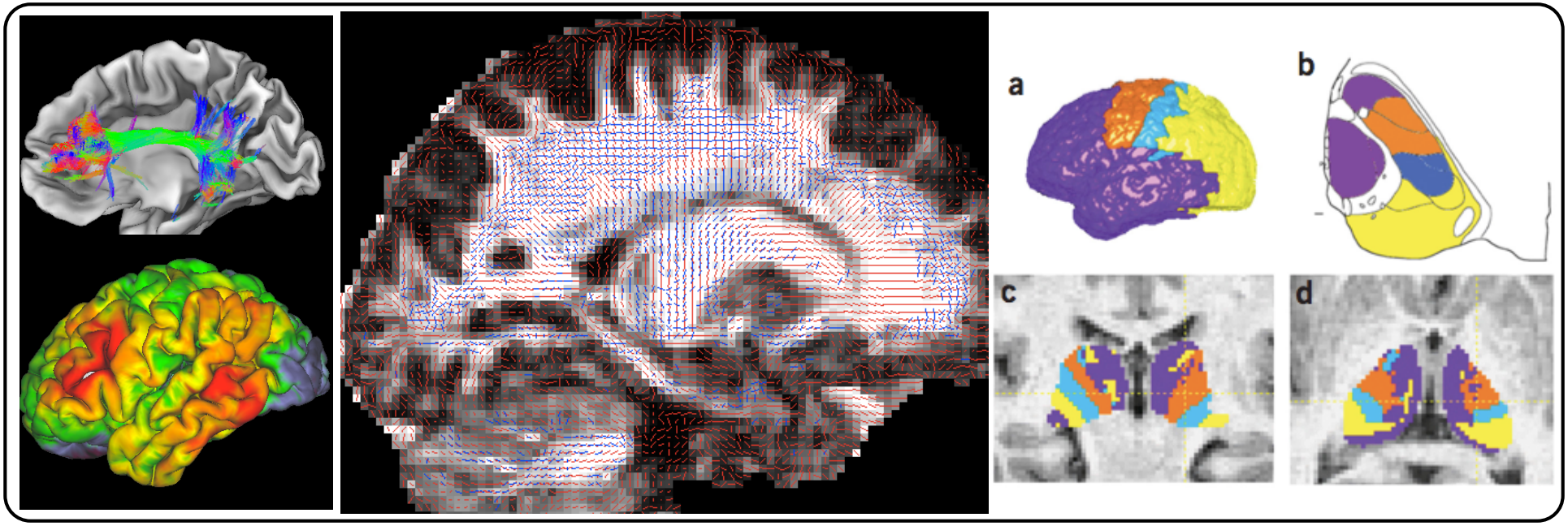
Overview

- Goal of tractography
- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- ProbtrackX outputs
- Tractography limitations

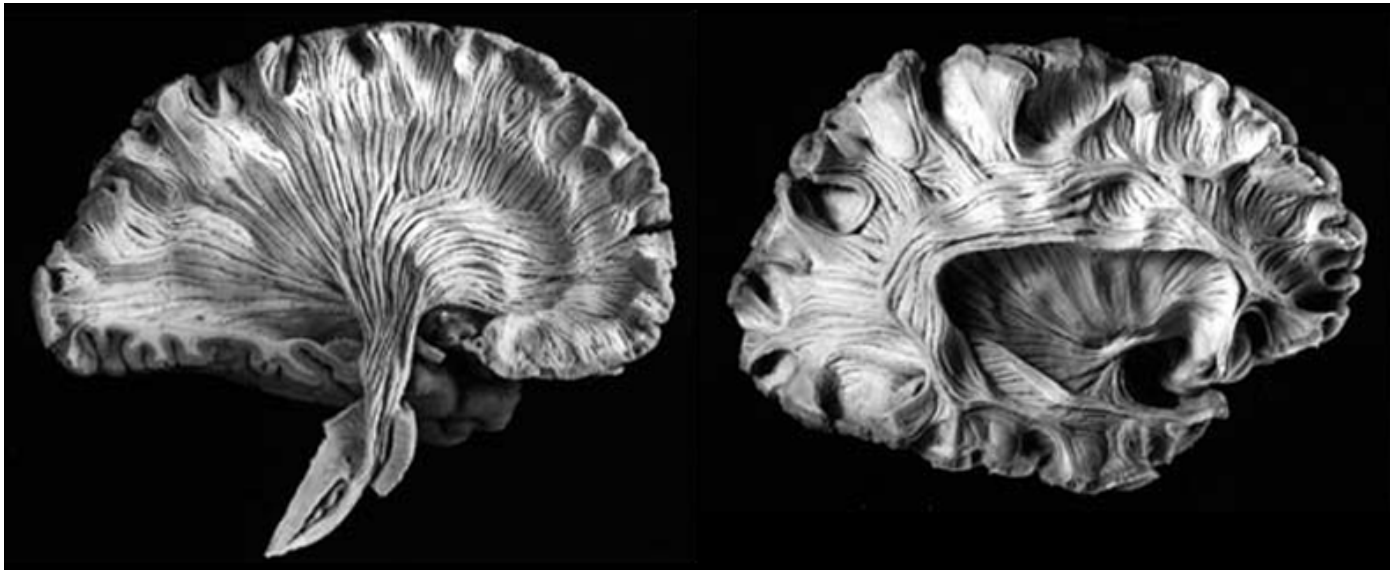


Overview

- Goal of tractography
- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- ProbtrackX outputs
- Tractography limitations



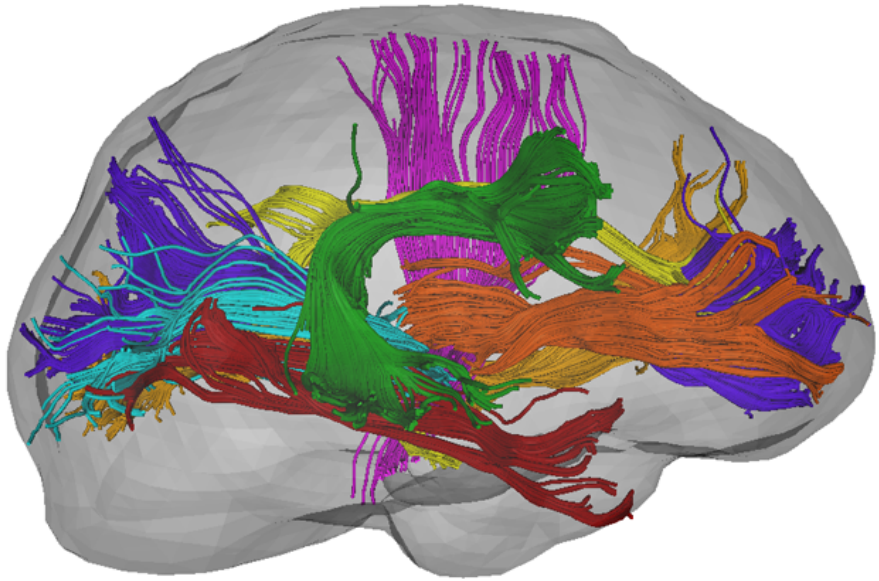
What is Tractography?



Post-mortem dissection of some white matter fibre bundles (tracts)

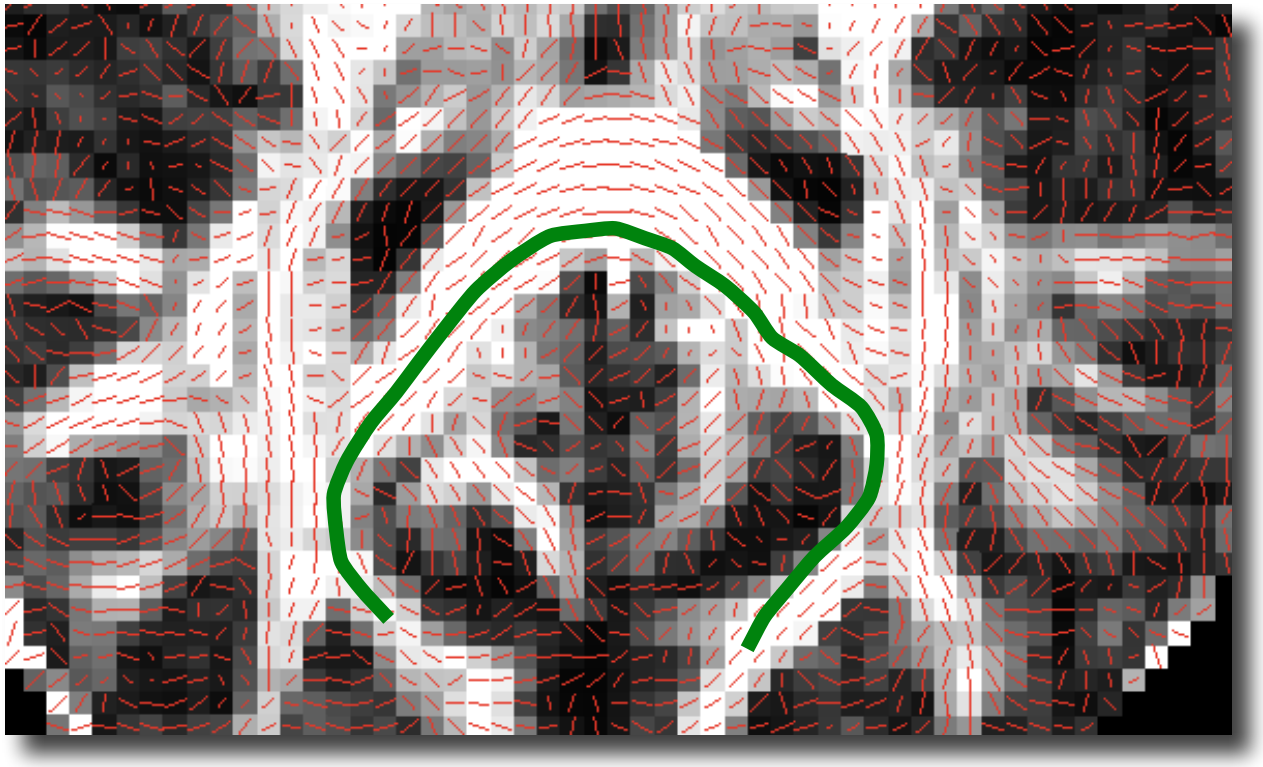
Williams, Gluhbegovic, and Jew, "The Human Brain`; Dissections of the Real brain", Virtual Hopstital, Universitoy of Iowa, 1997

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

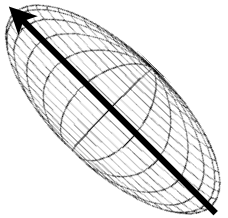


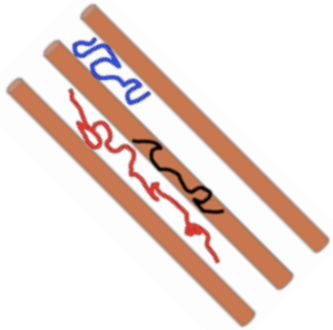
DTI tractography

$\mathbf{v}_1$ map
Principal Diffusion Direction



Principal Diffusion Direction

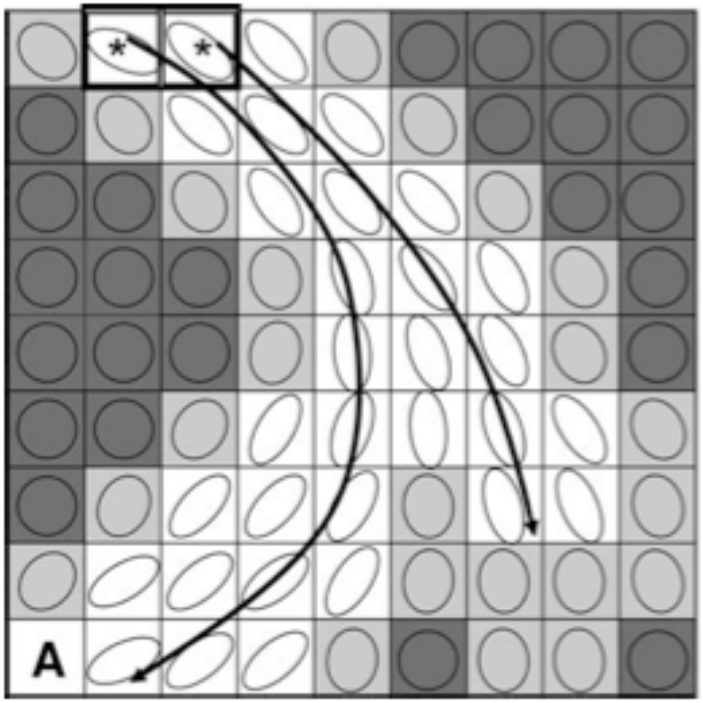




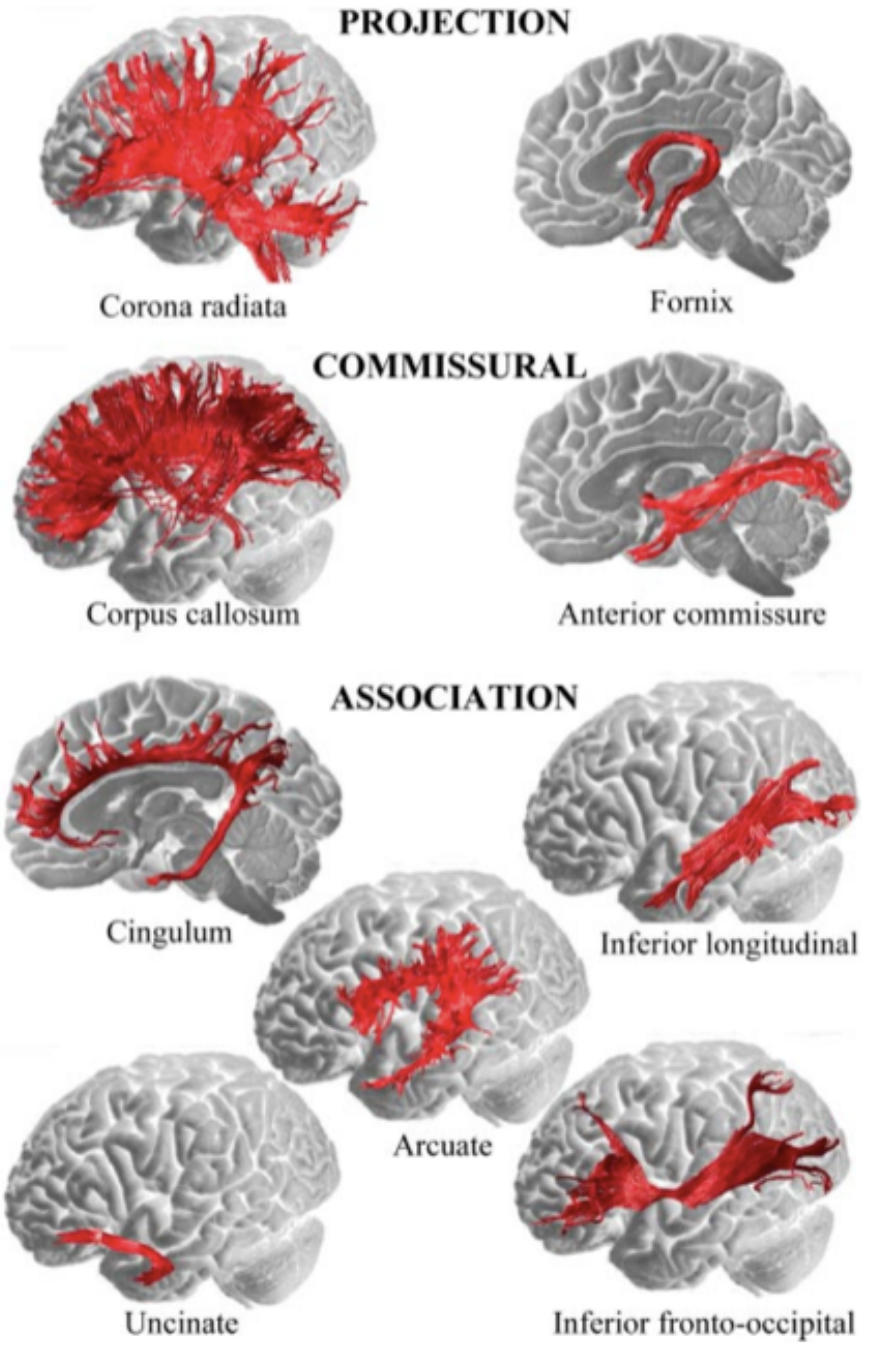
<u>Assumption</u>:

Direction of maximum diffusivity
(in anisotropic voxels)
is an **<u>estimate</u> of the major fibre orientation**.

DTI tractography



[Basser et al, Magn Reson Med, 2000]

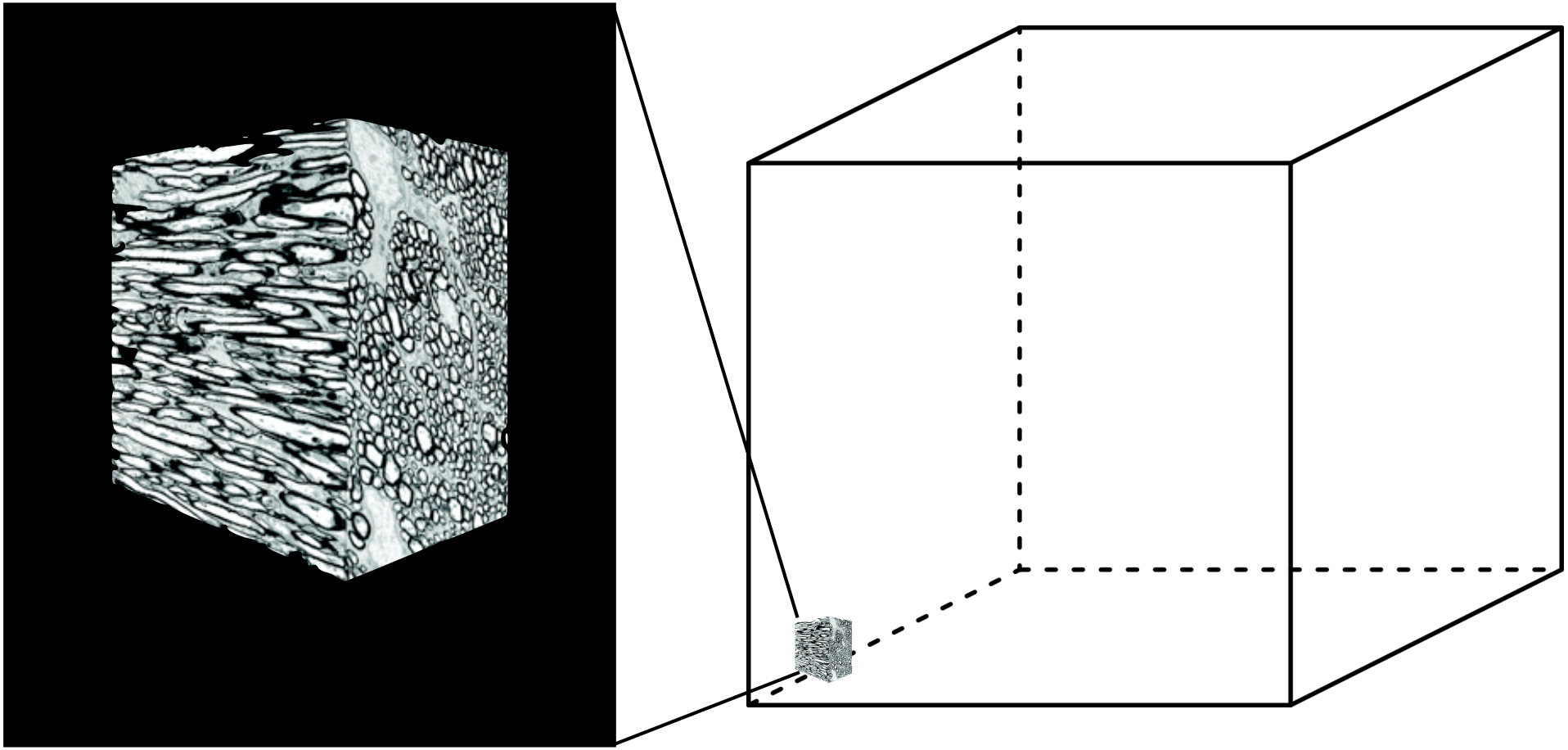


[Catani et al, NeuroImage, 2003]

Problems of scale

Microscopic view of white matter axon size (~µm)

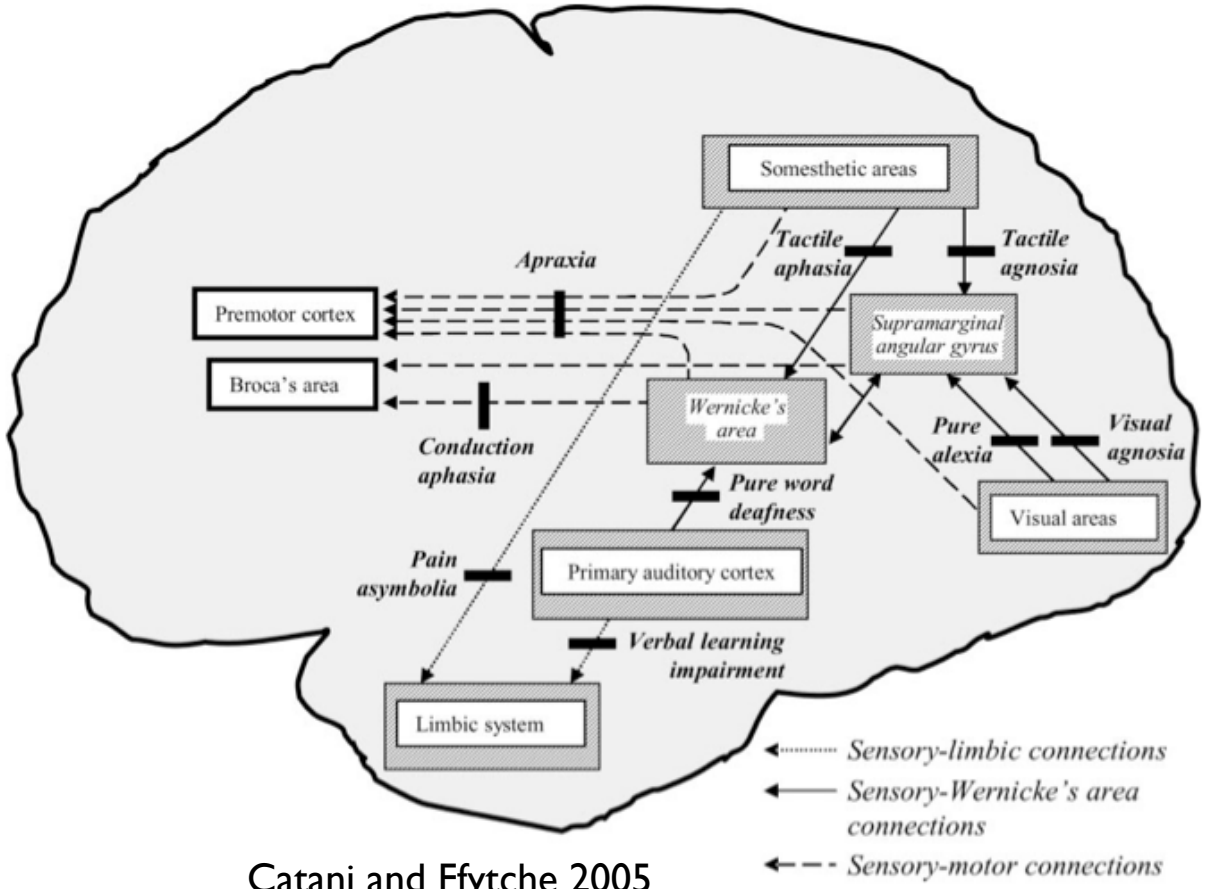
MRI voxel size (~mm)



Ohno et al. 2013

Connectivity - Why do we care?

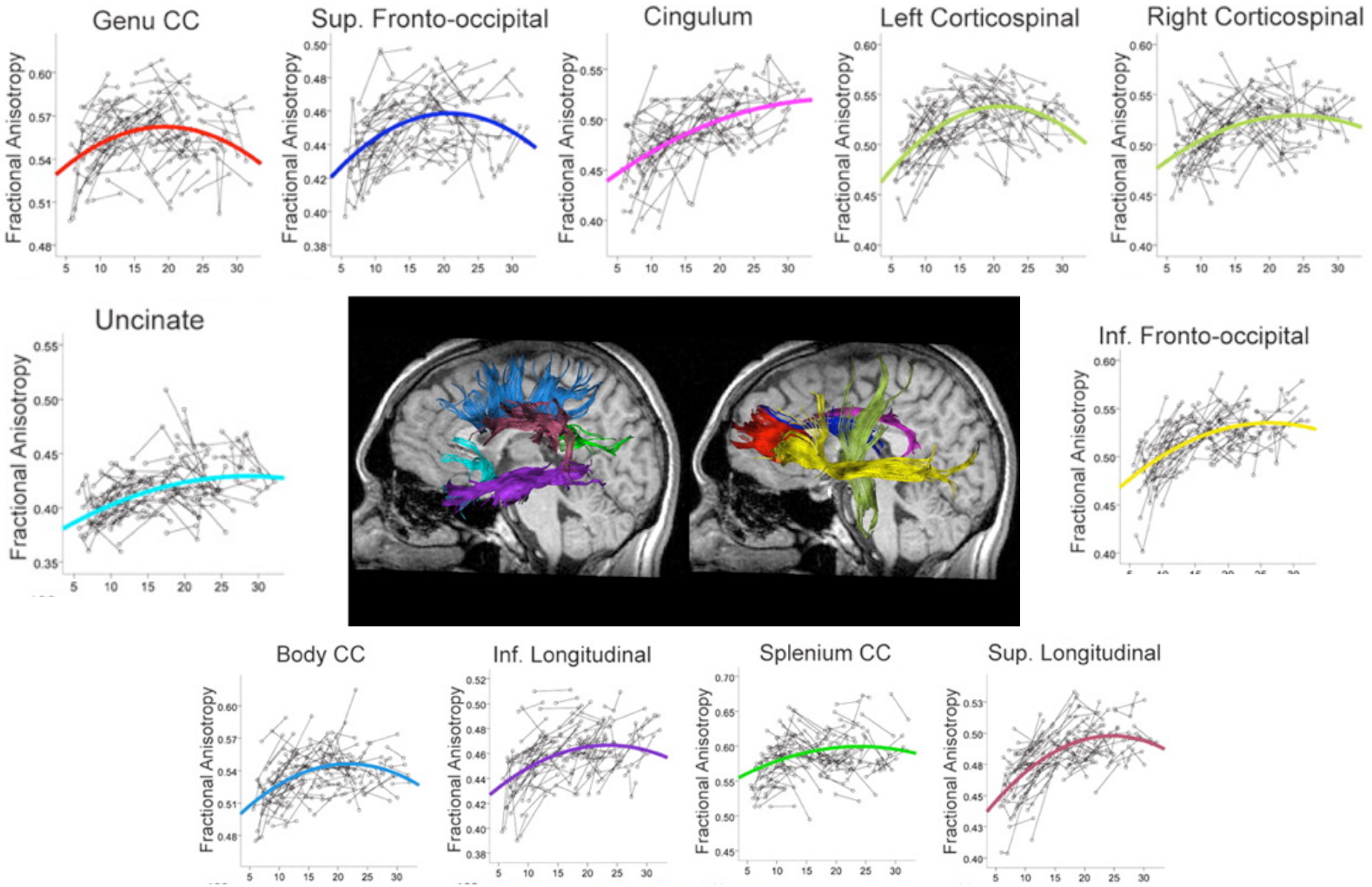
- White matter (dys)connectivity is thought to form the substrate for many different neurological and psychiatric disorders.



Catani and Ffytche 2005

Connectivity - Why do we care?

- Tractography provides non-invasive localisation and semi-quantitative biomarkers

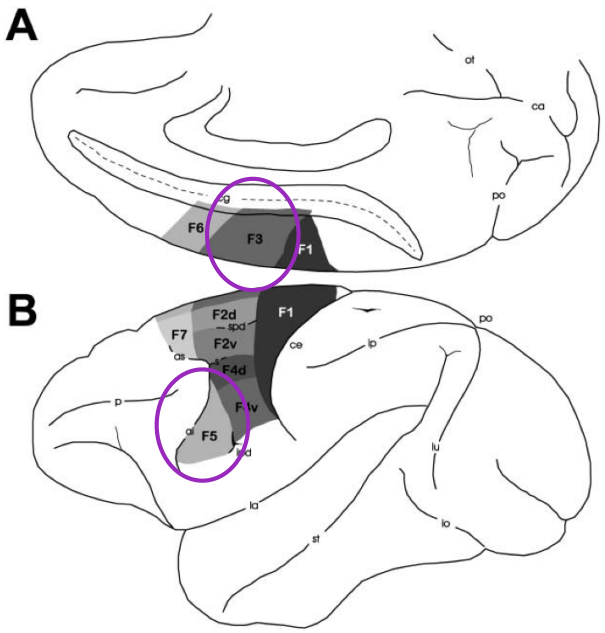


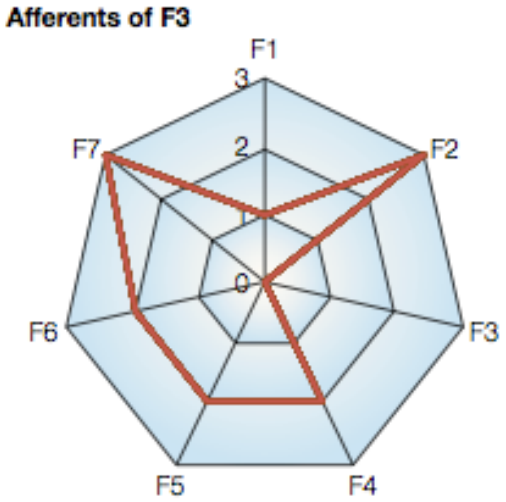
Lebel, Beaulieu J Neuroscience 2011

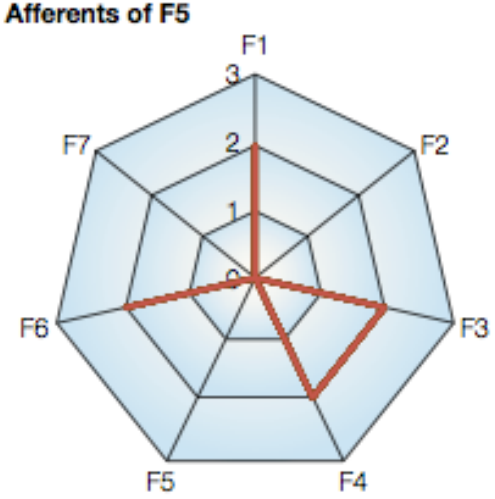
Connectivity - Why do we care?

- Connections constrain function

- Different regions have distinct connectivity fingerprints



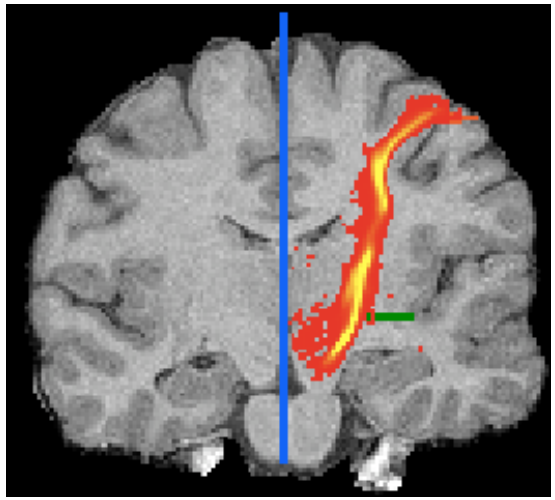


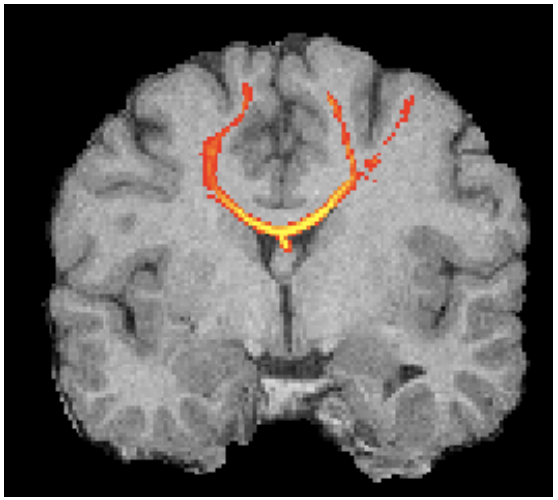


Passingham et al. 2002

Tractography outputs

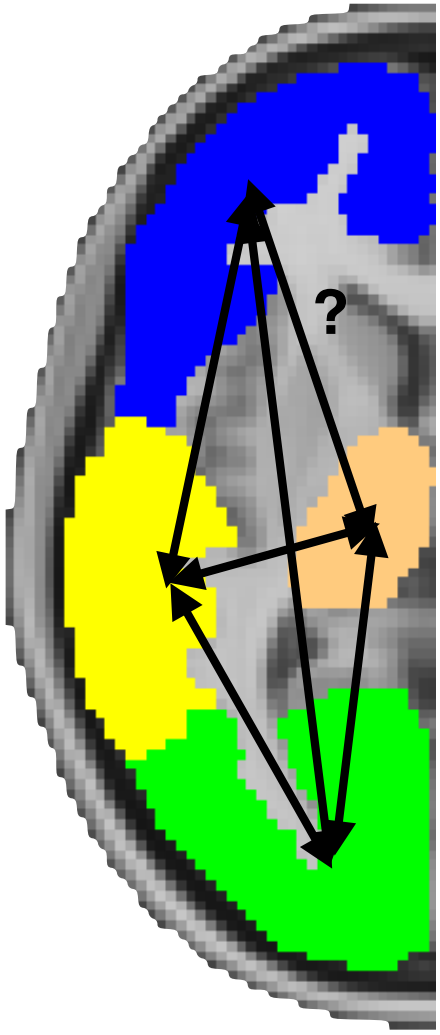
Known white matter tracts



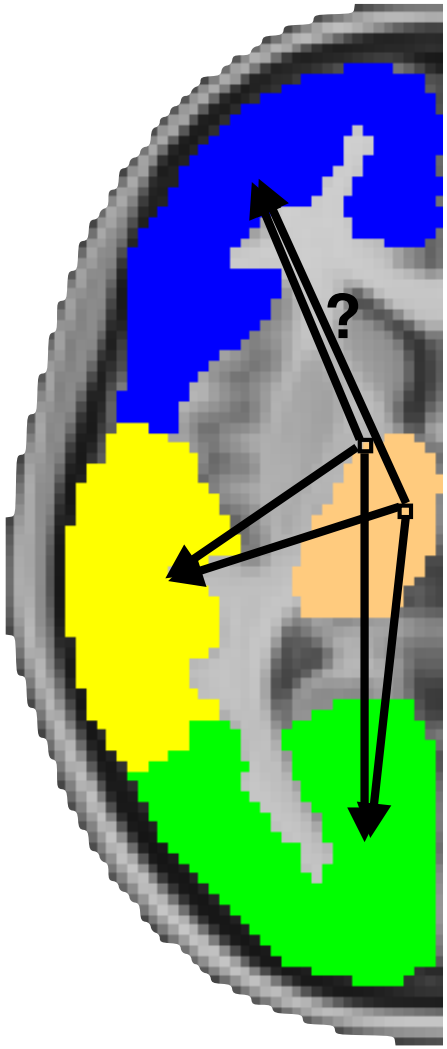


Connectivity matrices

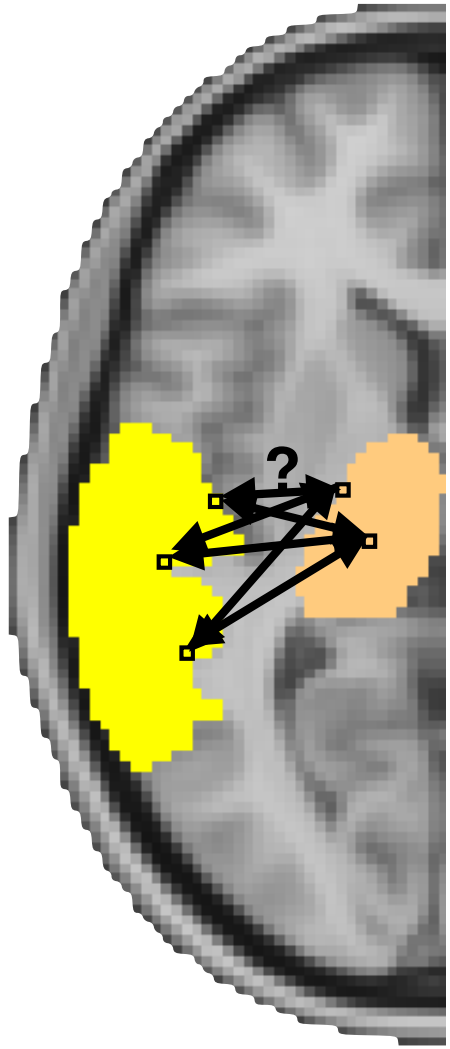
ROI by ROI



voxel by ROI

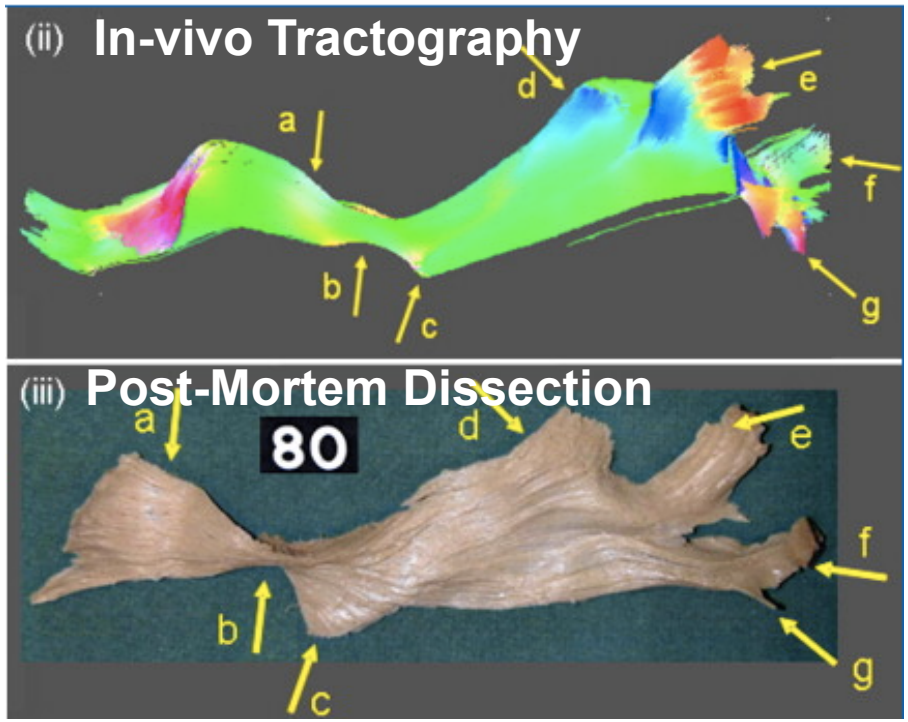


voxel by voxel



What does tractography offer?

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

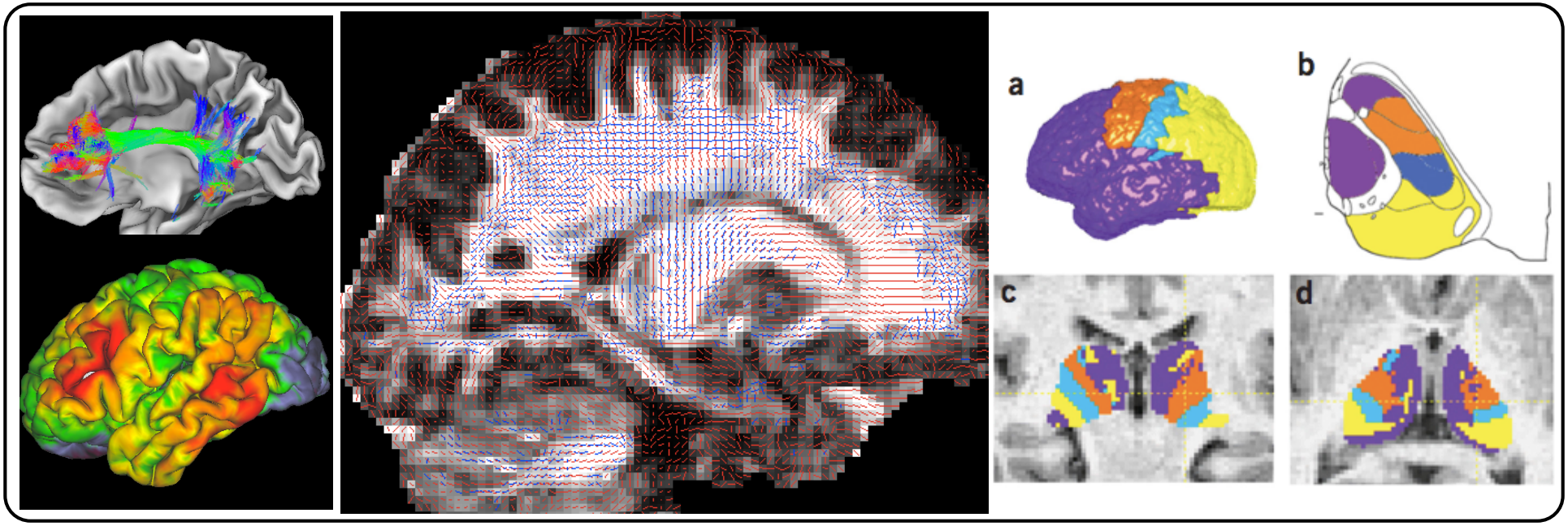


Lawes et al. 2008

...But
- low resolution (large bundles)
- indirect (diffusion paths)
- error prone (MRI is noisy)
- difficult to interpret quantitatively

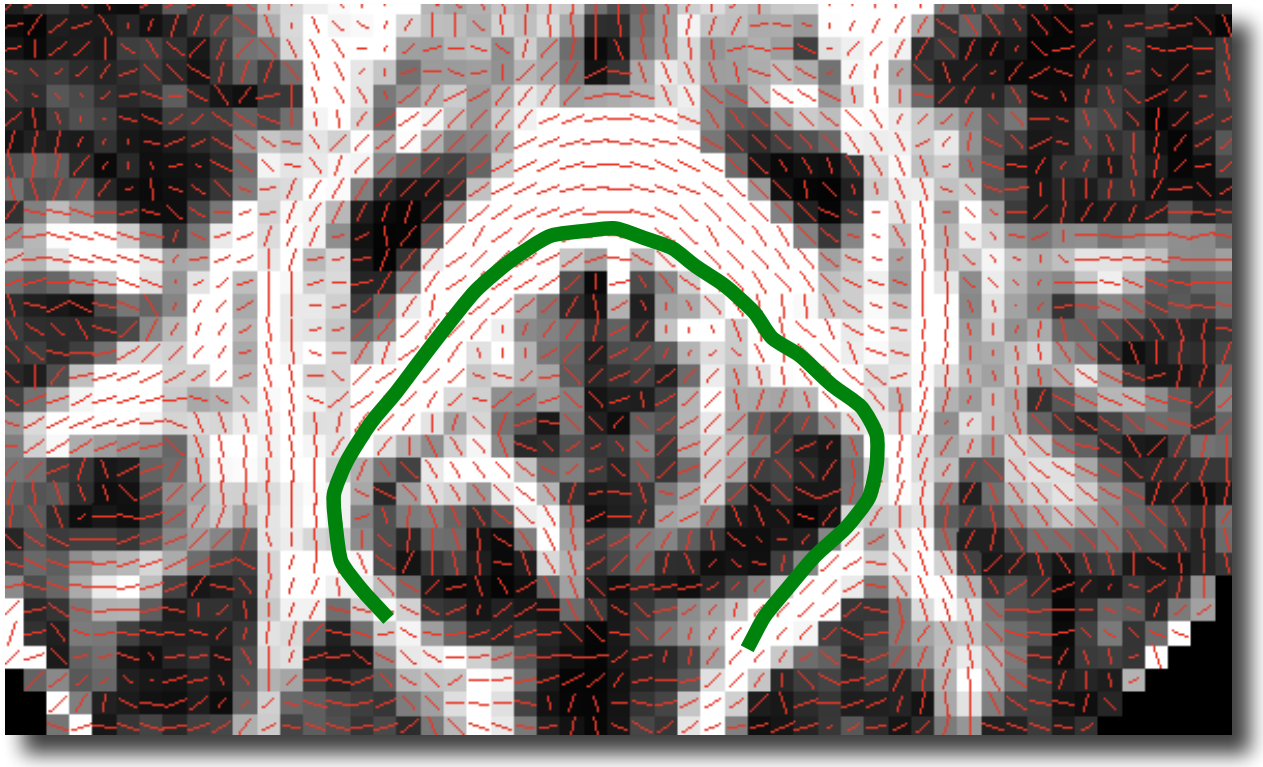
Overview

- Goal of tractography
- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- ProbtrackX outputs
- Tractography limitations

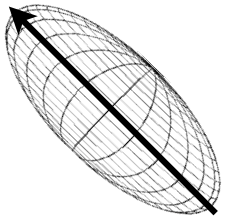


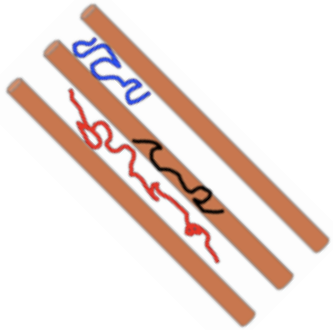
DTI tractography

$\mathbf{v}_1$ map
Principal Diffusion Direction



Principal Diffusion Direction

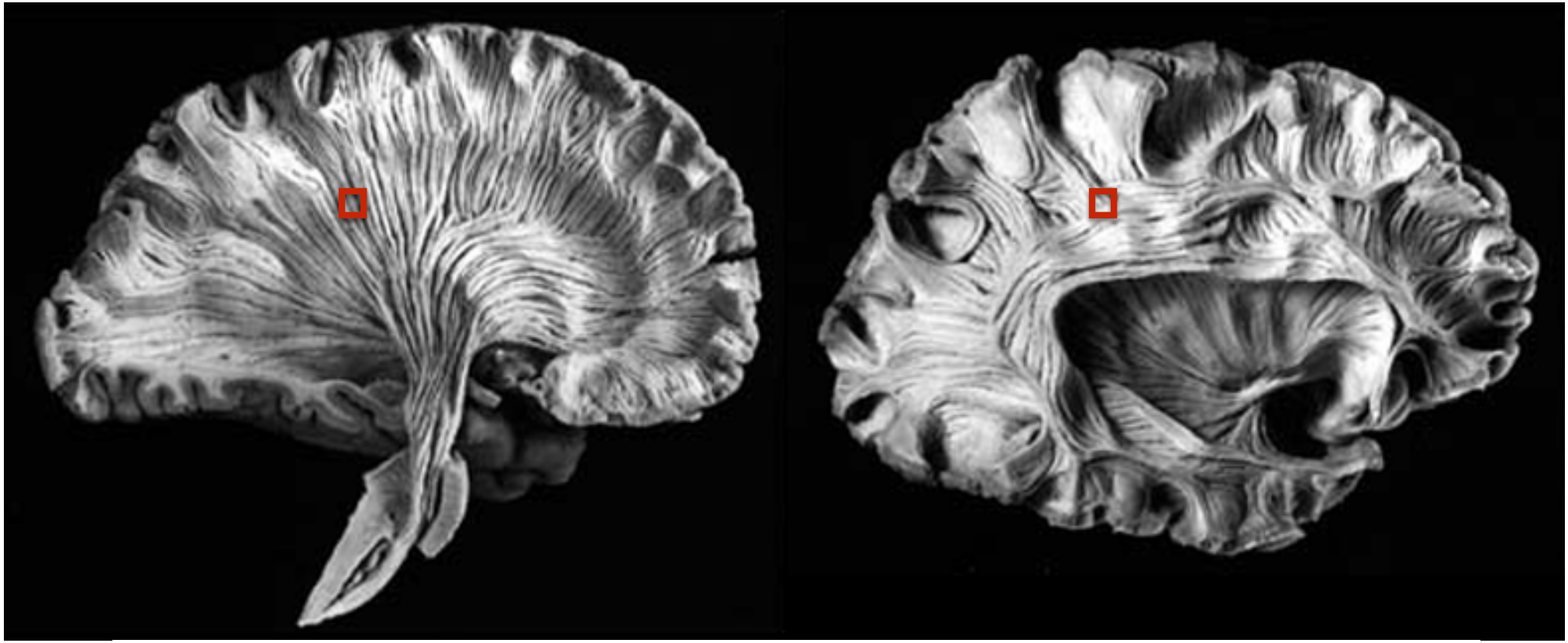




<u>Assumption</u>:

Direction of maximum diffusivity
(in anisotropic voxels)
is an **<u>estimate</u> of the major fibre orientation**.

But is WM always coherently organised within a voxel?



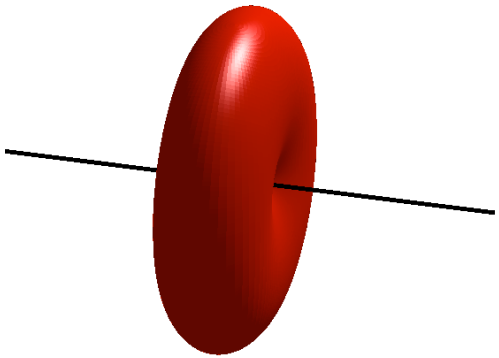
Unfortunately not, complex fibre patterns (e.g. crossings) are very common at the voxel scale.

Williams, Gluhbegovic, and Jew, "The Human Brain`; Dissections of the Real brain", Virtual Hopstital, Universitoy of Iowa, 1997

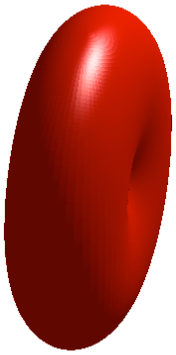
Predictions from the tensor model
no crossing fibres

One orientation

Measured Signal Shape

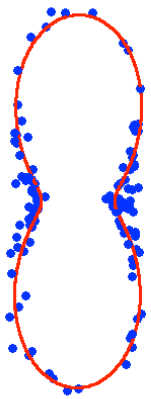


Predicted Signal Shape



DTI Ellipsoid

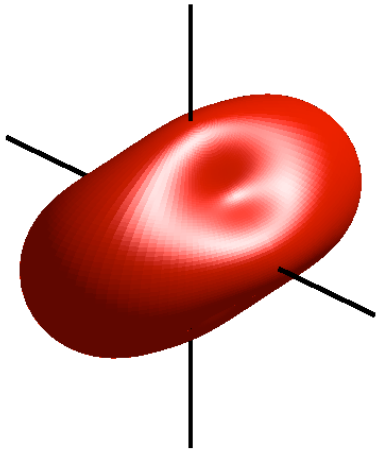
Prediction & Measurements in 2D



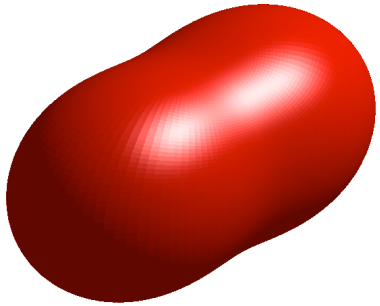
Predictions from the tensor model crossing fibres

Two orientations

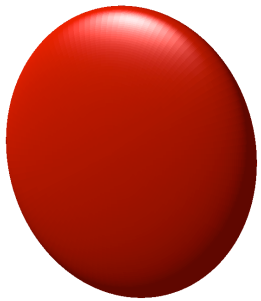
Measured Signal Shape



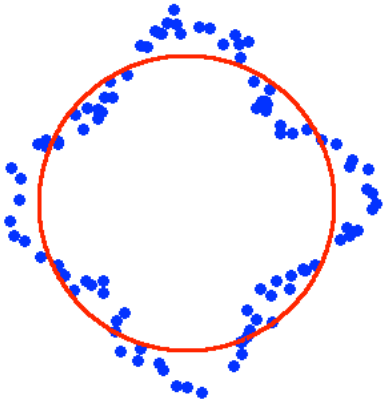
Predicted Signal Shape



DTI Ellipsoid



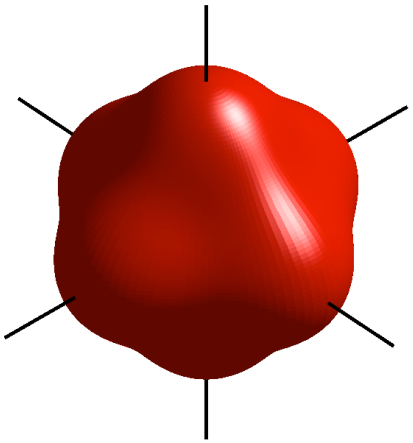
Prediction & Measurements in 2D



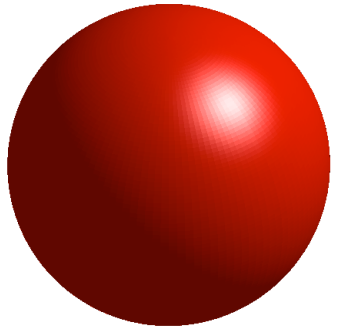
Predictions from the tensor model crossing fibres

Three Orientations

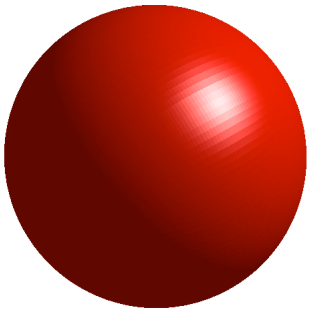
Measured Signal Shape



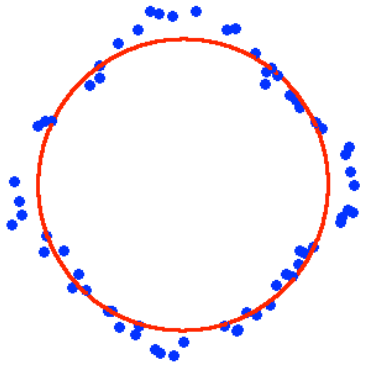
Predicted Signal Shape



DTI Ellipsoid



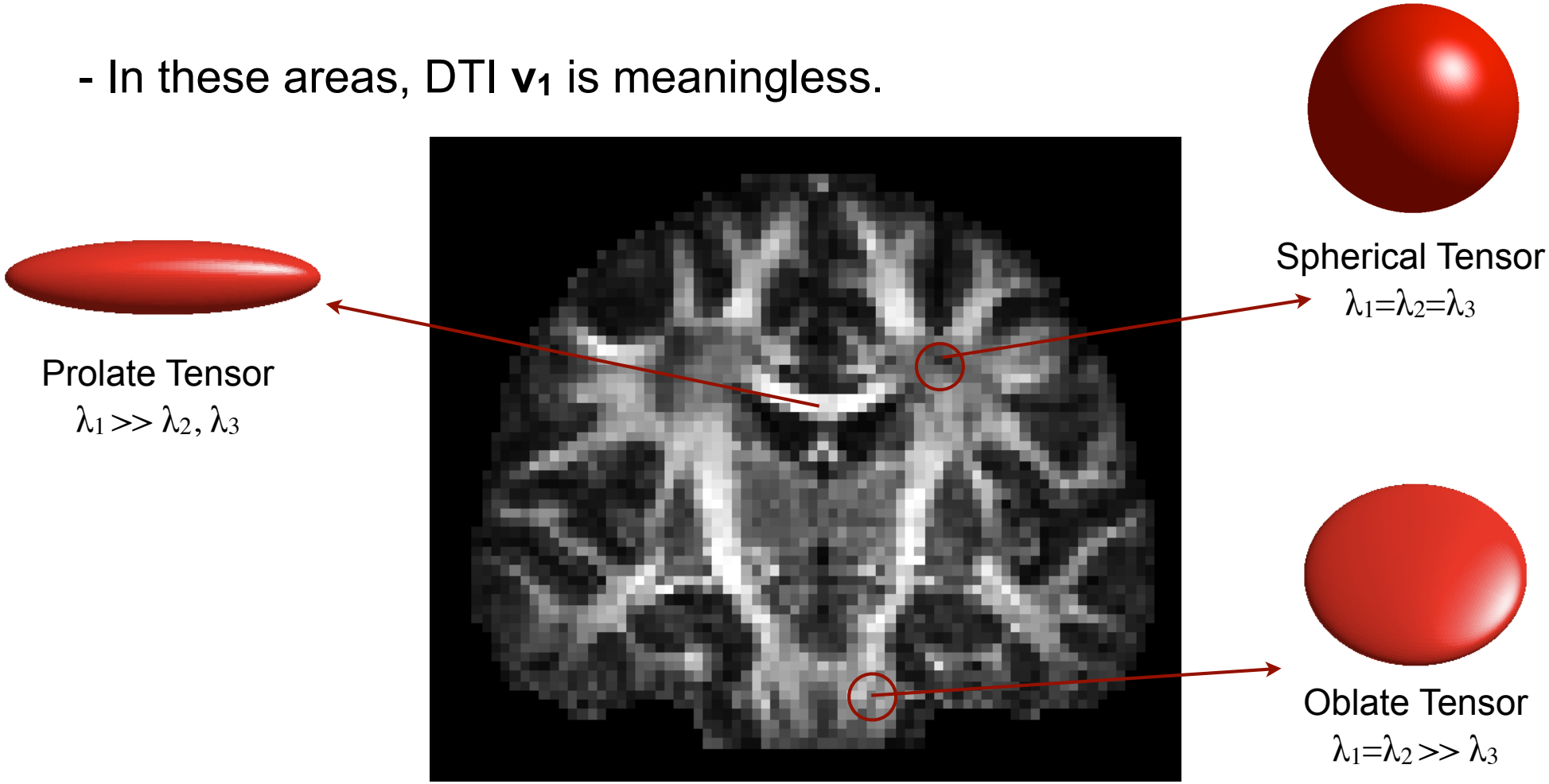
Prediction & Measurements in 2D



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 $\mathbf{v_1}$ is meaningless.

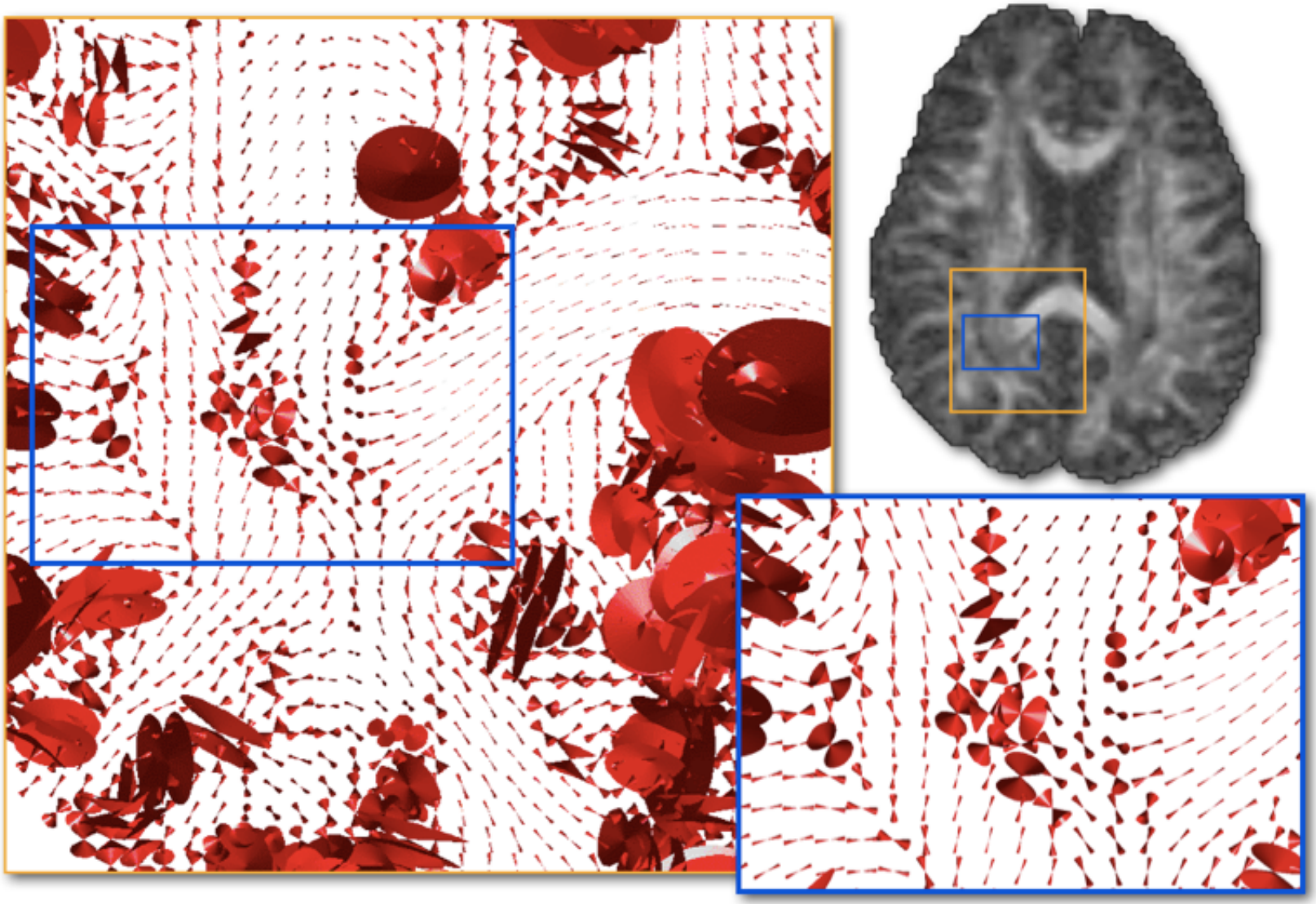


Uncertainty on DTI Fibre Orientation Estimates

Repeat an acquisition many times and obtain the variability in $\mathbf{v}_1$ from the different datasets.

Uncertainty Sources

- Modelling errors
- Noise



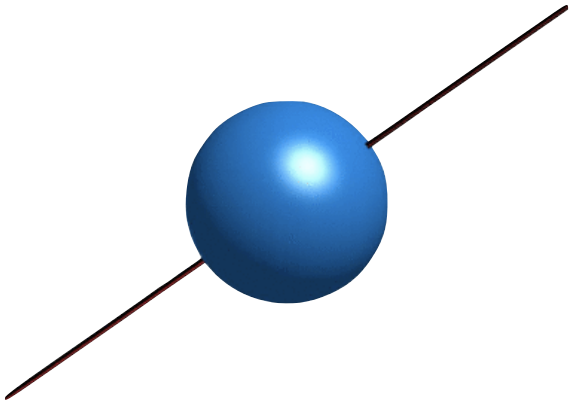
Cones of uncertainty on DTI $\mathbf{v}_1$

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)



$$s_j = s_0 [(1-f)\exp(-b_j\, d) + f \exp(-b_j\, d(\mathbf{x}_j^{\mathrm{T}}\mathbf{v})^2)]$$

Anisotropic Volume Fraction (unknown)

Diffusivity (unknown)

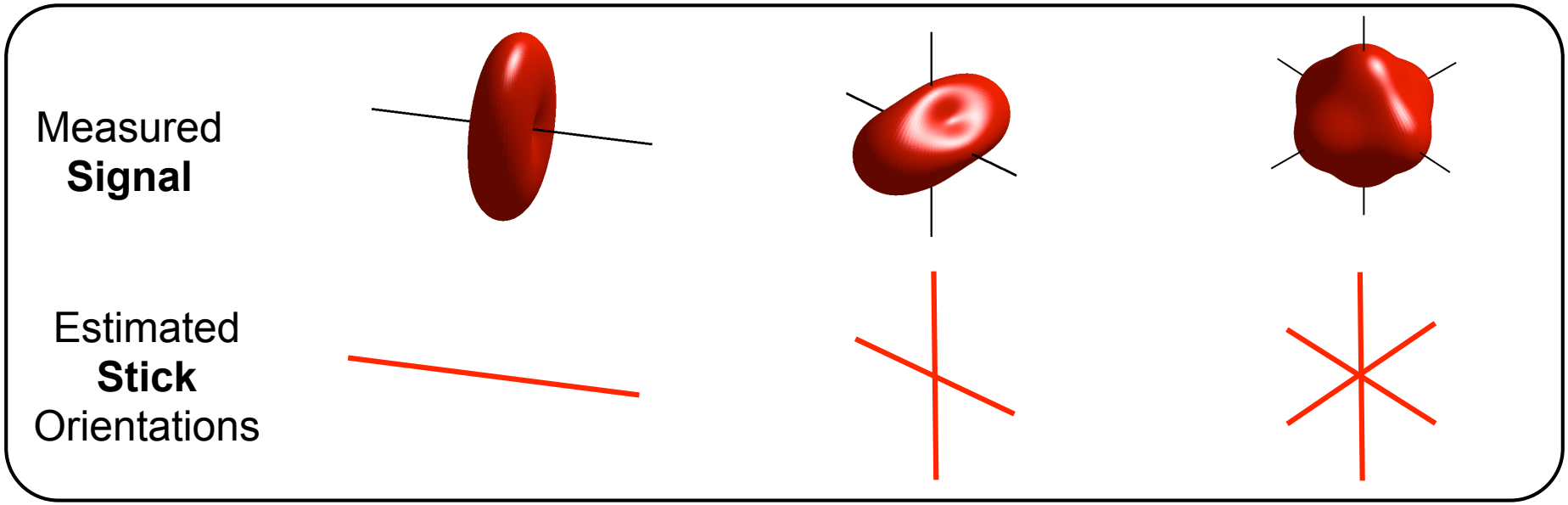
Fibre Orientation (unknown)

Measured Signal for Gradient *j*

b-value for gradient *j* (known)

Unit vector representing the direction of gradient *j* (known)

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

Anisotropic Volume Fractions (unknown)

Diffusivity (unknown)

Max number of sticks (user-defined)

Fibre Orientation (unknown)

$$s_j = s_0 \left[(1-\Sigma f_n)\exp(-b_j\, d)+\Sigma f_n \exp(-b_j\, d(\boldsymbol{x}_j^{\mathrm{T}}\boldsymbol{v}_n)^2)\right]$$

Measured Signal for Gradient *j*

b-value for gradient *j* (known)

Unit vector representing the direction of gradient *j* (known)

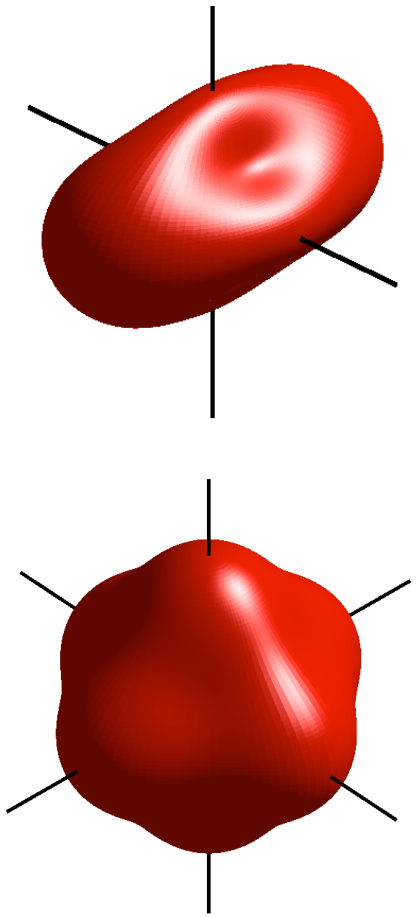
Predictions from the ball and sticks model crossing fibres

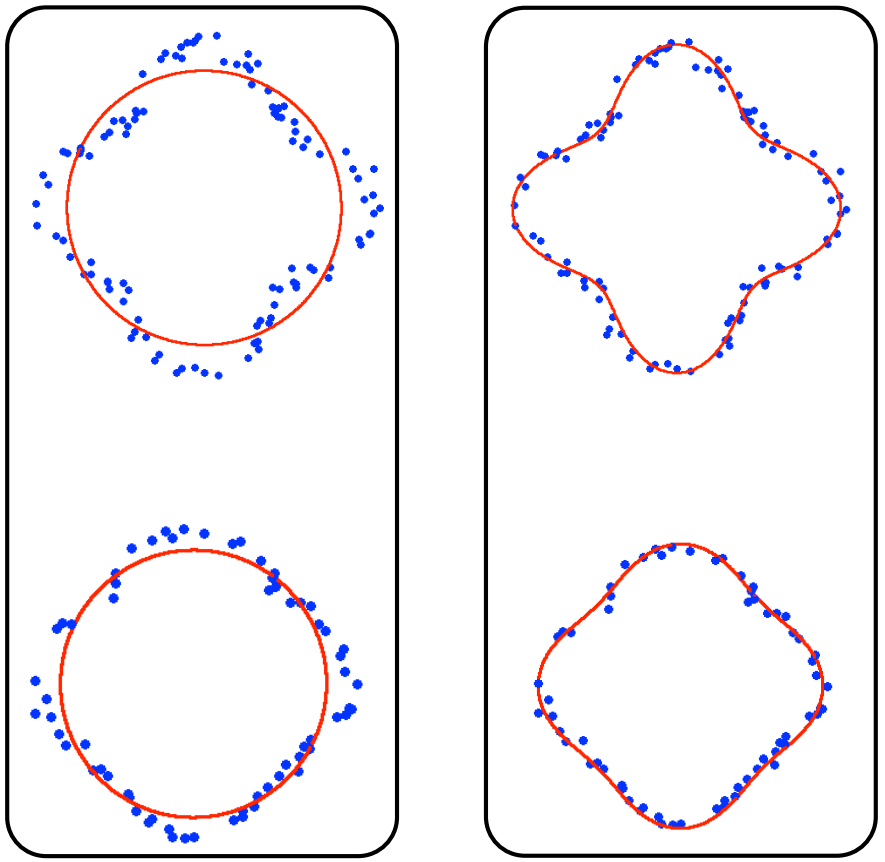
Measured Signal Shape

Prediction & Measurement in 2D

Two orientations

Three orientations

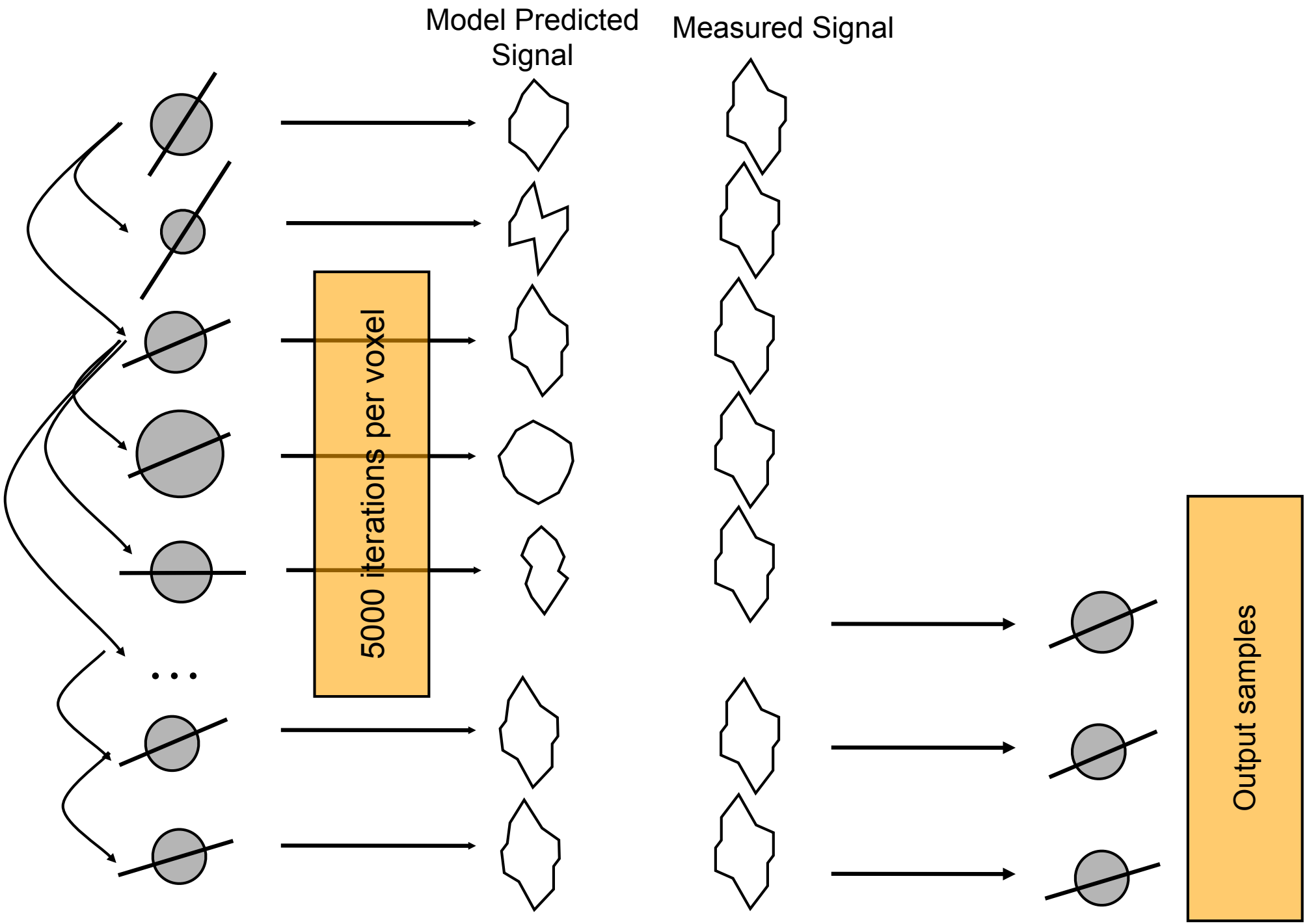




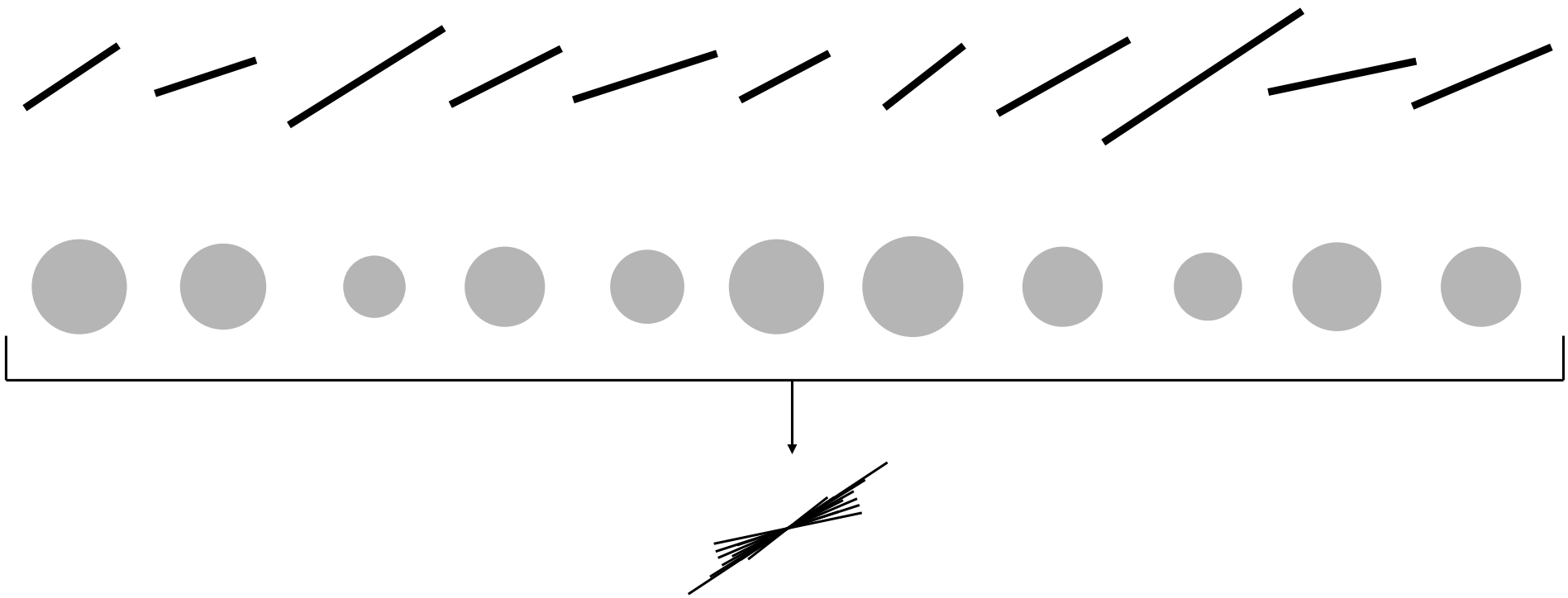
How can we estimate uncertainty?

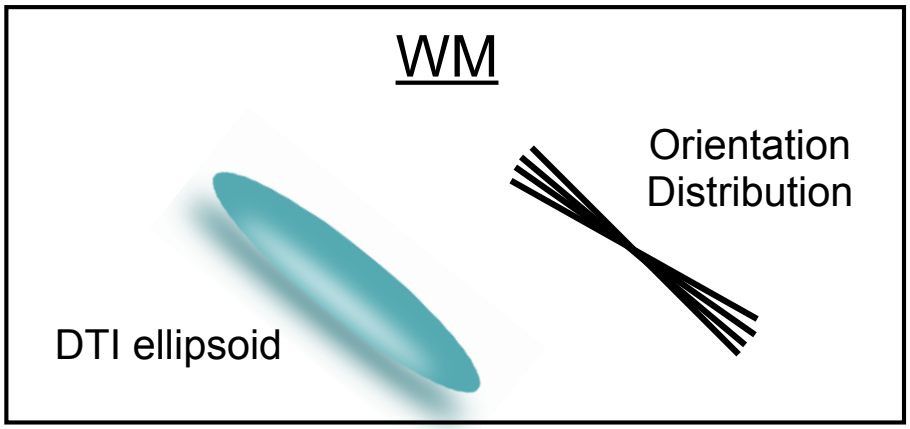
- Remember ... a long time ago in the world of fMRI ...
- We estimated two things:
  - A cope file (the parameters)
  - A varcope file (uncertainty in these parameters)
- We estimated our parameters, and their uncertainty from a single dataset.
- Can we do a similar thing with parameters estimated for the ball & sticks model?
  - In the context of GLM, we have analytic formulas
  - For diffusion (especially orientations) we don't

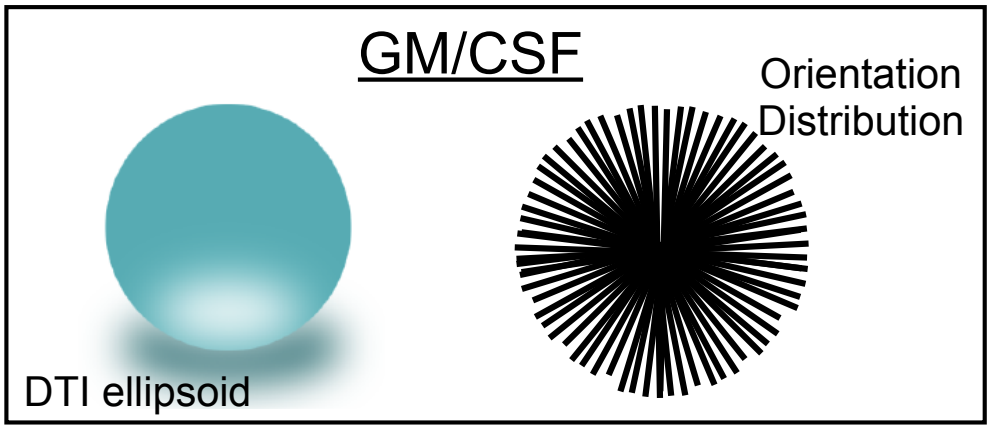
Markov Chain - Monte Carlo (MCMC) Sampling



Output in Each voxel = Distributions of Parameters

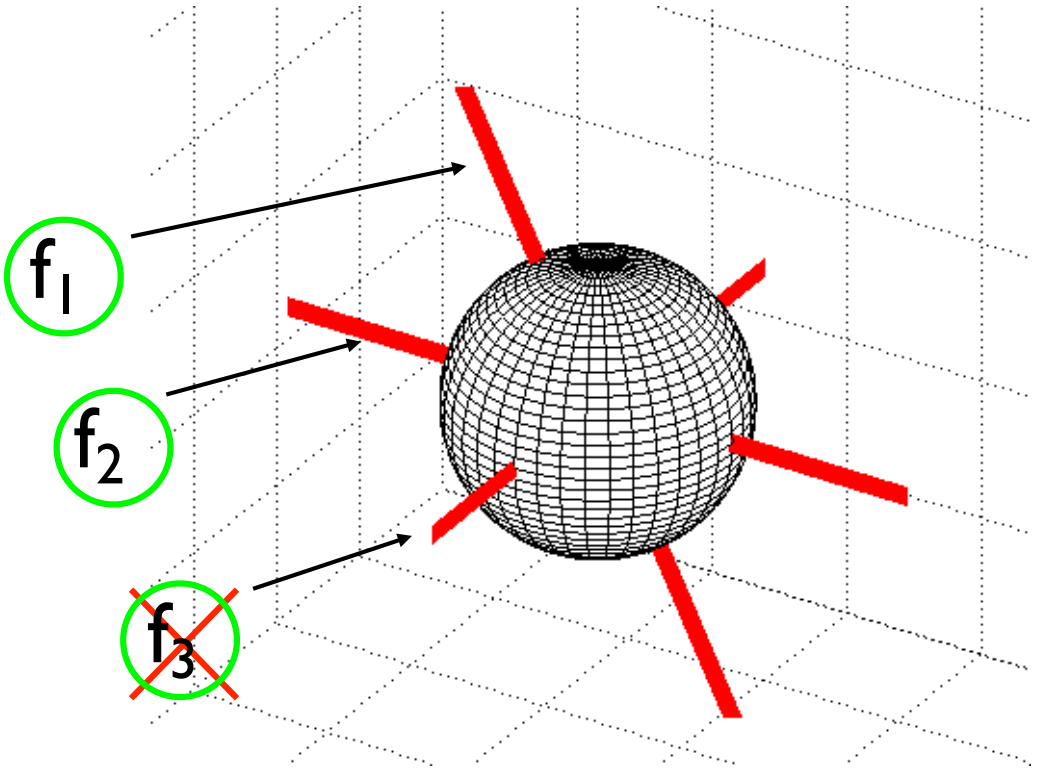






Ball & Sticks Model Selection

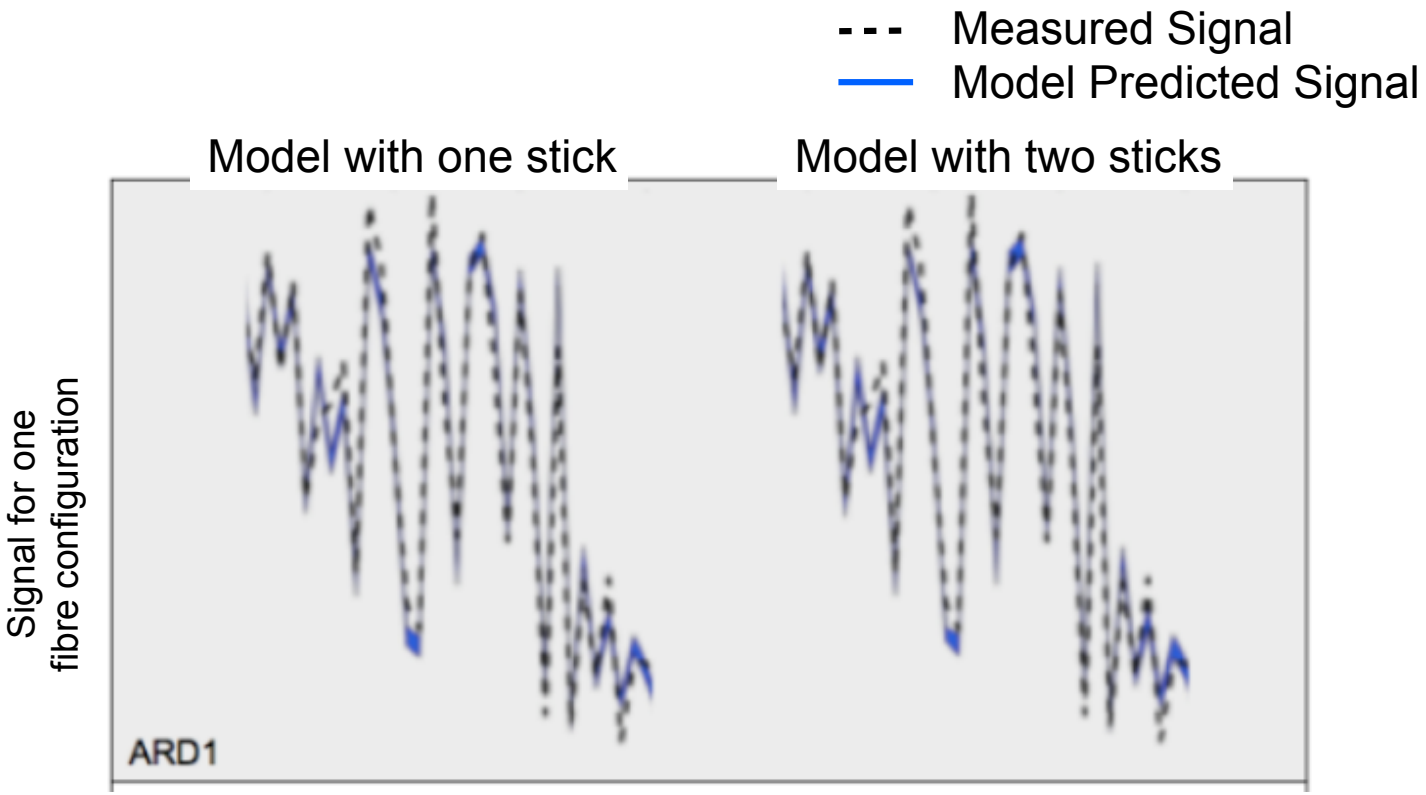
- Model selection problem: One, two or more fibres within a voxel?
- Automatic Relevance Determination: Only estimate complexity that is supported by the data



Modelling Complex Fibre Architectures

Automatic Relevance Determination (A.R.D.)

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

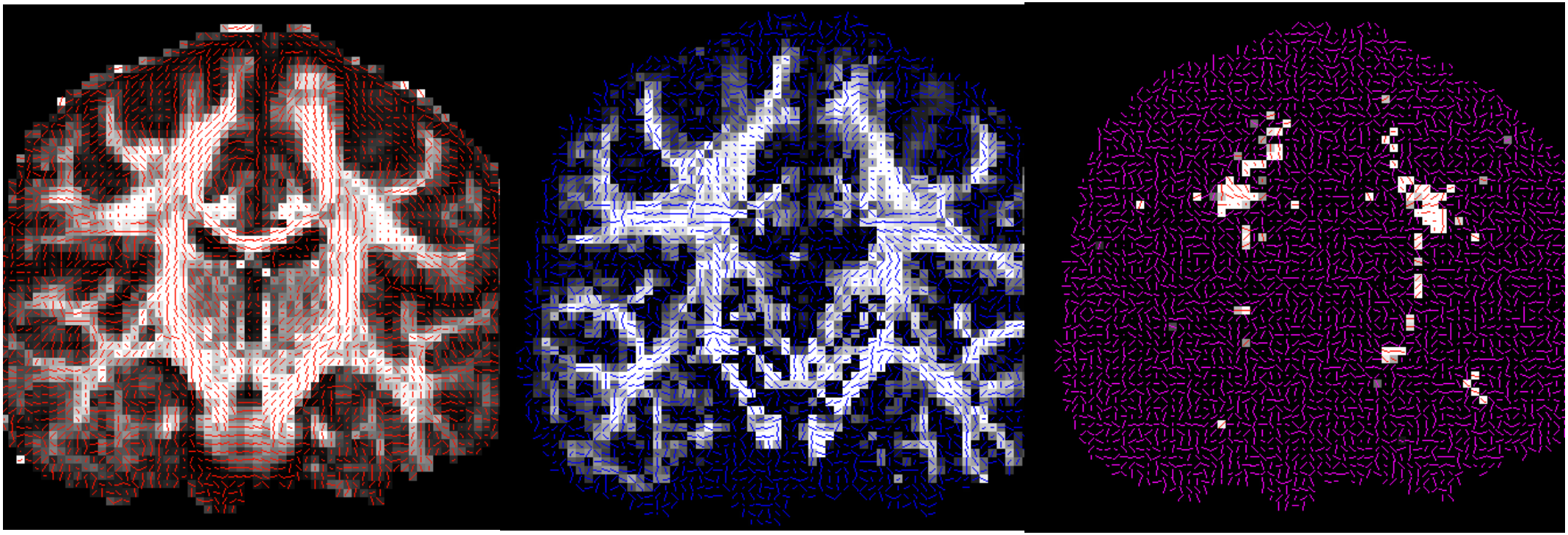


Modelling Complex Fibre Architectures

Automatic Relevance Determination (A.R.D.)

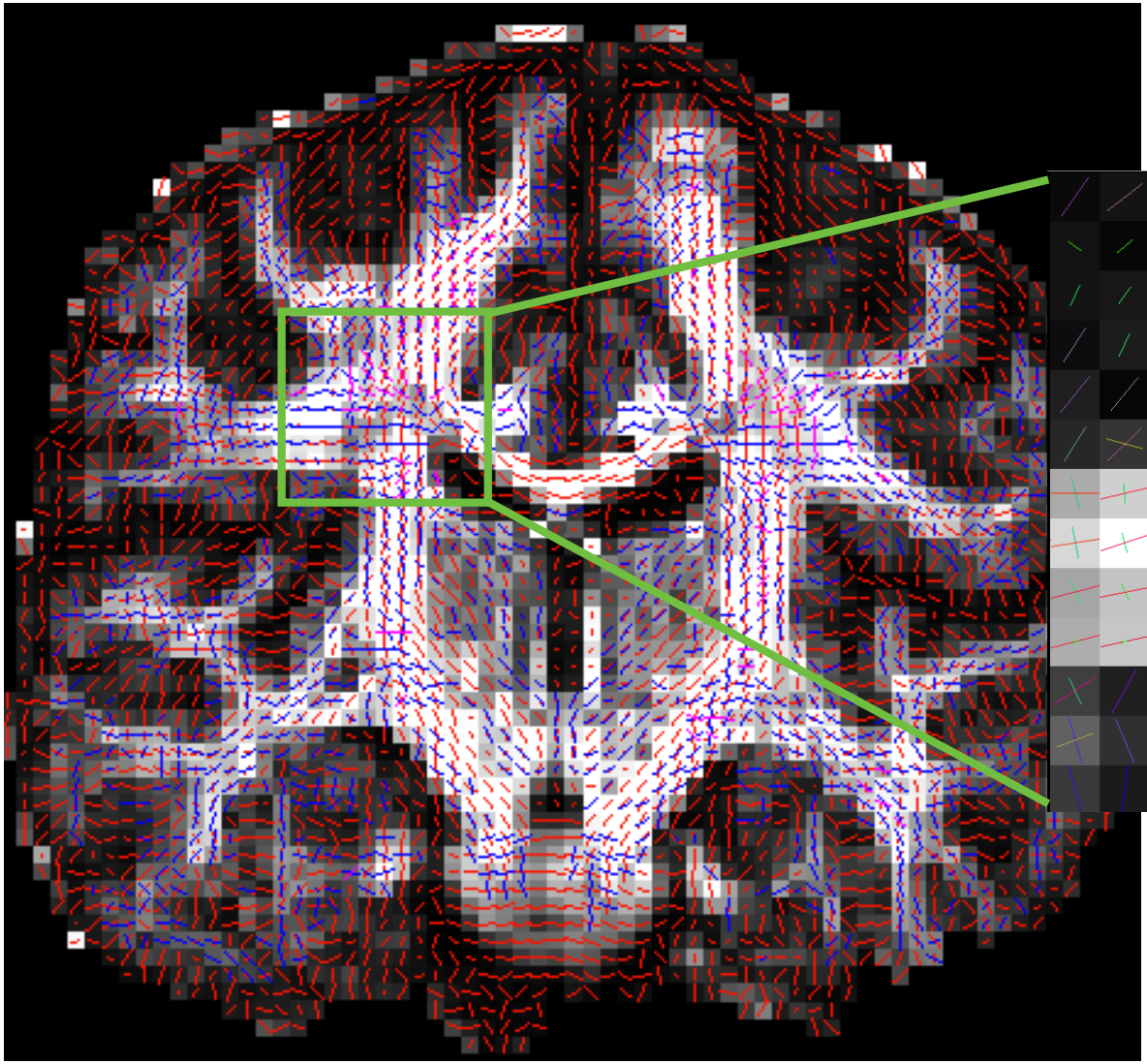
- After running BedpostX all voxels will have estimated parameters for the maximum number of sticks requested.
- But due to ARD, the sticks that are not supported in a voxel will have an almost zero volume fraction.
- We use a threshold (e.g. >5%) to **exclude sticks with tiny volume fraction**.

Stick1 Stick2 Stick3

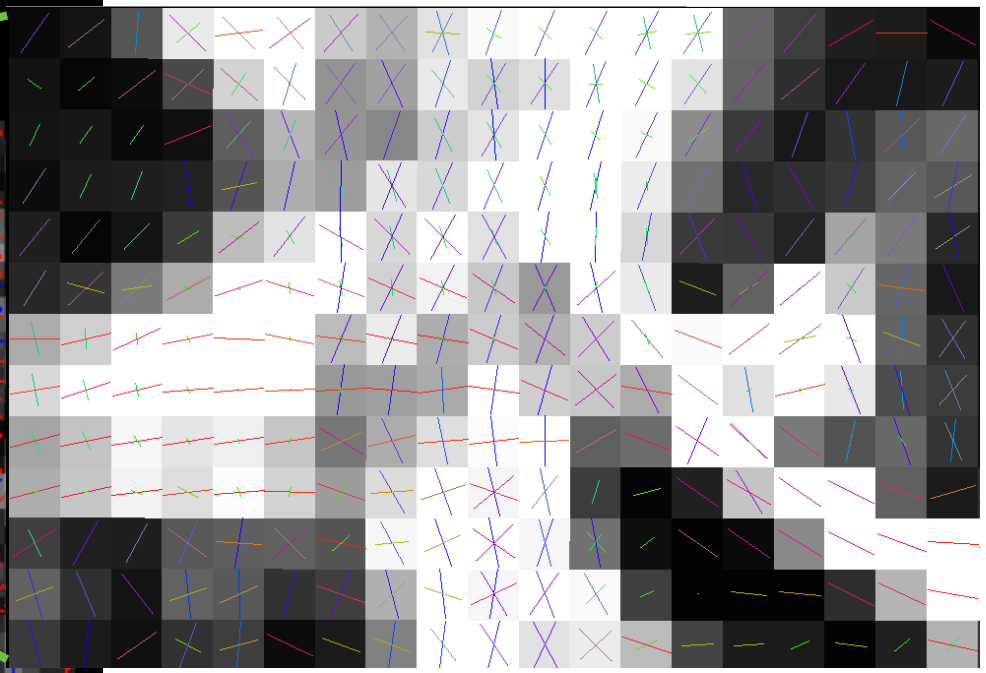


Ball & Sticks Orientations

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

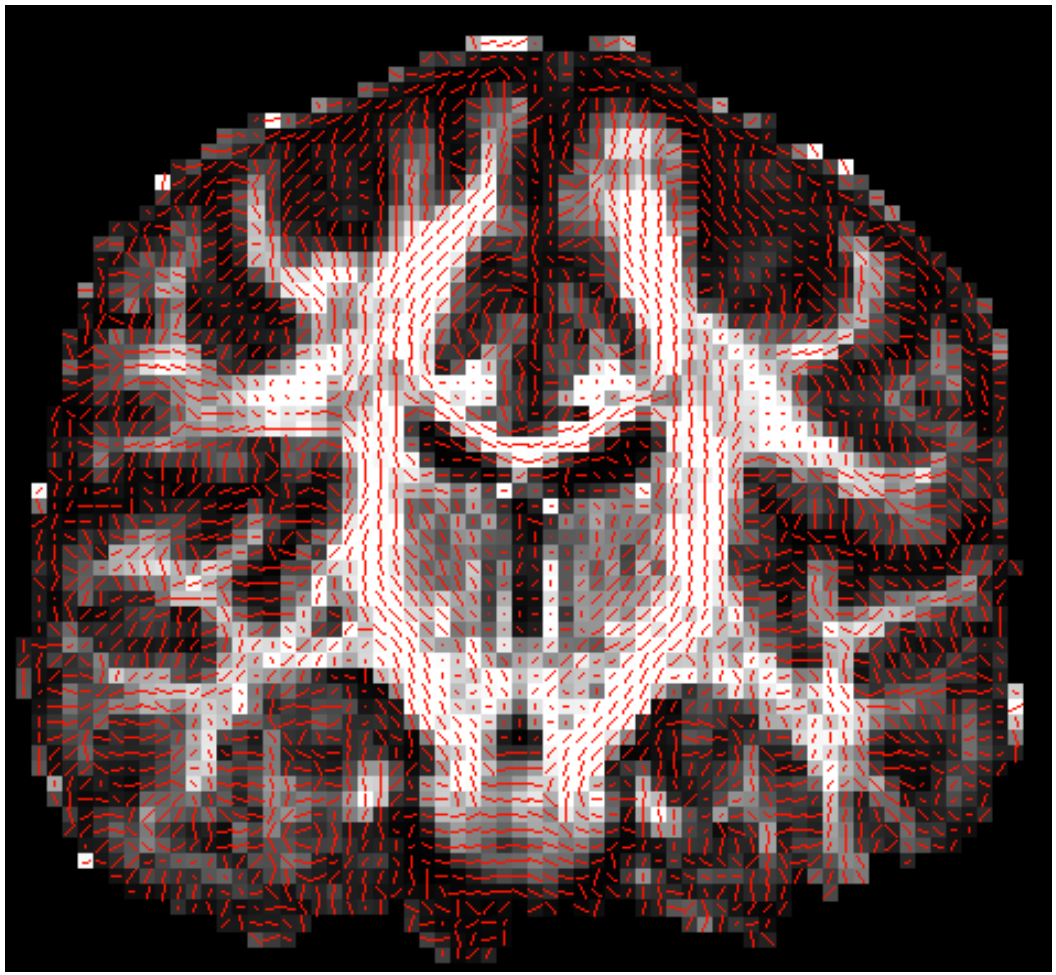


Orientations RGB-colour coded

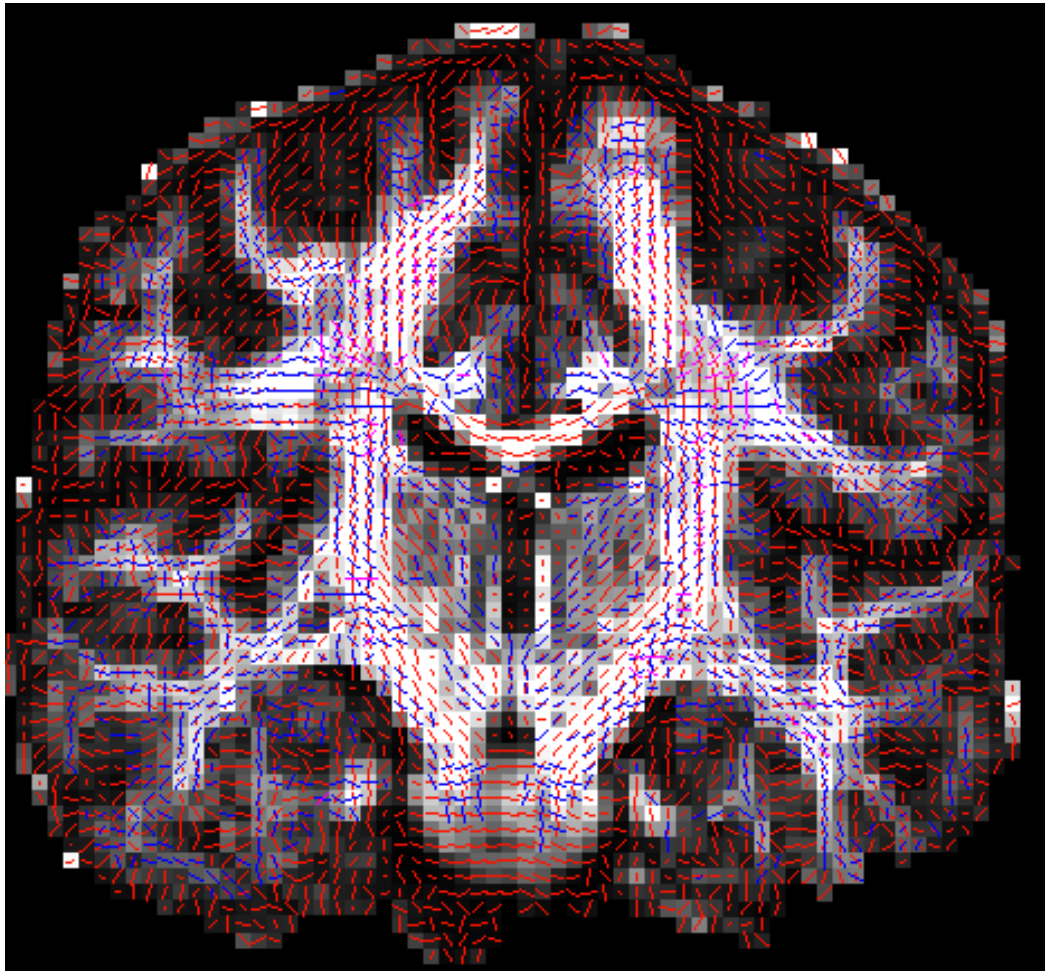


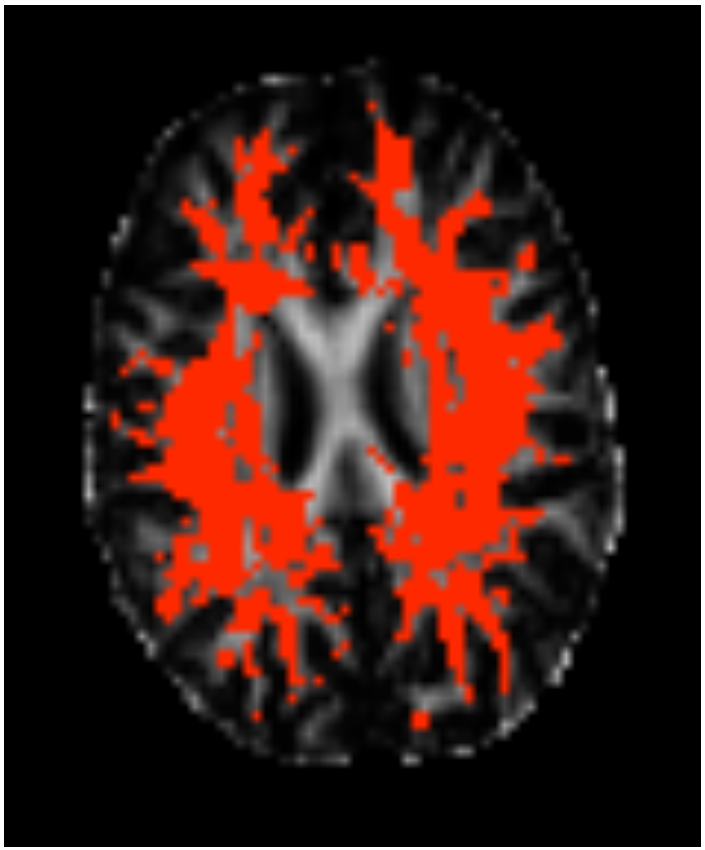
DTI vs Ball & Sticks Orientations

DTI

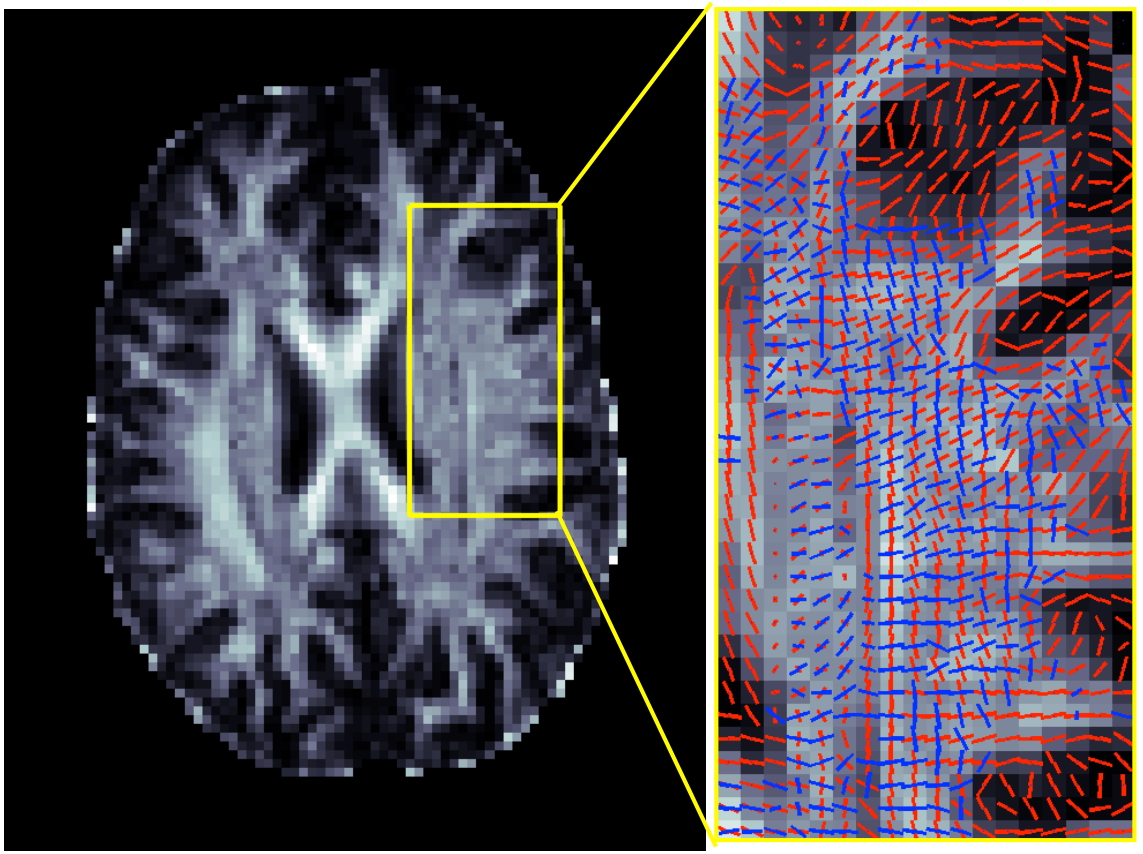


Ball & Sticks





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)

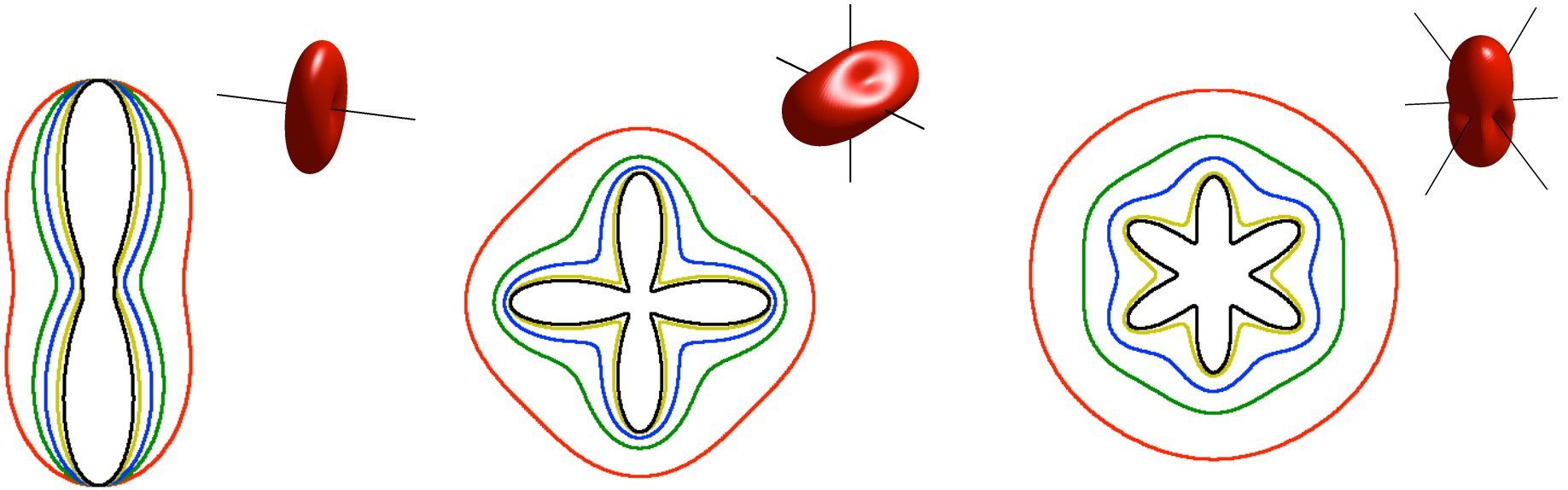
b=1000

b=2000

b=3000

b=4000

b=5000



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)

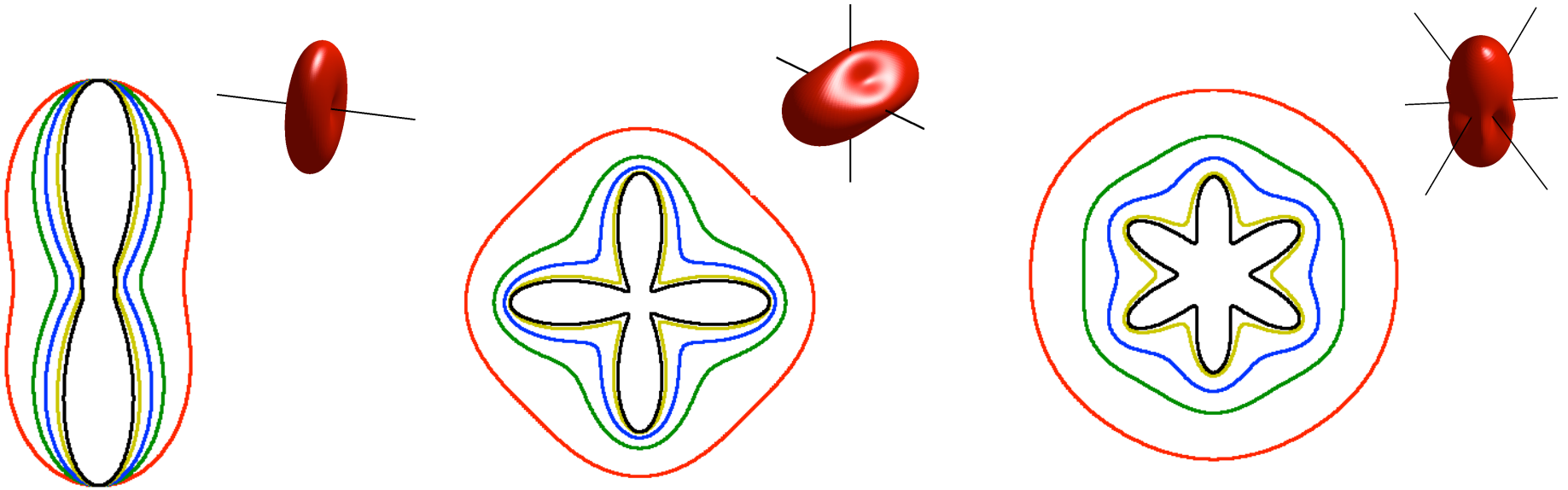
b=1000

b=2000

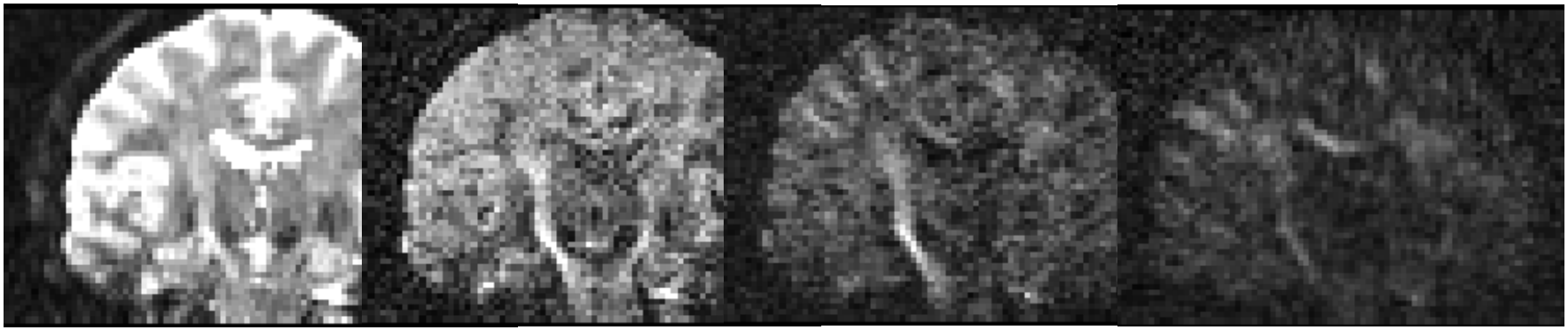
b=3000

b=4000

b=5000



b=300 b=1000 b=2000 b=3000

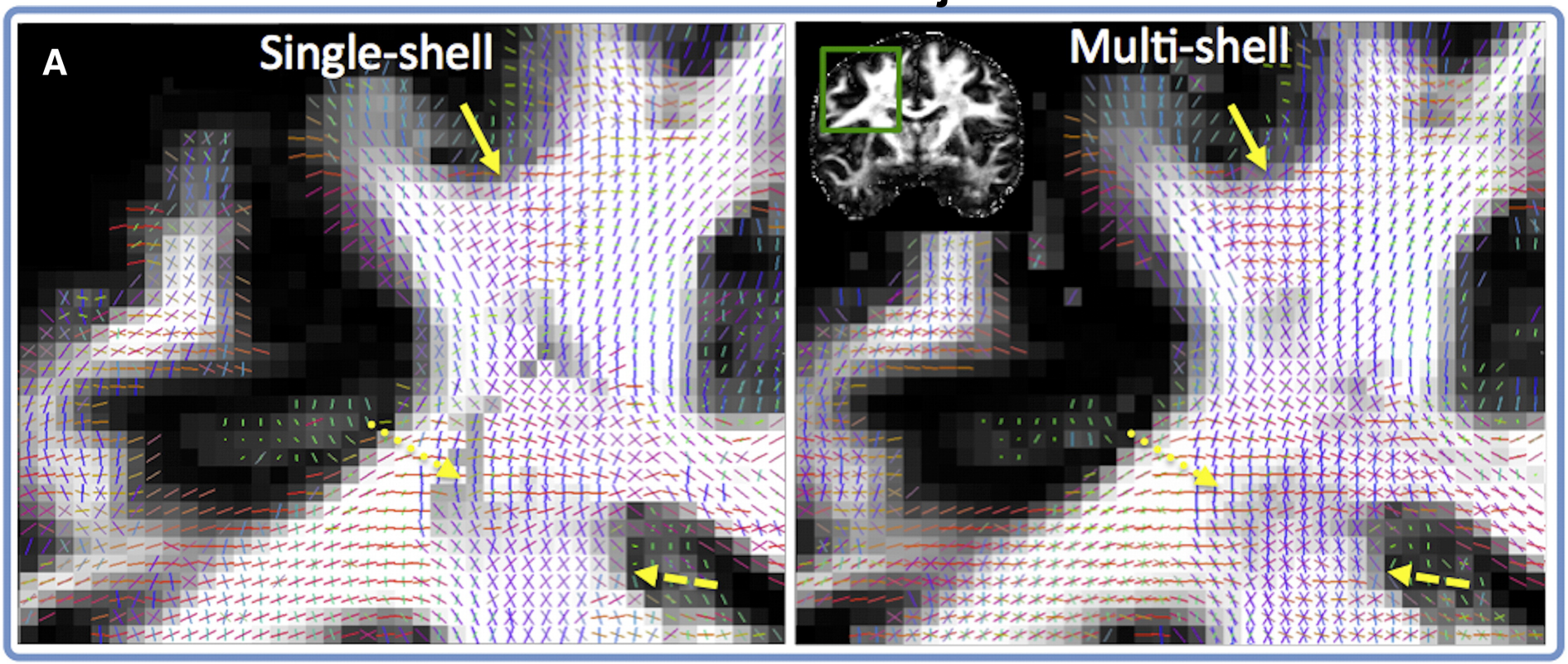


But SNR goes down very quickly with b…

Generalised Ball & sticks Model
Gets best of both worlds

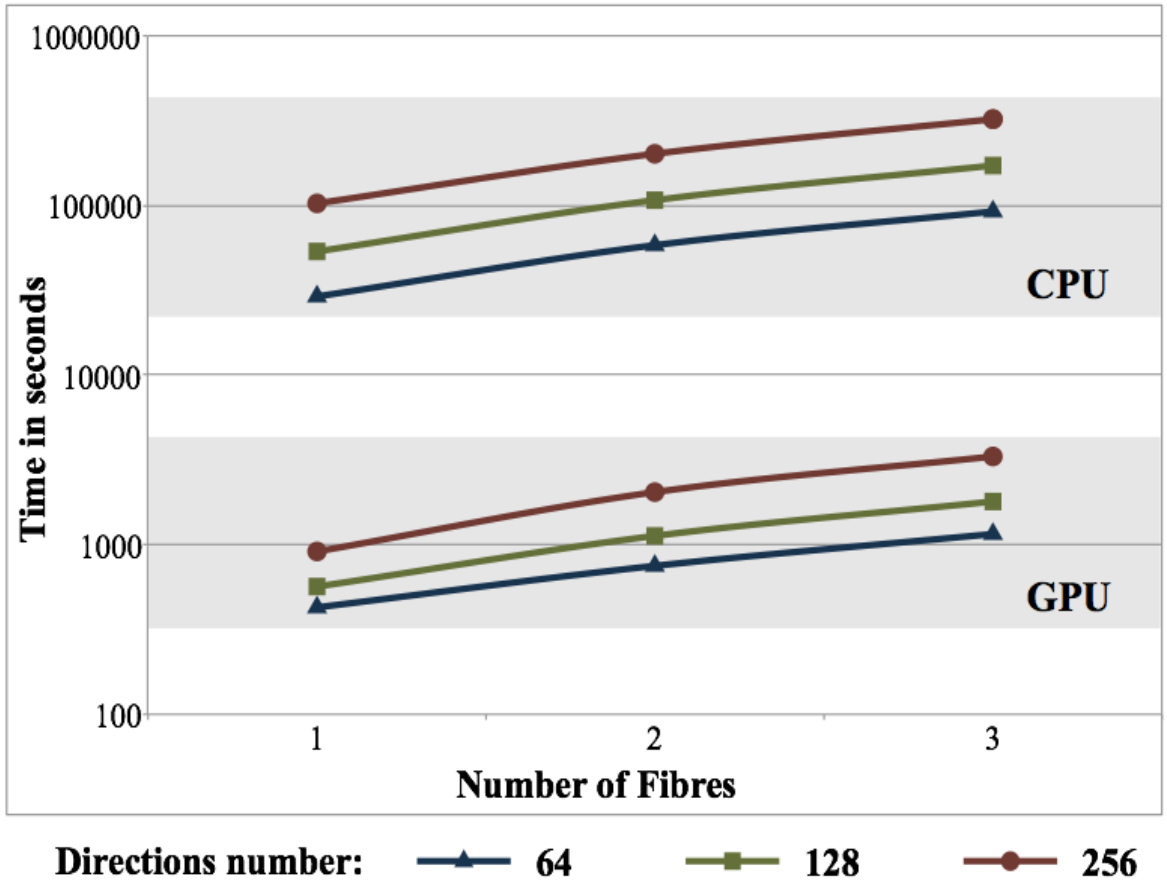
- Multi-shell model (or model=2) in Bedpostx options.
- Allows representation of multiple diffusivities within a voxel (rather than just one).
- More accurate model for multi-shell data & partial volume effects.

Human Connectome Project Data



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

Faster bedpostx on GPUs

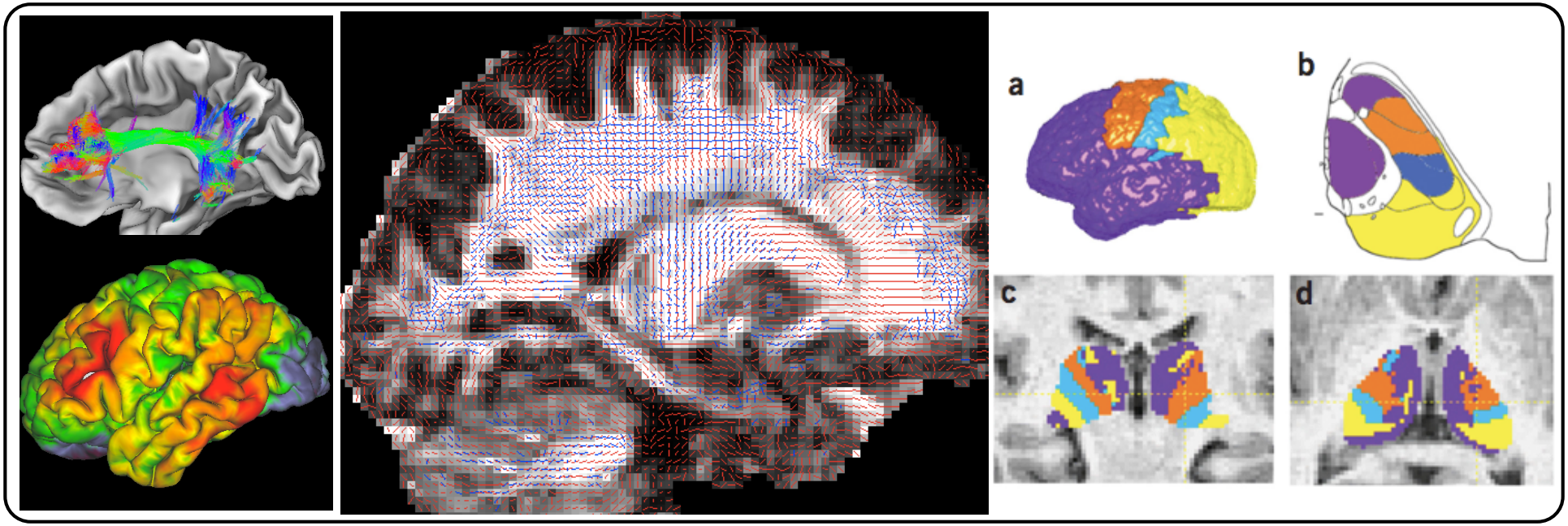


50x-150x Speedup using GPUs

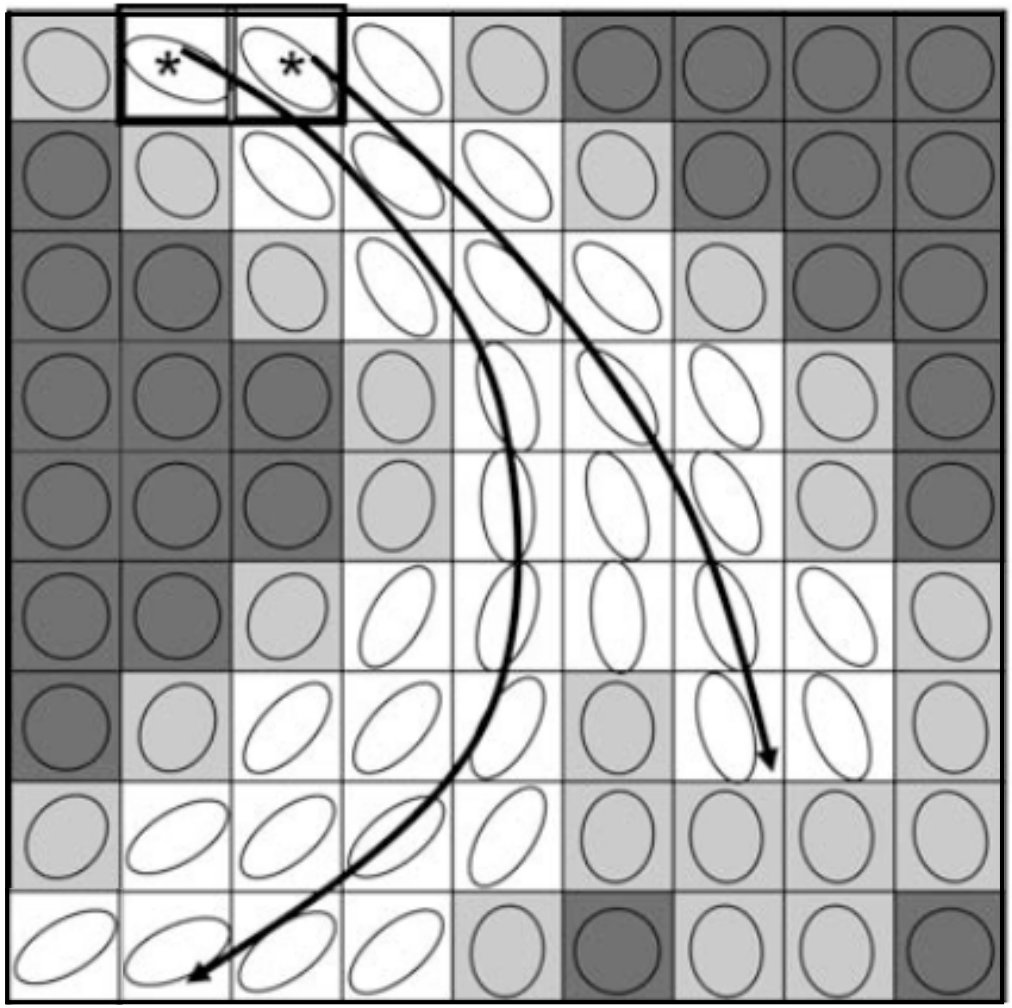
Hernandez et al, Plos One 2013

Overview

- Goal of tractography
- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- ProbtrackX outputs
- Tractography limitations



DTI Streamline Tractography



Mori S, Neuron 2006

Formally, we solve numerically the differential equation:

$$\frac{d\mathbf{r}(s)}{ds} = \mathbf{v_1}(\mathbf{r}(s)), \quad \mathbf{r}(0) = \mathbf{r}_0$$

Position along a curve

Principal eigenvector $\mathbf{v_1}$ at position $\mathbf{r}(s)$

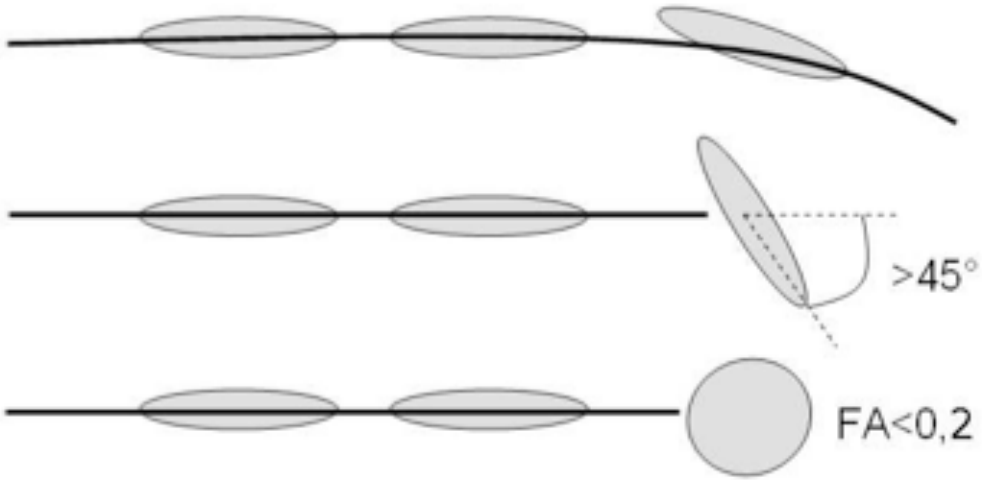
Starting Position

DTI Streamline Tractography

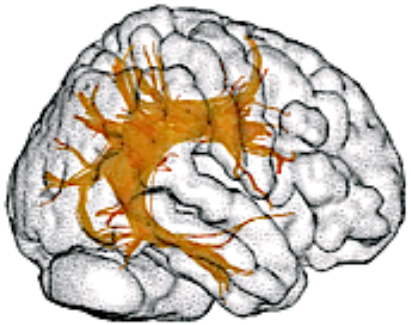
But When to Stop?
Heuristics to avoid error propagation.
+ Knowledge of the anatomy

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

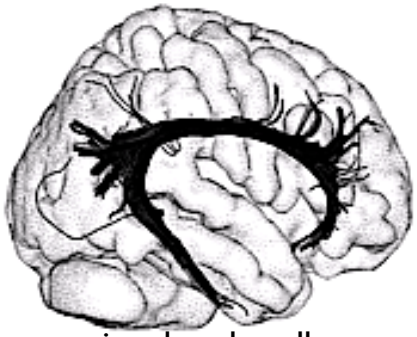
Anatomical criteria (e.g. reach grey matter)



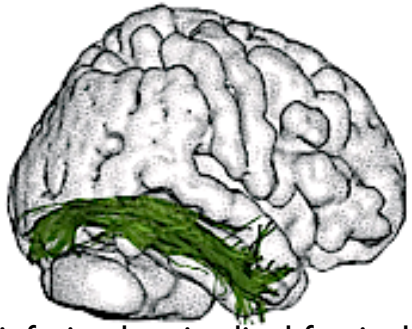
Streamline tractography can dissect major bundles



arcuate fasciculus

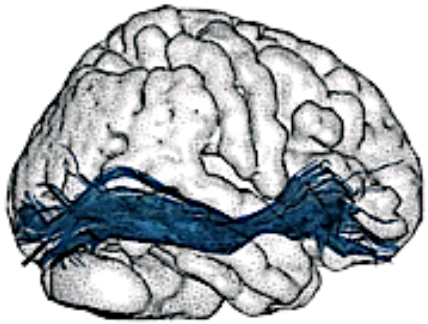


cingulum bundle

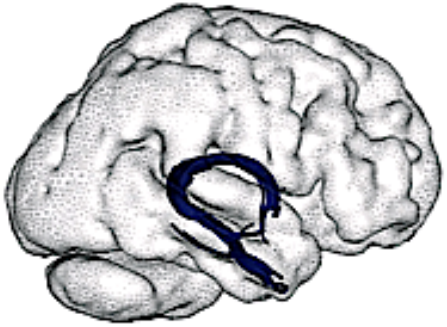


inferior longitudinal fasciculus

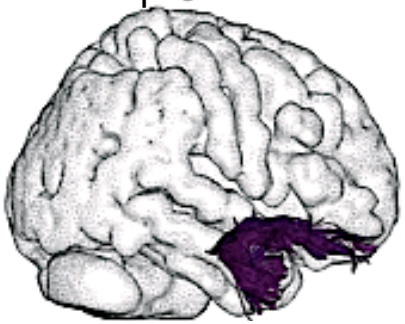
corpus callosum



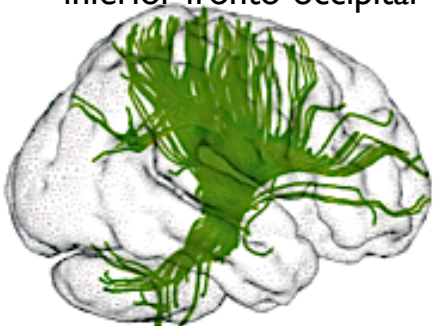
inferior fronto-occipital



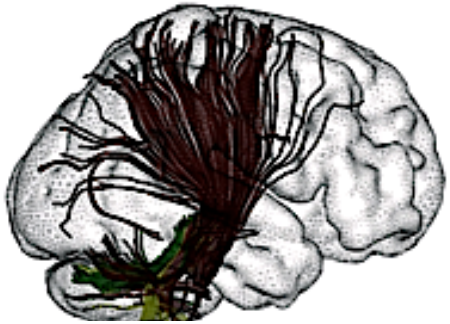
fornix



uncinate fasciculus



corona radiata



cerebellar tracts

Catani and Thiebaut de Schotten 2008

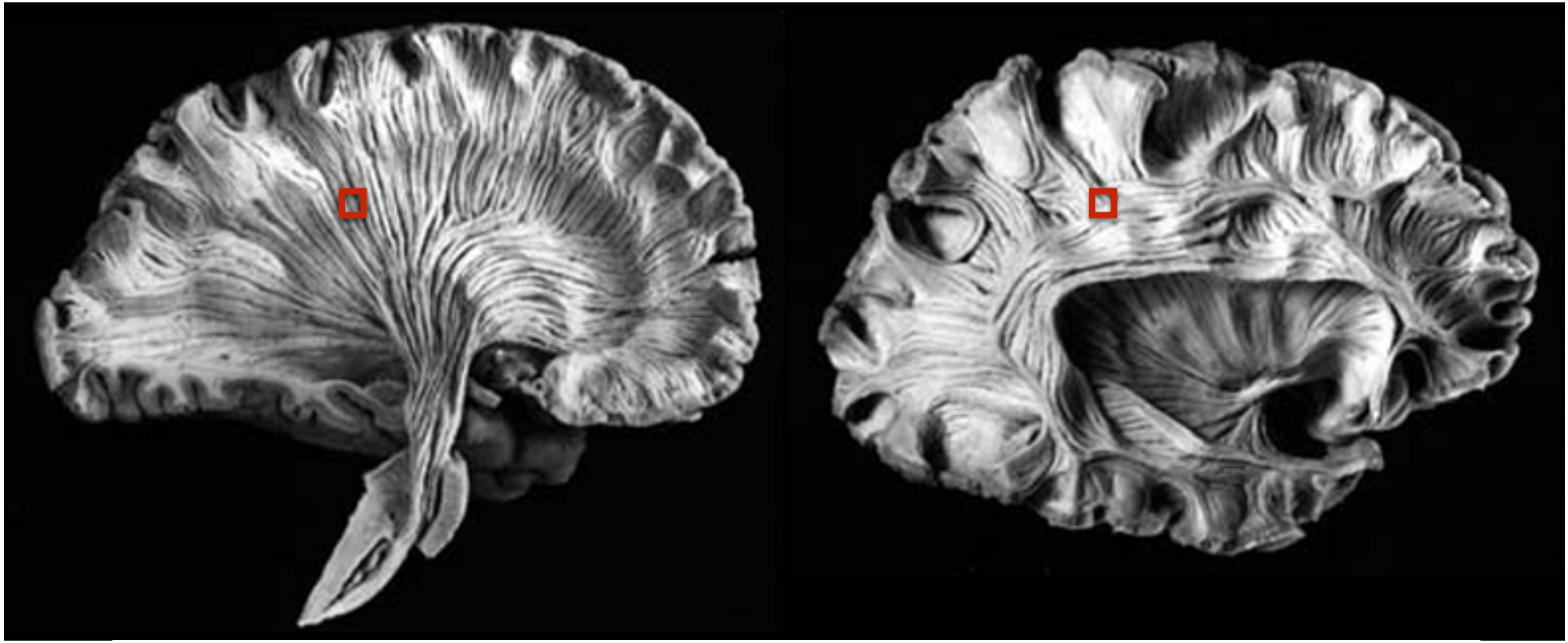
DTI Streamline Tractography Summary

- 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.

But is WM always coherently organised within a voxel?



Unfortunately not, complex fibre patterns (e.g. crossings) are very common at the voxel scale.

Williams, Gluhbegovic, and Jew, "The Human Brain`; Dissections of the Real brain", Virtual Hopstital, Universitoy of Iowa, 1997

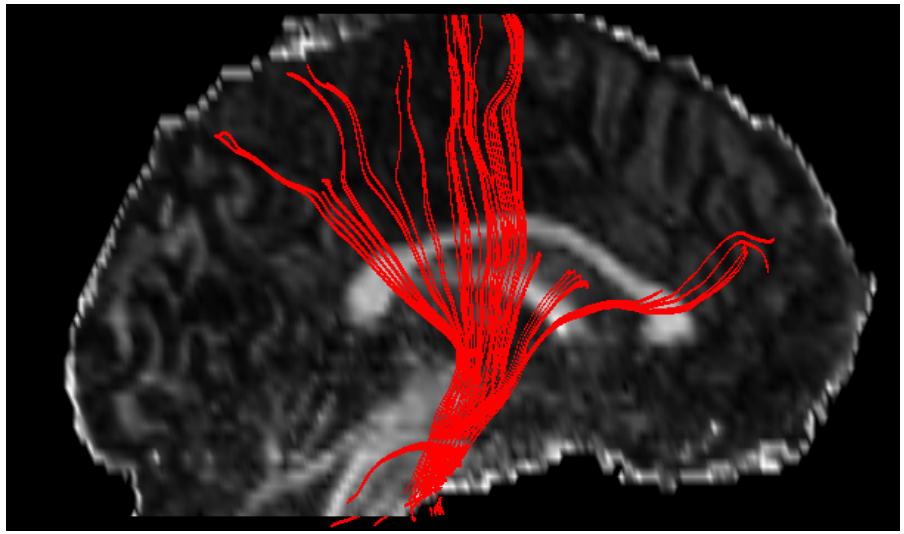
Streamlining reproducibility

Repeat an acquisition many times and repeat streamline tracking.

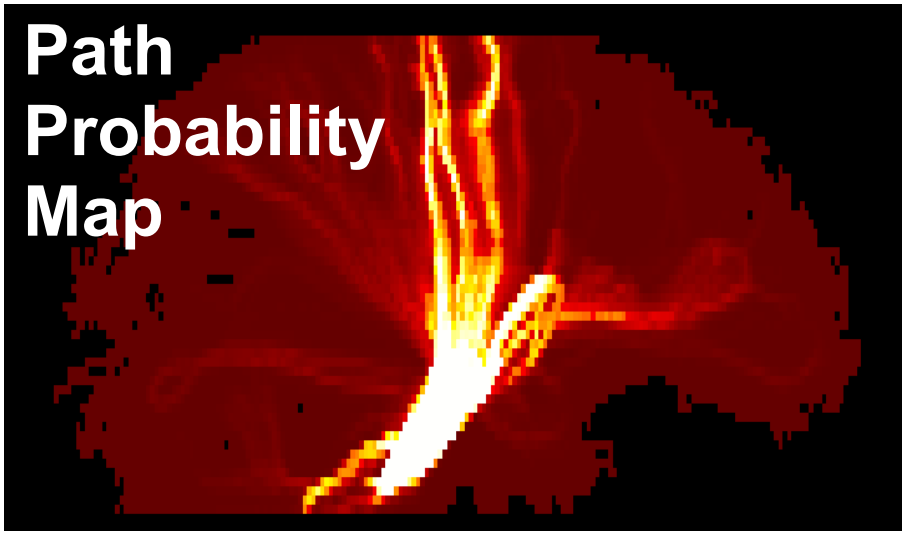
Due to uncertainty in $\mathbf{v}_1$, curves will not perfectly overlap

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



Low Reproducibility — High Reproducibility

Probabilistic Tractography

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

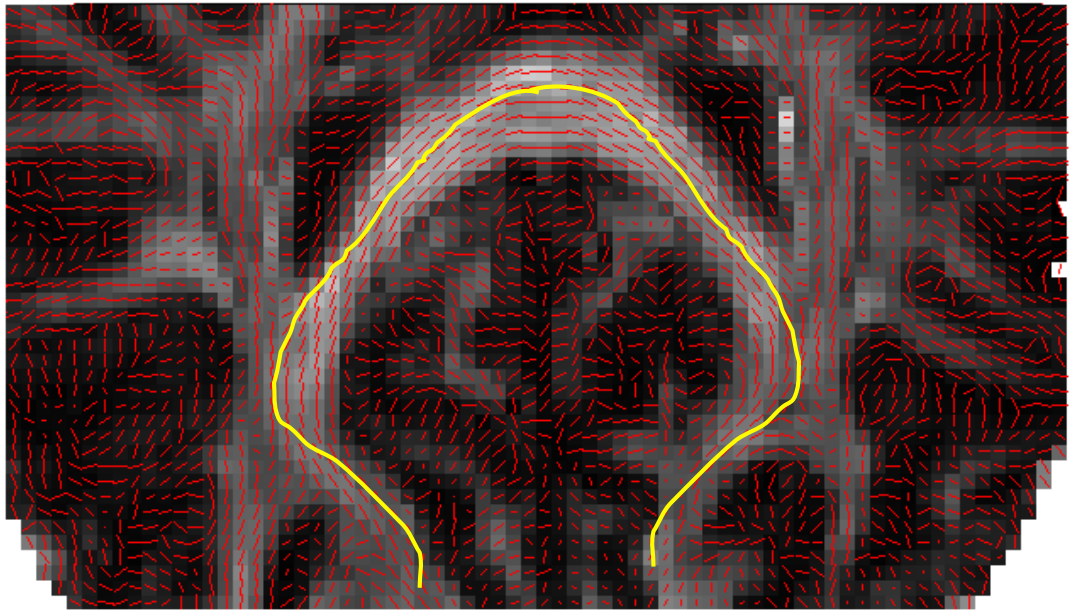
- Probabilistic Tractography as a two-step process:

a) Use DWI data and a model to infer a fibre orientation **and its uncertainty** in each voxel.

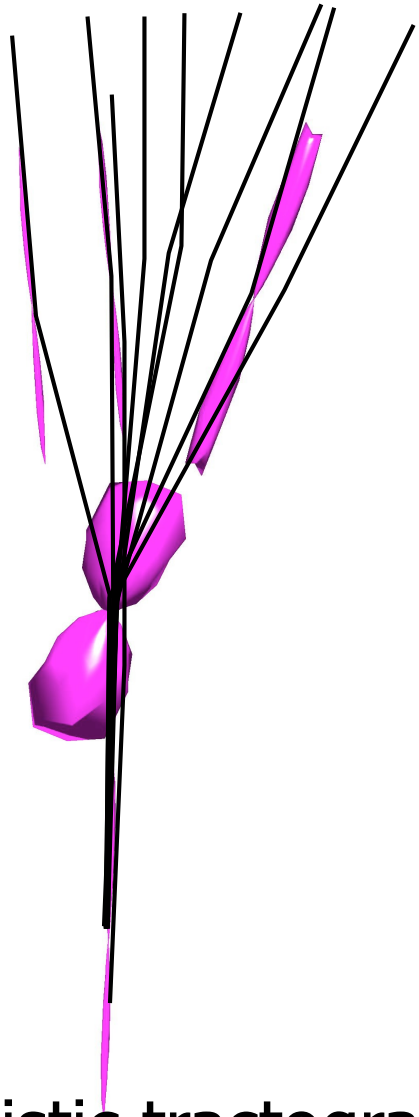
b) Use the estimates **and the uncertainty to build a path probability map** to a seed.

Probabilistic tractography

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



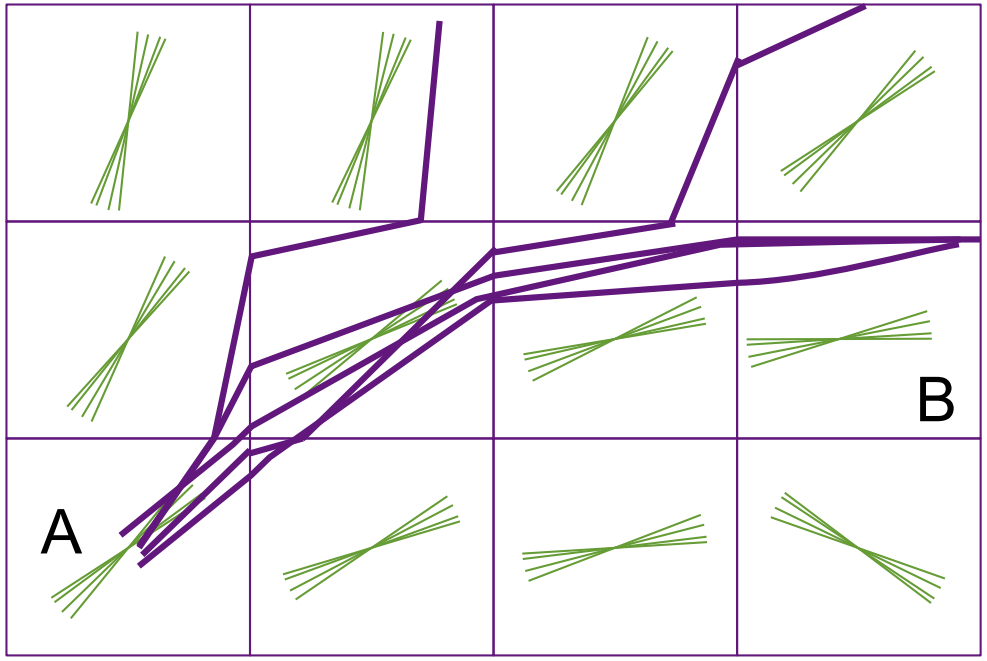
'Streamlining'



Probabilistic tractography

Behrens et al, 2003, Parker et al. 2003, Hagmann et al 2003, Jones et al. 2004

Probabilistic Tractography - Propagating the Uncertainty

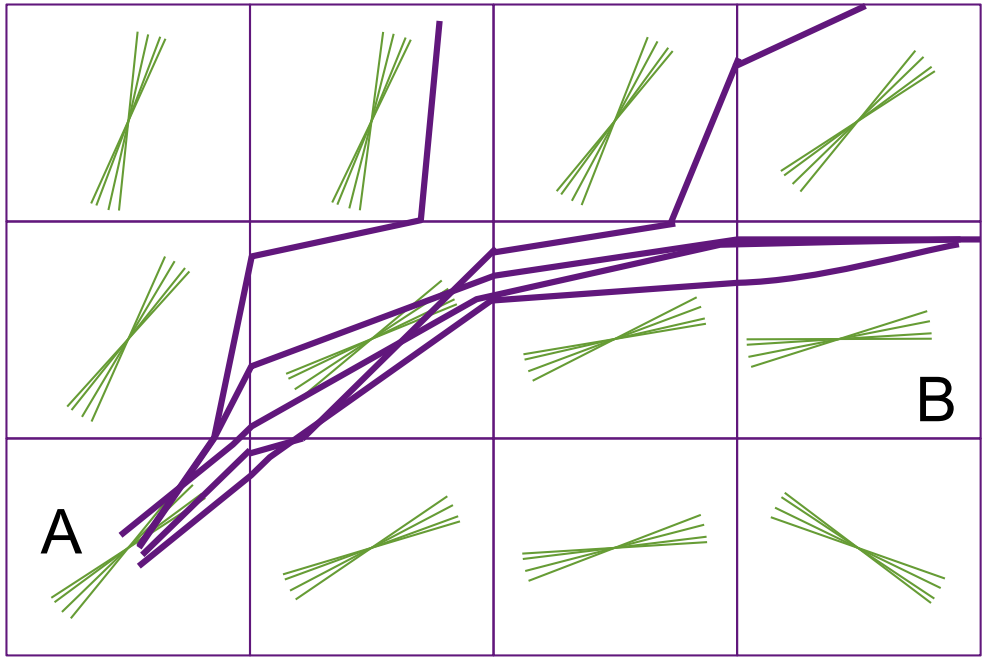


Behrens et al, 2003
Parker et al, 2003

- 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

Probabilistic Tractography - Propagating the Uncertainty



Behrens et al, 2003
Parker et al, 2003

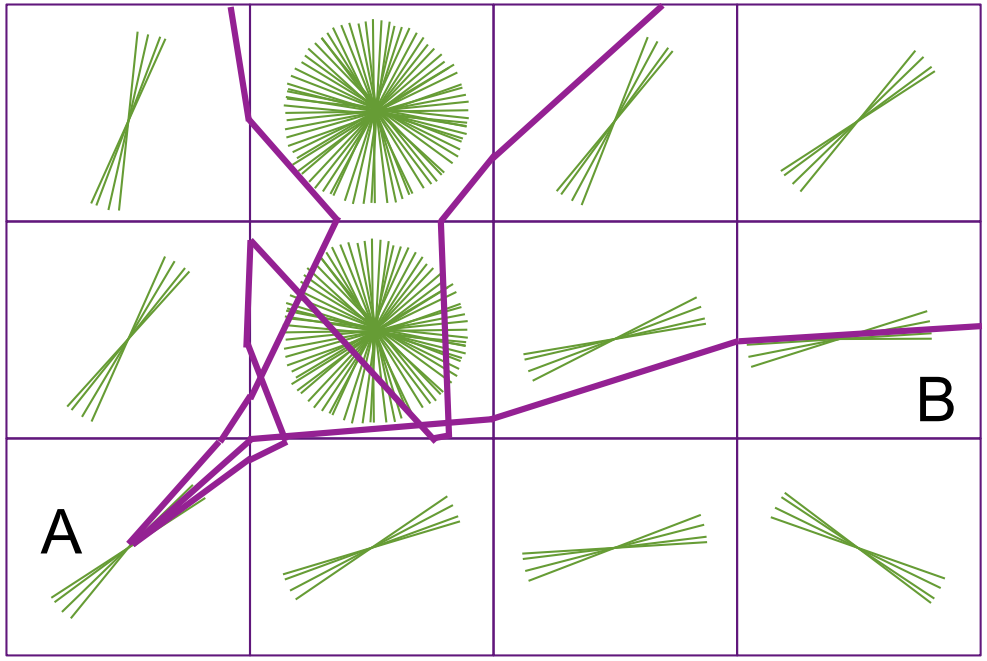
Define the degree of overlap at each location B, as:

$$P_{AB} = M/N$$

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.

Probabilistic Tractography - Propagating the Uncertainty



Behrens et al, 2003
Parker et al, 2003

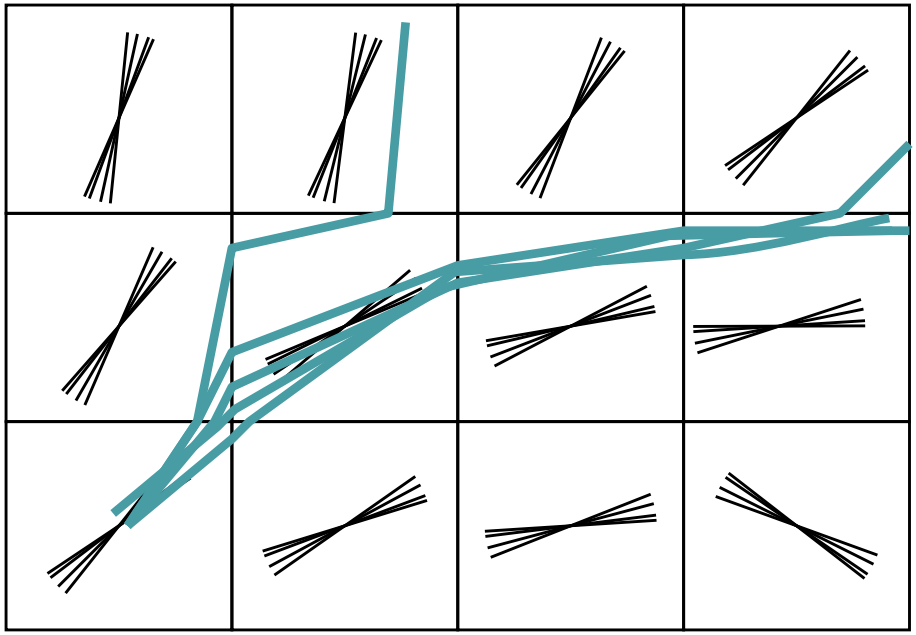
- Can now propagate through isotropic regions (e.g. GM).

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

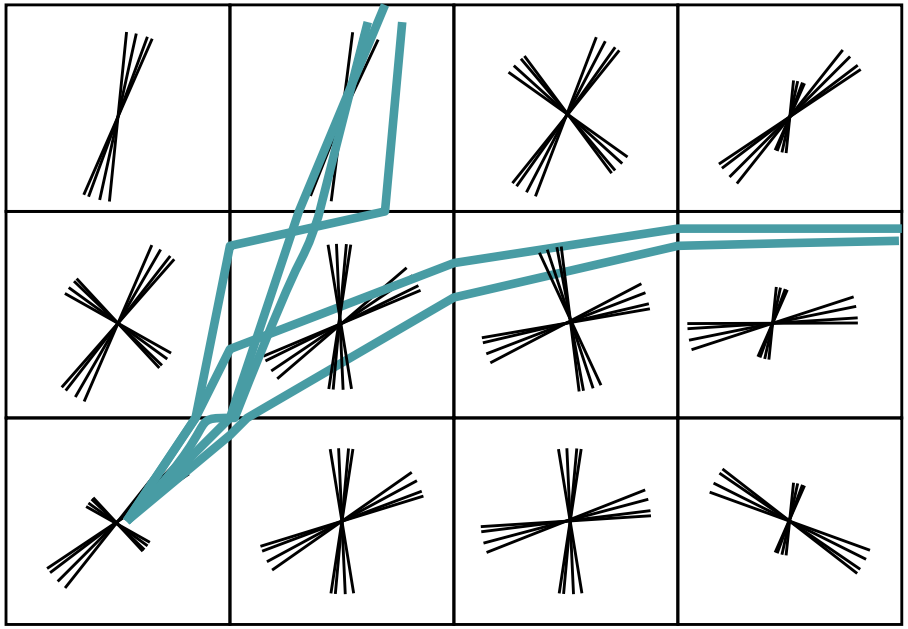
- The high uncertainty will be reflected in the probability map.

-Still impose a curvature threshold to avoid swirled trajectories.

Probabilistic Tractography in Multi-Fibre Fields



Behrens et al, 2003, Parker et al. 2003,
Hagmann et al 2003, Jones et al. 2004



Parker & Alexander 2003,
Behrens et al, 2007

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

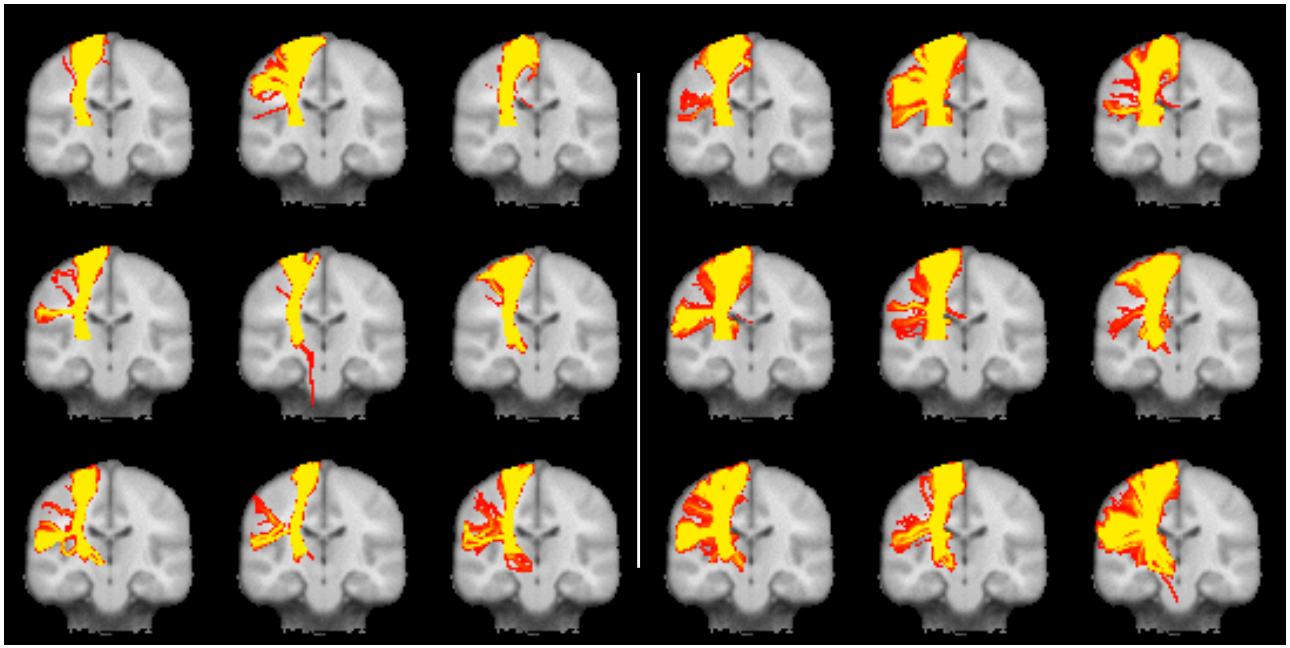
Probabilistic Tractography in Multi-Fibre Fields
Examples

Cortico-spinal tracts.
9 subjects

Behrens et al, 2007

SLF

Internal capsule ---- Primary motor cortex



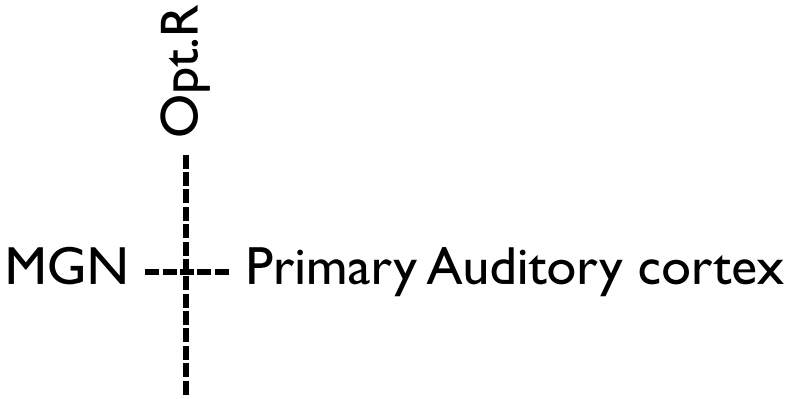
one fibre two fibres

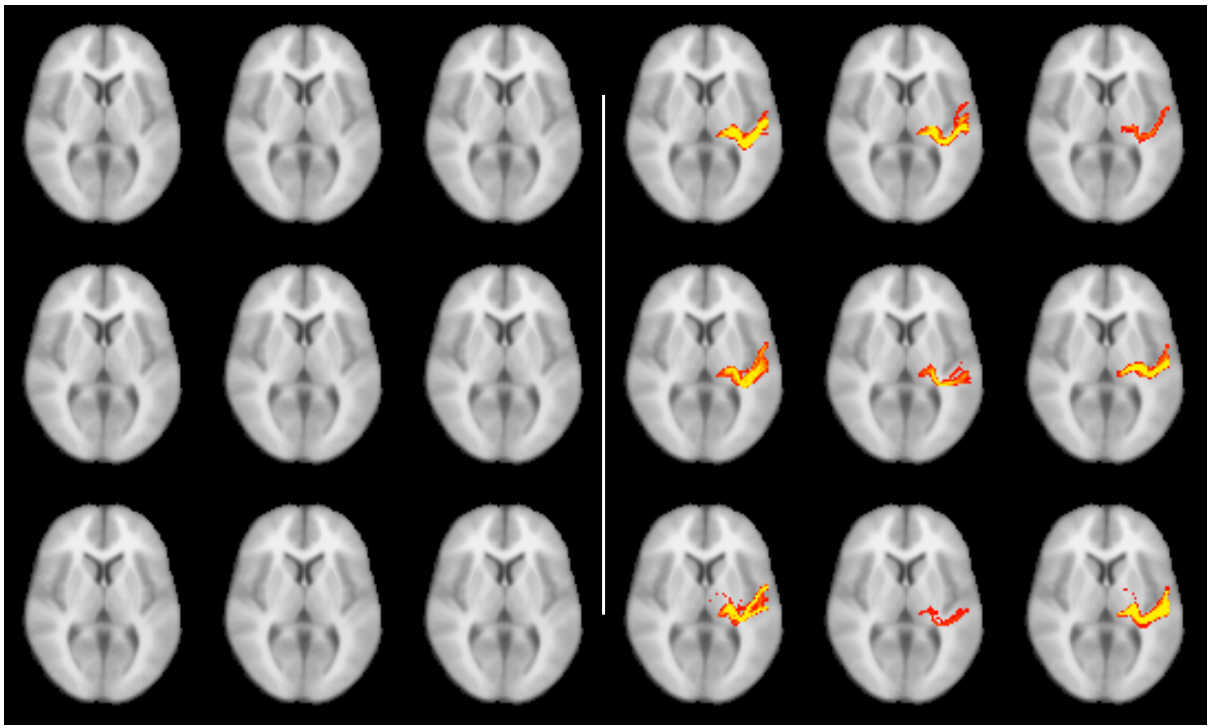
* If one fibre is modelled and we track through a crossing, a) we may not make it through the crossing, b) if we make it, the connectivity index will be relatively low.

Probabilistic Tractography in Multi-Fibre Fields
Examples

Acoustic radiations.
9 subjects

Behrens et al, 2007





one fibre

two fibres

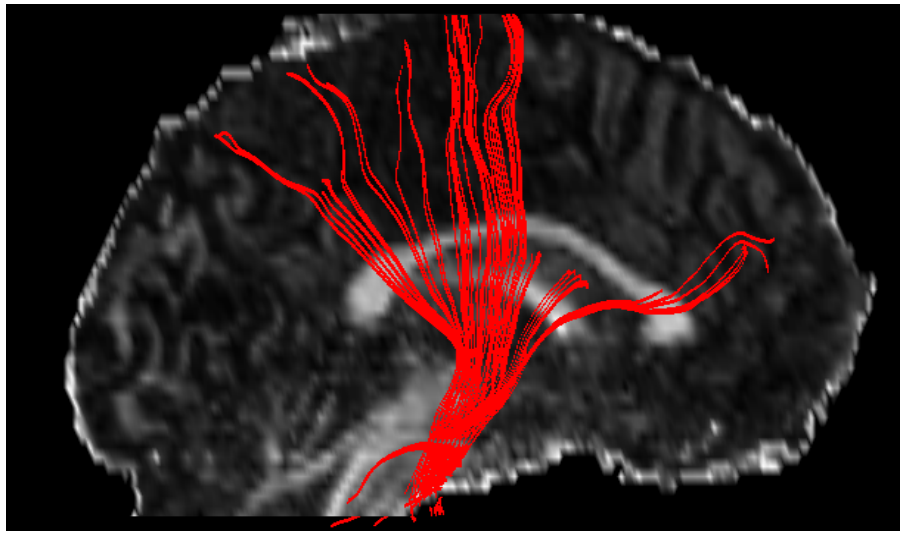
Path Probability Map

- Recall that it assesses how reproducible results are

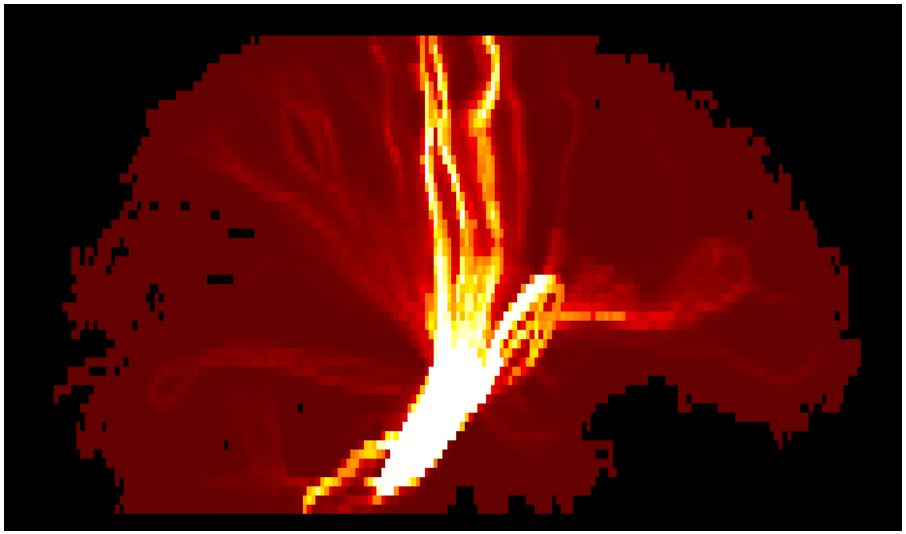
- Often called “connection probability”, “connectivity index”, “connectivity strength”. But it does not quantify how strong a connection is...

- Rather, how robust it is against noise/uncertainty

Deterministic Tractography



Probabilistic Tractography



Low Probability

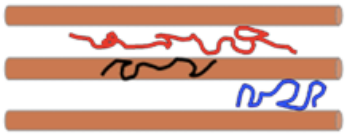
High Probability

Probabilistic Streamline Tractography Summary

- 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!

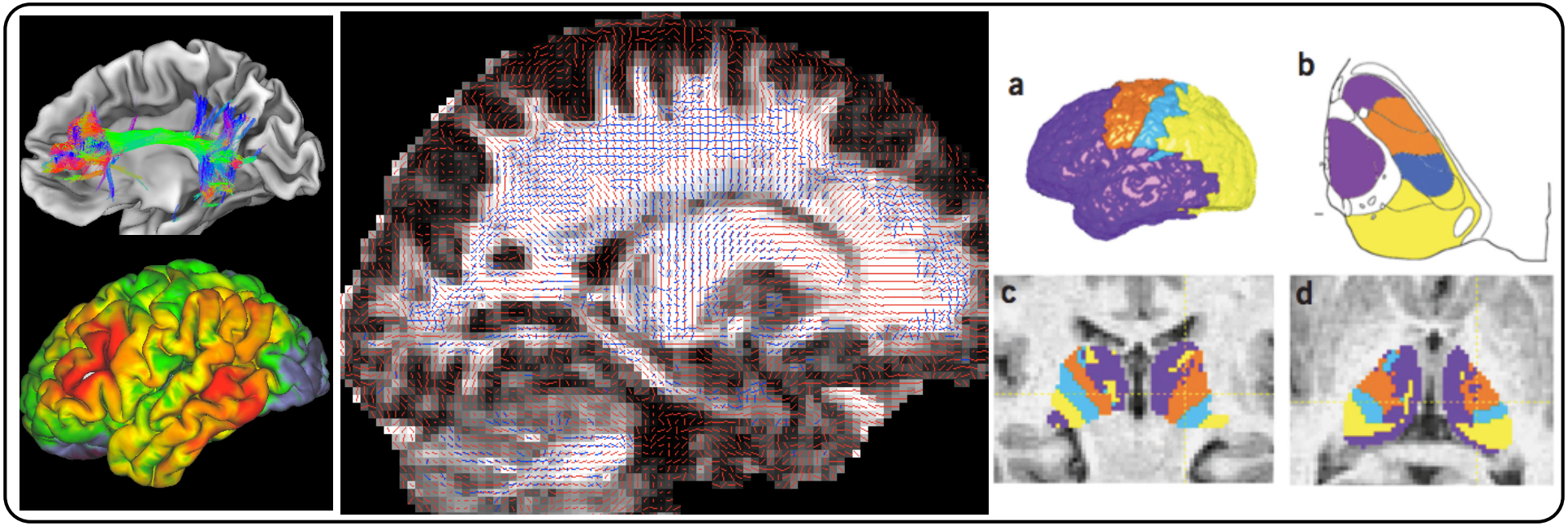
- Propagate streamlines repeatedly from a seed, but the orientation field is no longer deterministic. In each propagation step choose randomly an orientation from the underlying distribution.

- A connection probability value>=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.**



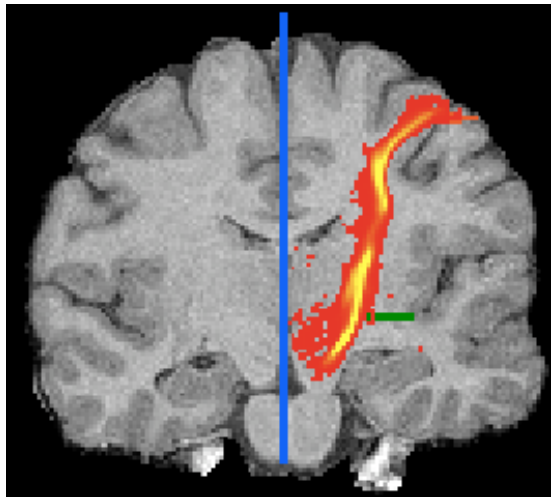
Overview

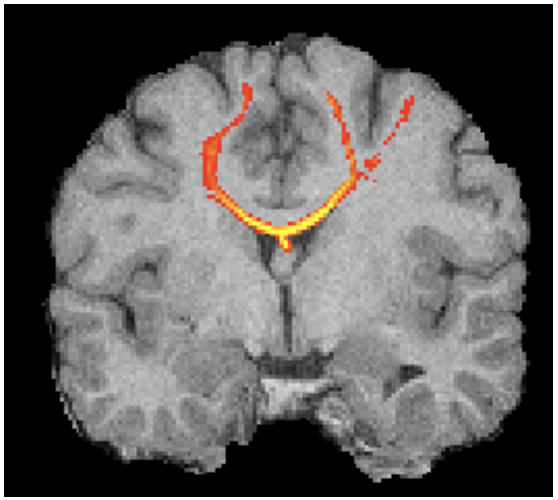
- Goal of tractography
- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- ProbtrackX outputs
- Tractography limitations



ProbtrackX outputs

Known white matter tracts



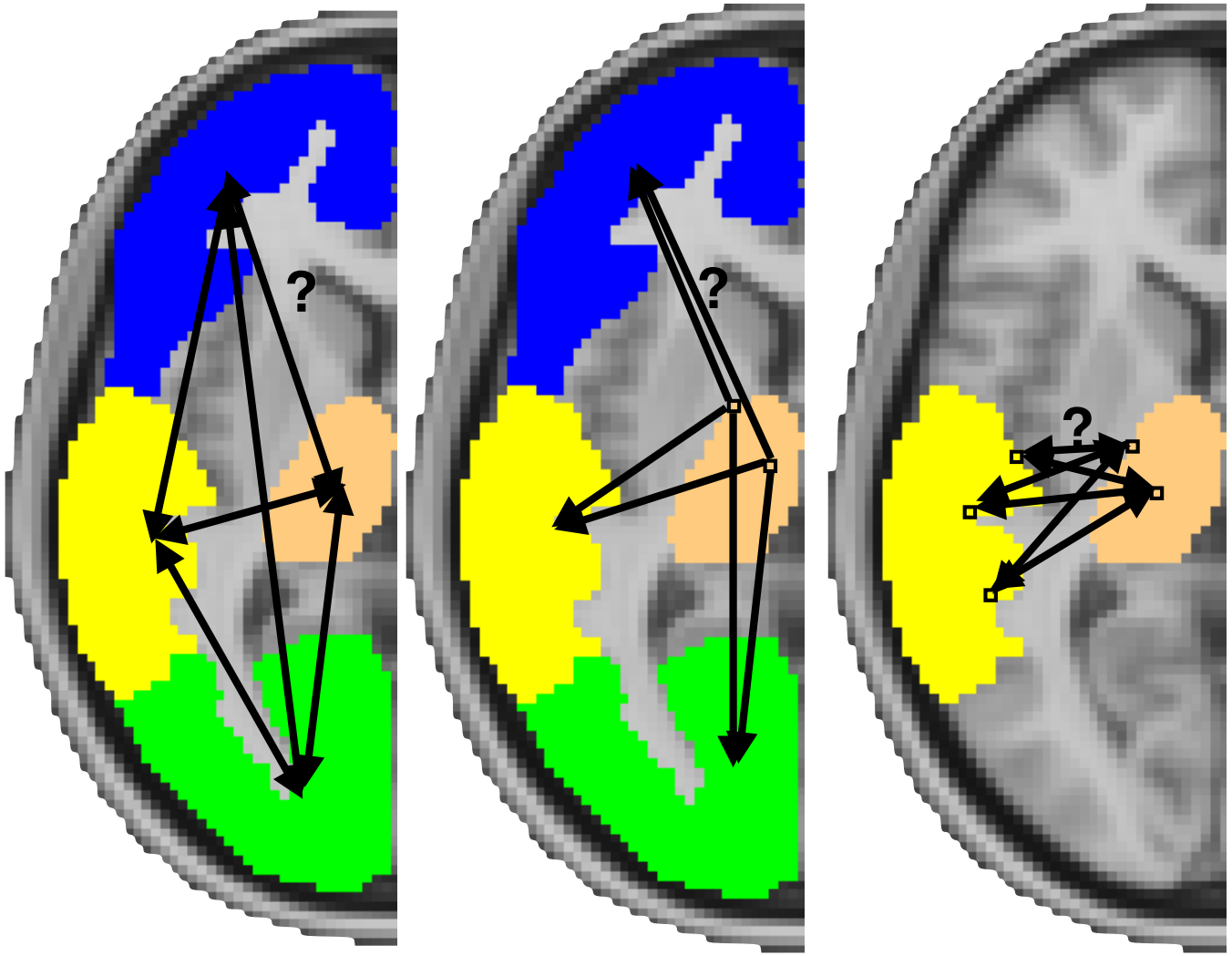


Connectivity matrices

ROI by ROI

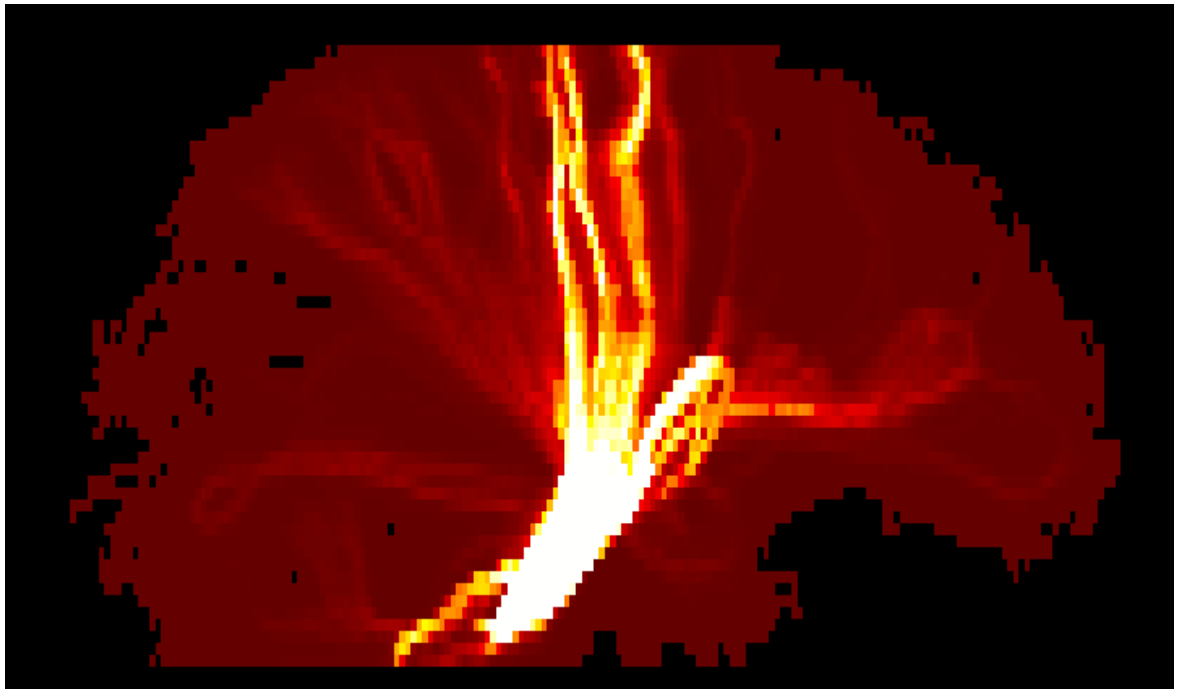
voxel by ROI

voxel by voxel



Adding Prior Knowledge to Tractography

- Because of the uncertainty propagation, the spatial distribution of paths is often very wide.

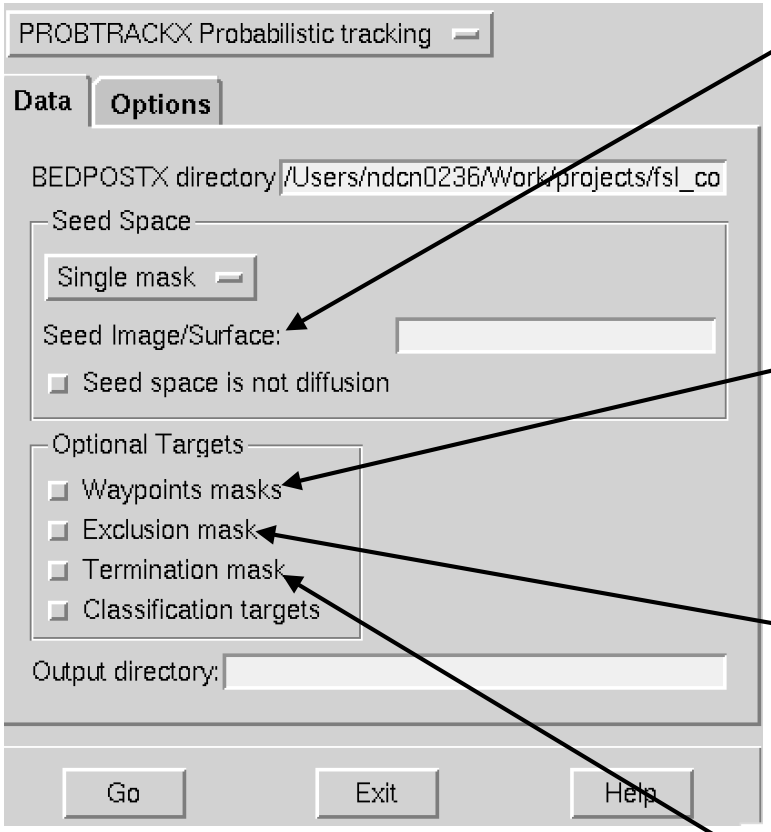


Low Probability

High Probability

Adding Prior Knowledge to Tractography

Fdt GUI:

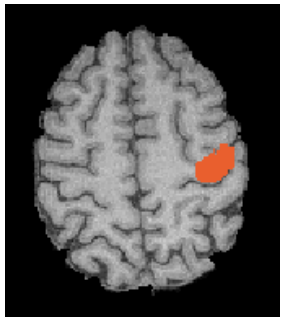


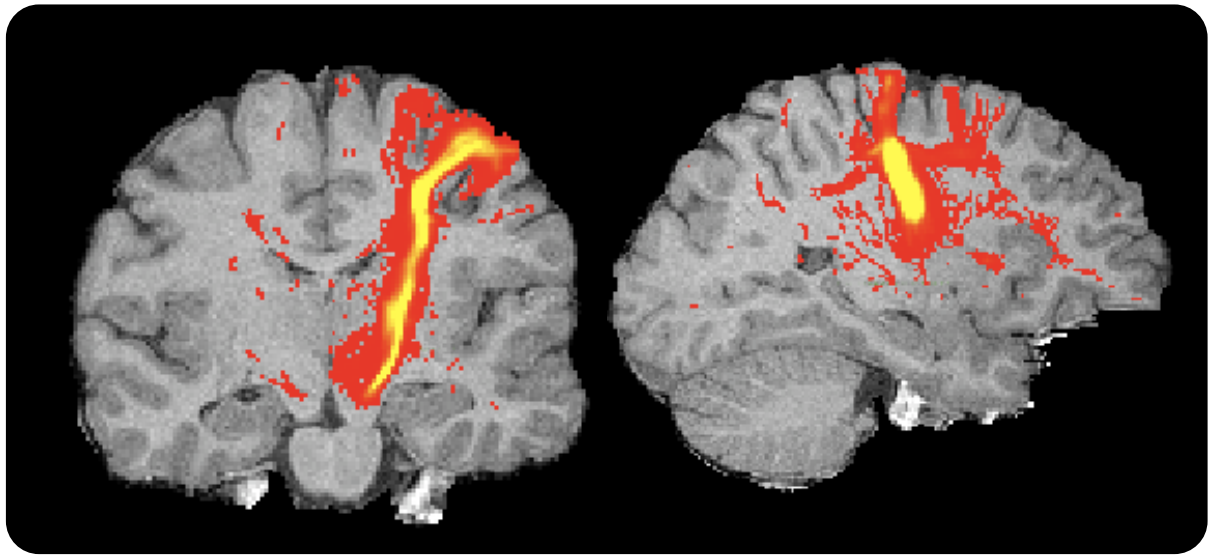
- Once a seed is specified, prior anatomical knowledge can be imposed to assist the dissection of a specific tract.
- **Waypoint** ROIs
  If a curve does not go through, it is discarded.
- **Exclusion** ROI
  If a curve goes through, it is discarded.
- **Termination** ROI
  If a curve goes through, it is terminated.

Adding Prior Knowledge to Tractography

Cortico-spinal tract

Seed: M1, hand area



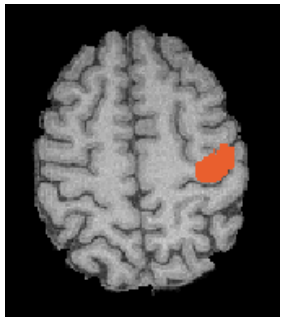


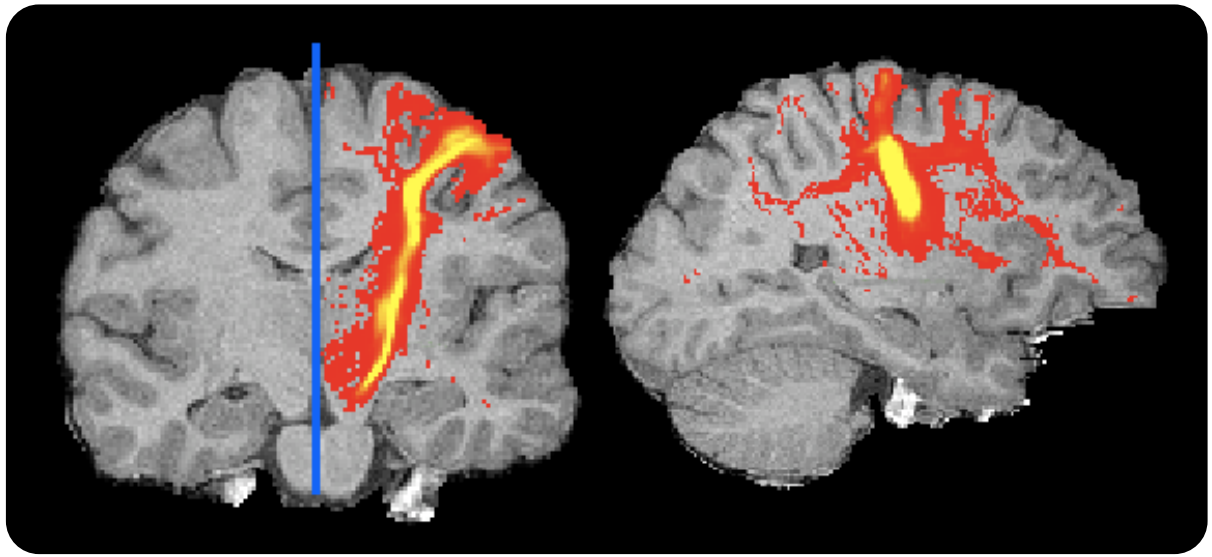
No ROIs

Adding Prior Knowledge to Tractography

Cortico-spinal tract

Seed: M1, hand area



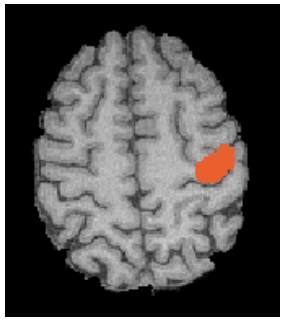


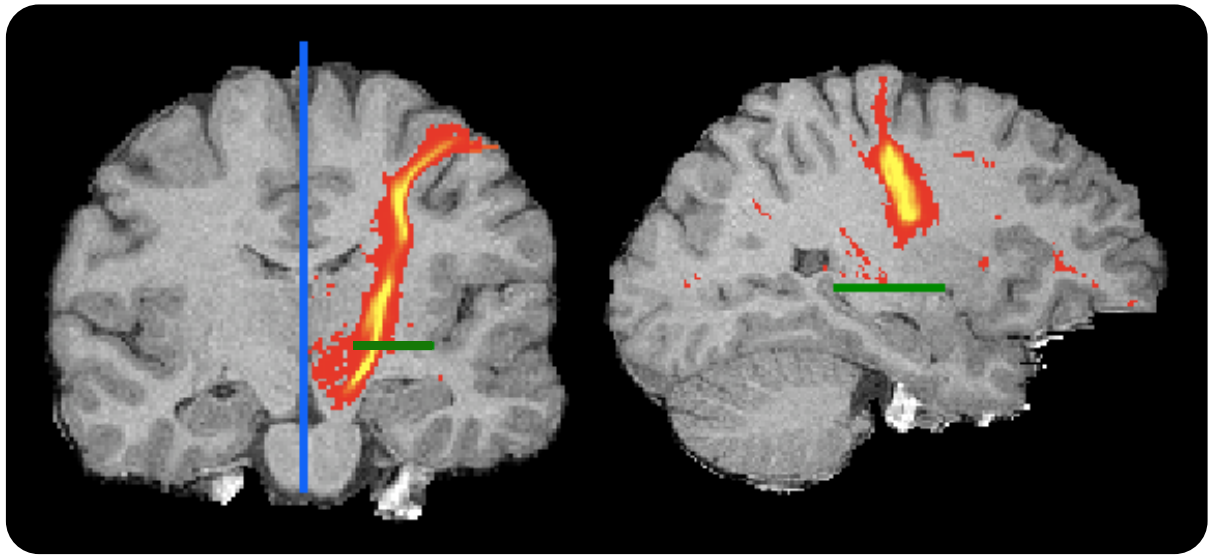
Exclusion: Mid-Sagittal plane

Adding Prior Knowledge to Tractography

Cortico-spinal tract

Seed: M1, hand area



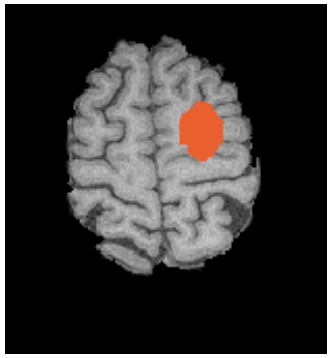


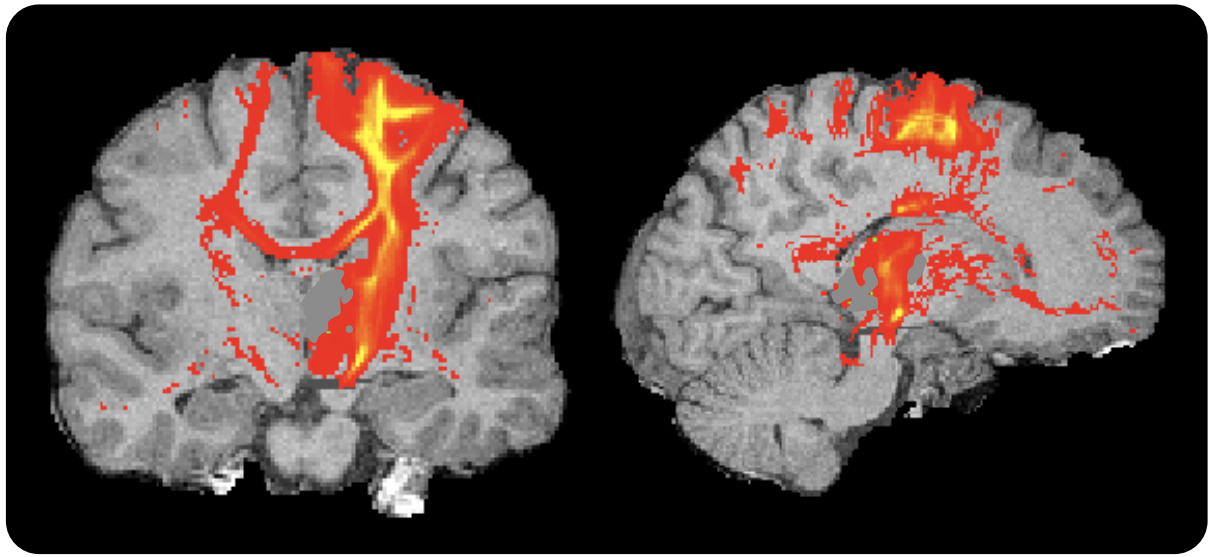
Waypoint: Internal Capsule

Adding Prior Knowledge to Tractography

Corpus Callosum

Seed: dorsal PMC



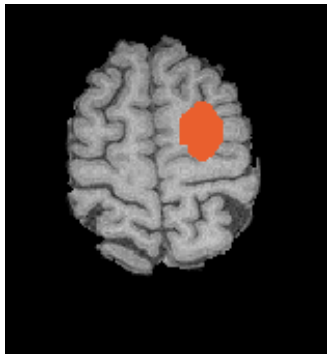


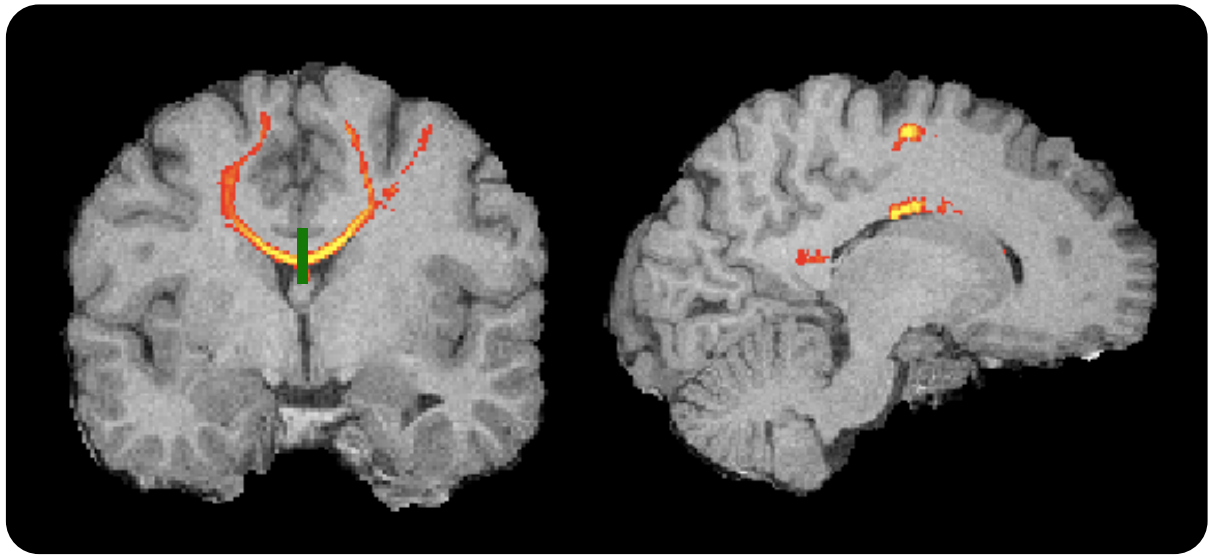
No ROIs

Adding Prior Knowledge to Tractography

Corpus Callosum

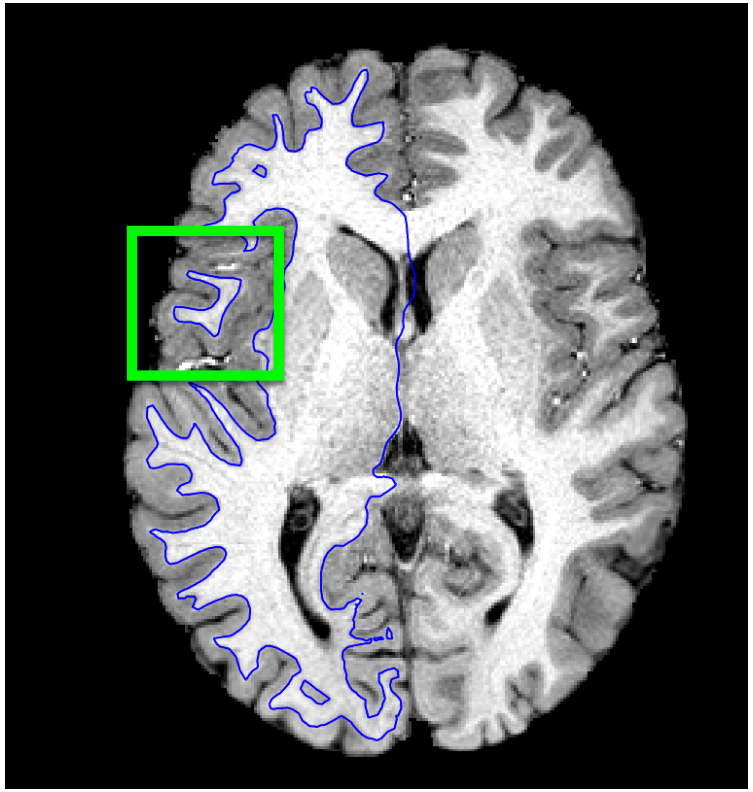
Seed: dorsal PMC



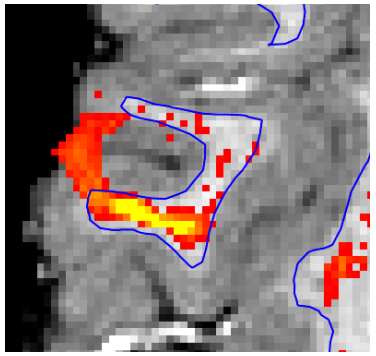


Waypoint: Corpus Callosum

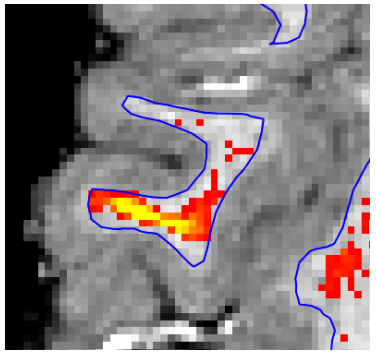
Surfaces as constraints



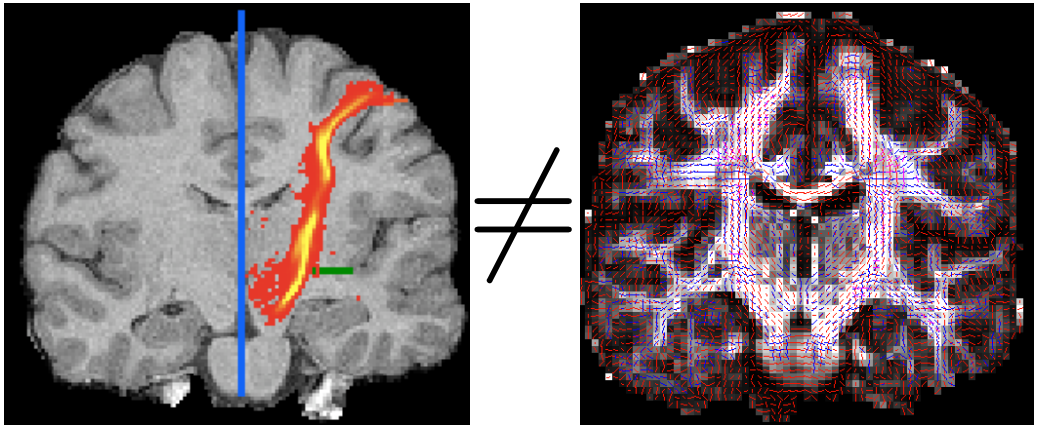
No surface constraint



Surface as termination mask

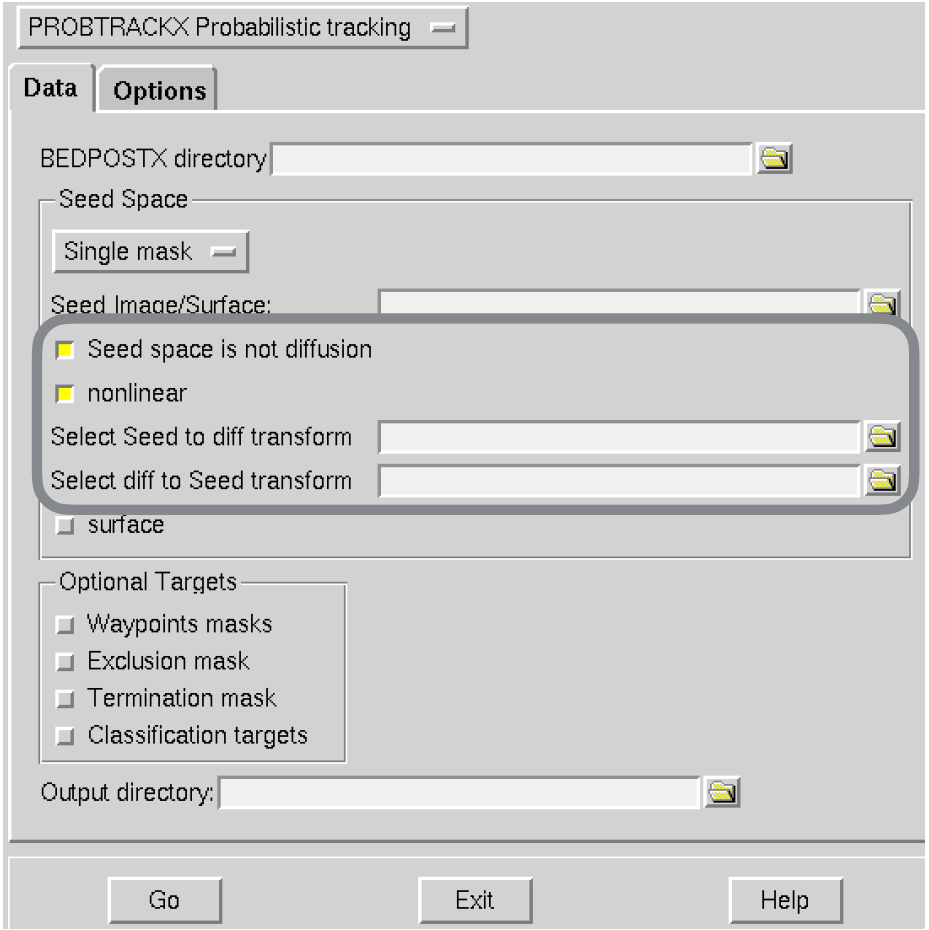


How to use masks in standard space?

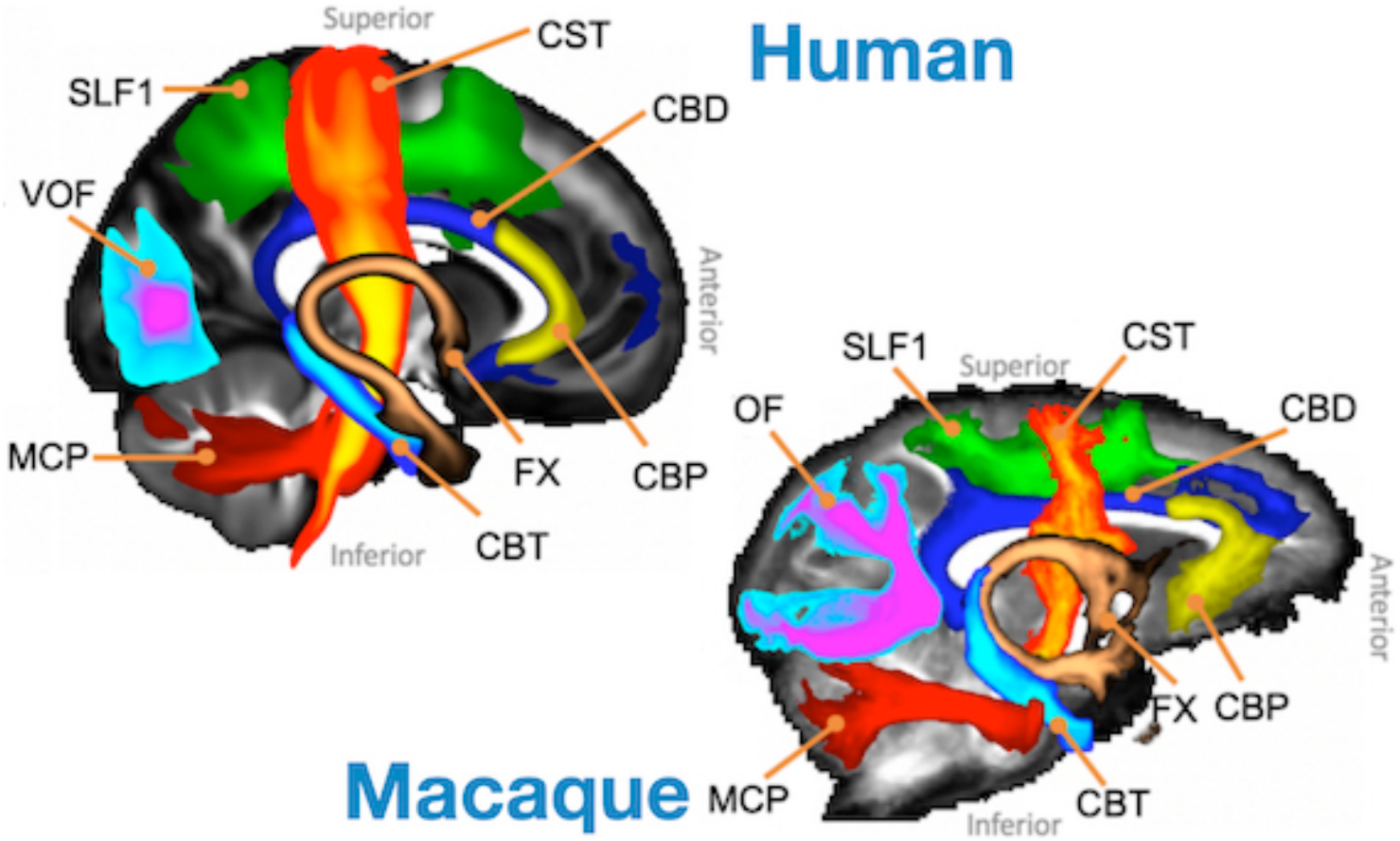


- Register to standard space
  - b0 or FA -> T1w -> standard T1w
  - FA -> standard FA
- **Don't** transform masks -> diffusion space
- **Don't** transform diffusion -> standard space

Tell probtrackX about transform:



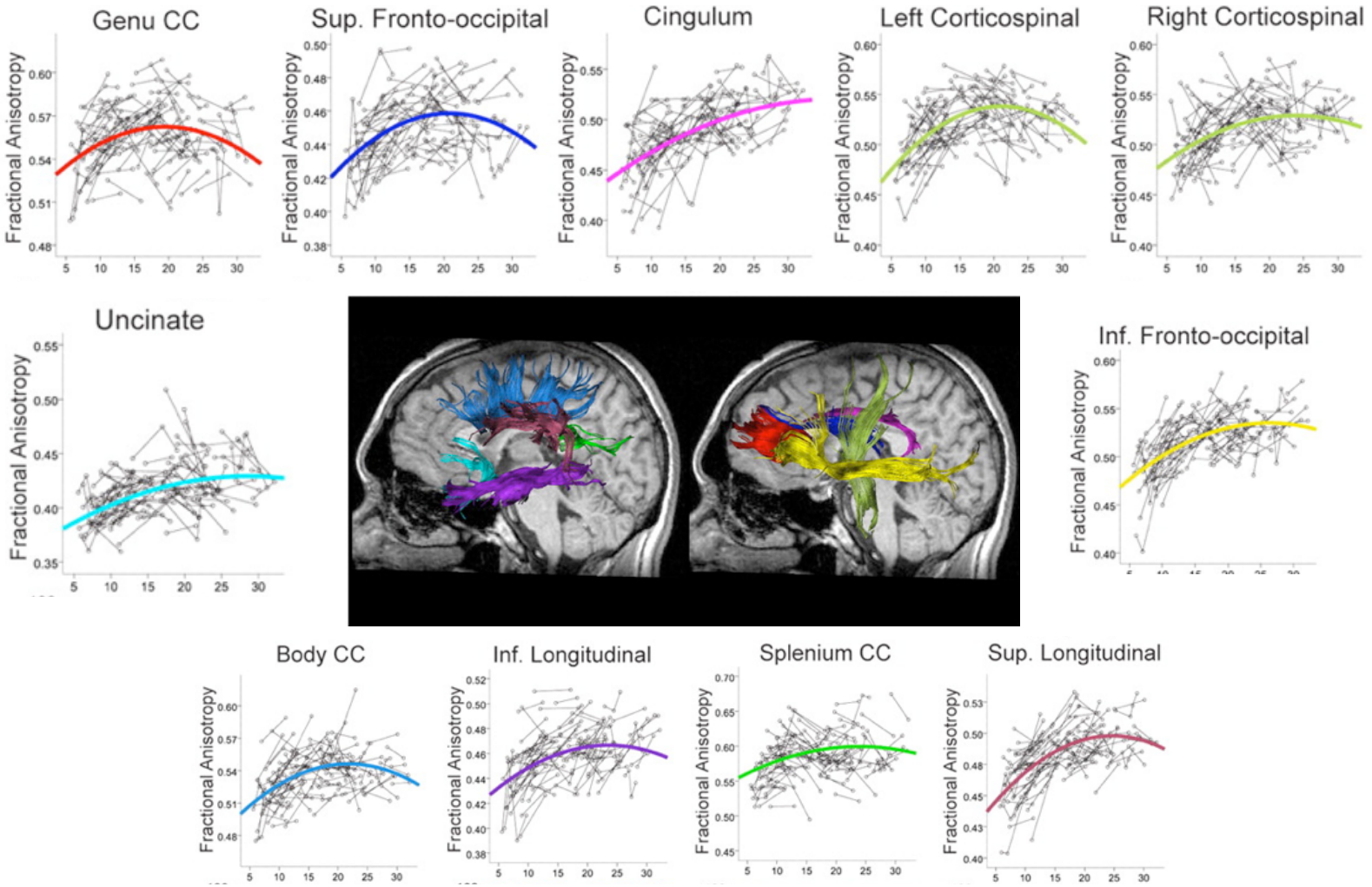
XTRACT: generating tracts for you



https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/XTRACT

Connectivity - Why do we care?

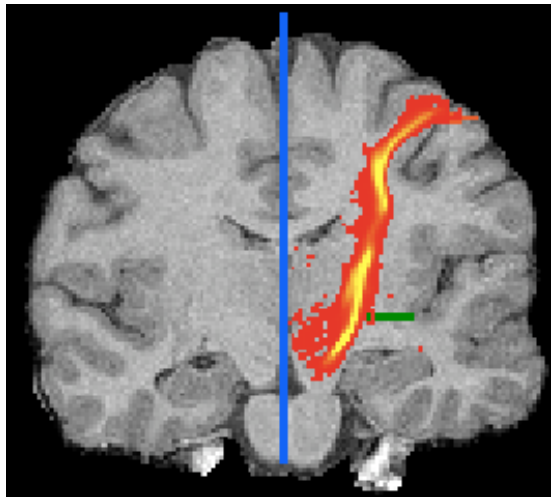
- Tractography provides non-invasive localisation and semi-quantitative biomarkers

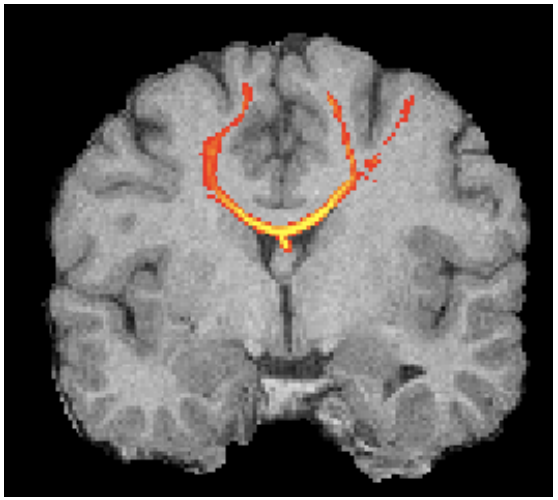


Lebel, Beaulieu J Neuroscience 2011

ProbtrackX outputs

Known white matter tracts



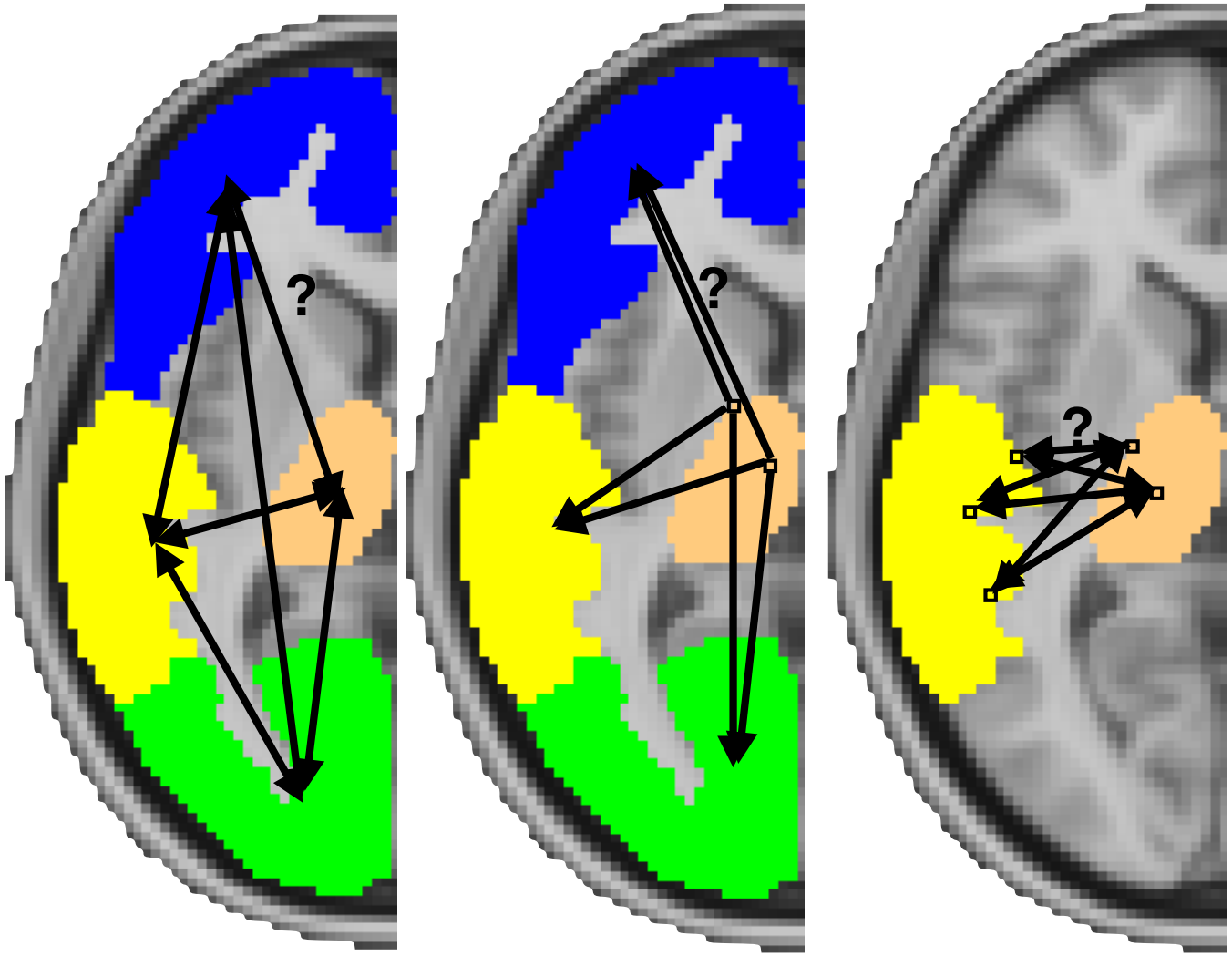


Connectivity matrices

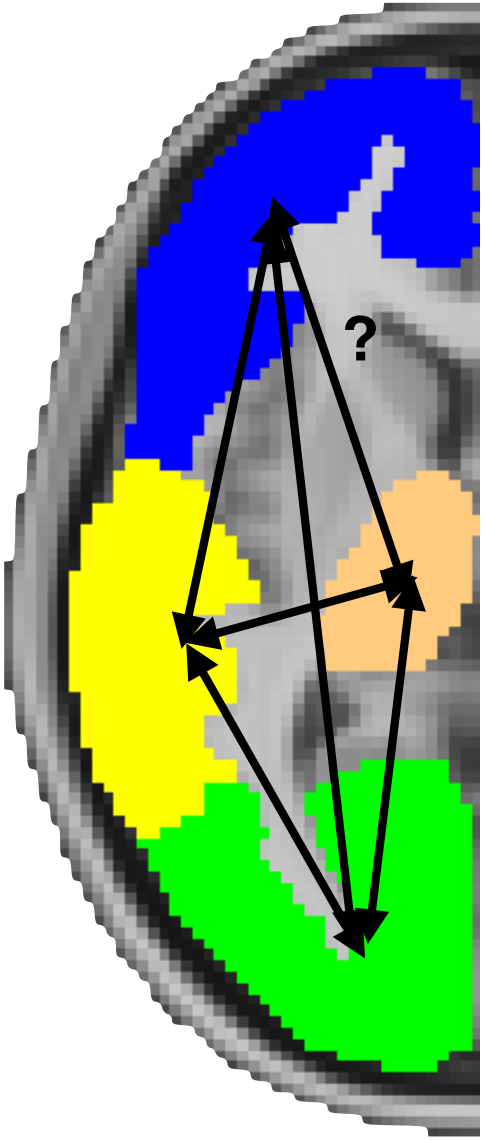
ROI by ROI

voxel by ROI

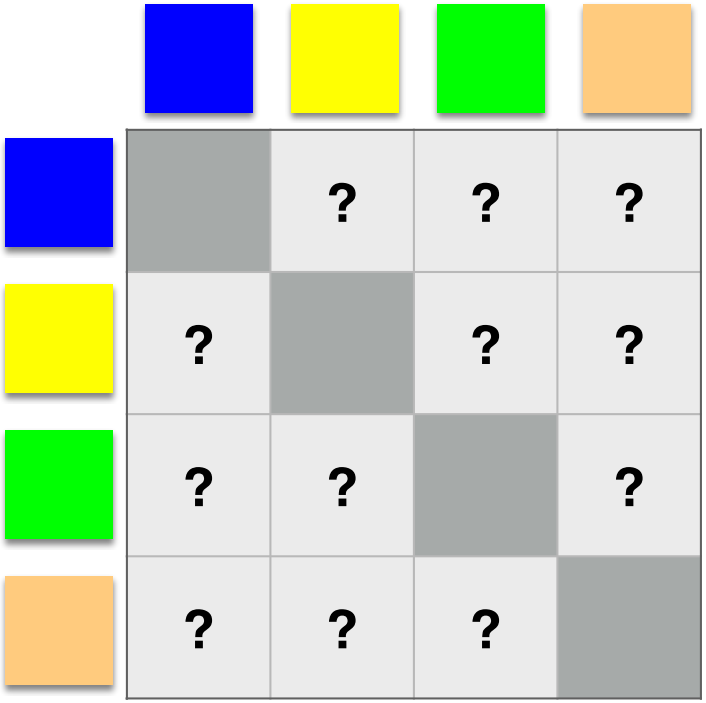
voxel by voxel



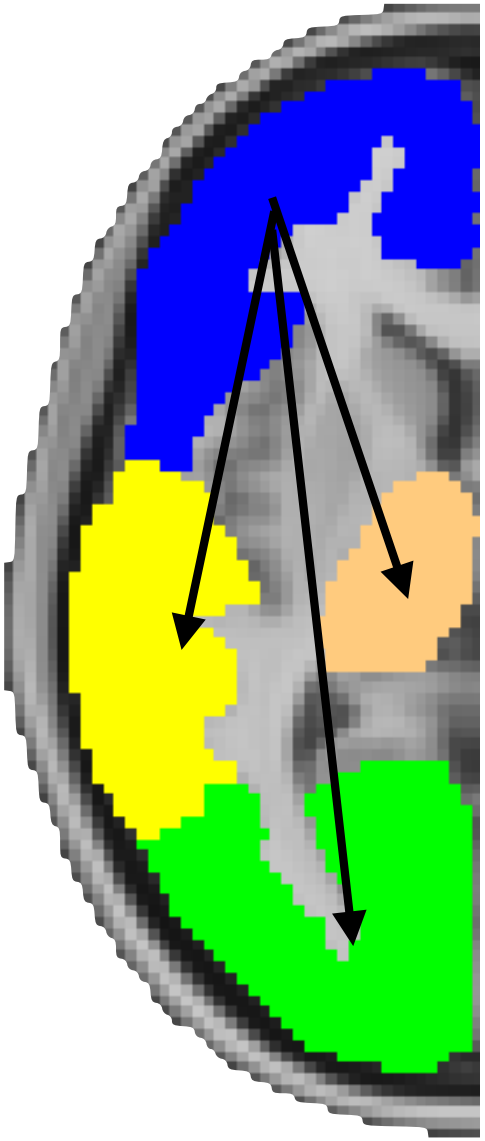
Connectivity between ROIs



Resulting matrix:

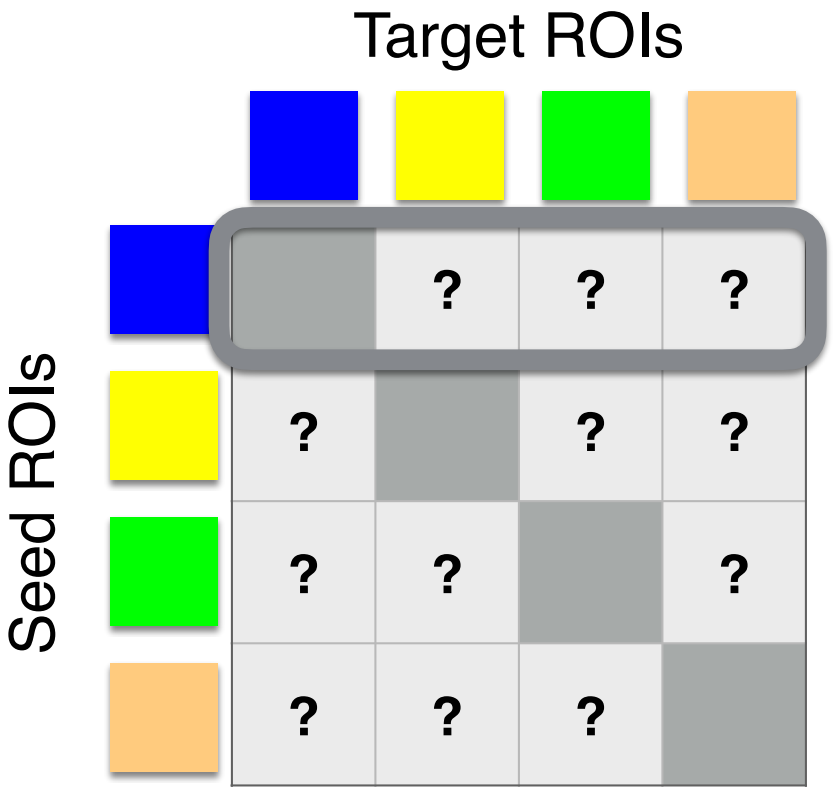


Connectivity between ROIs

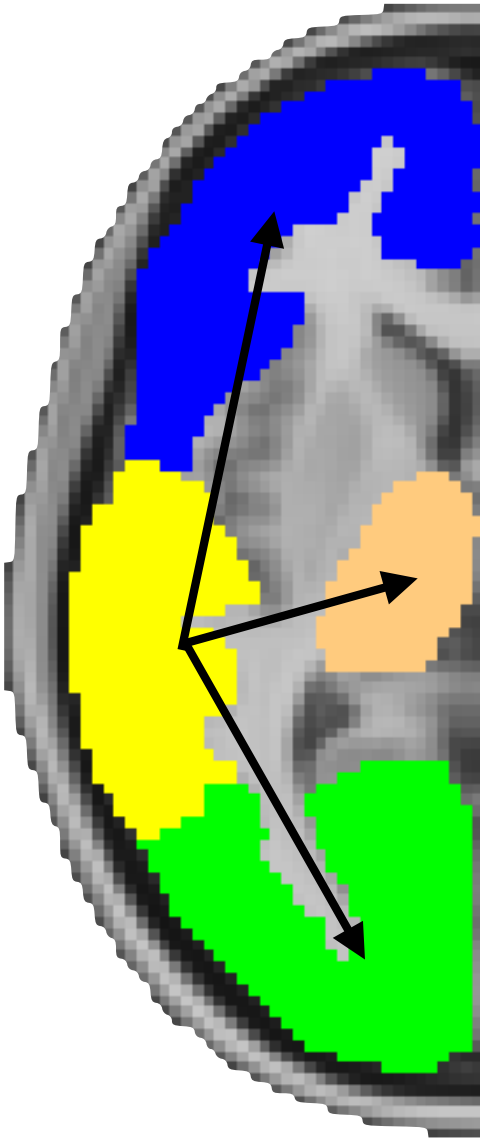


- Seed from blue
- Other ROIs are waypoints
- Fill first row of matrix

Resulting matrix:

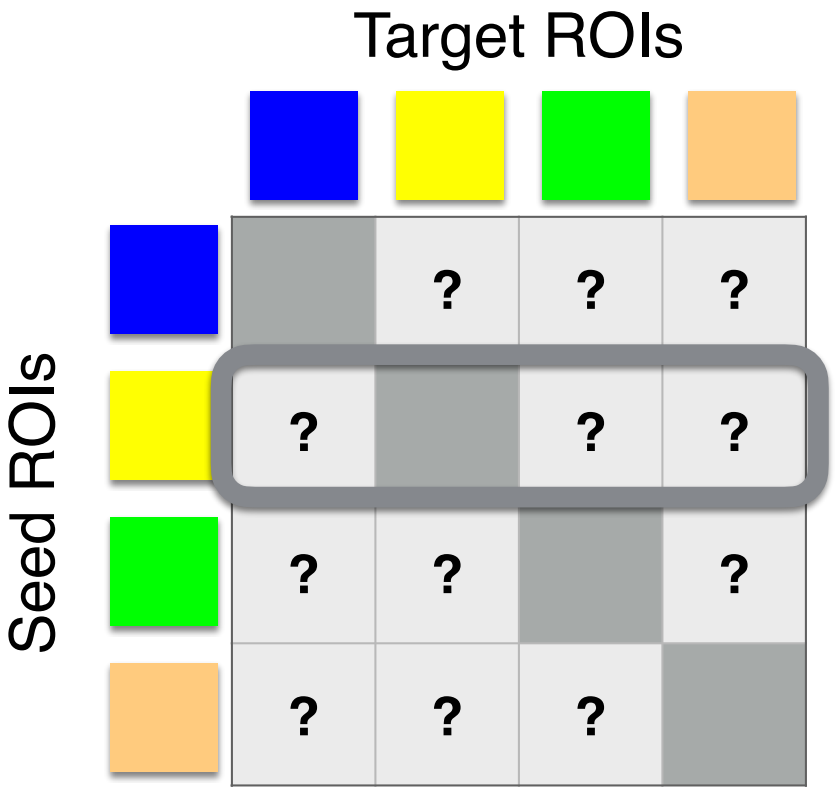


Connectivity between ROIs

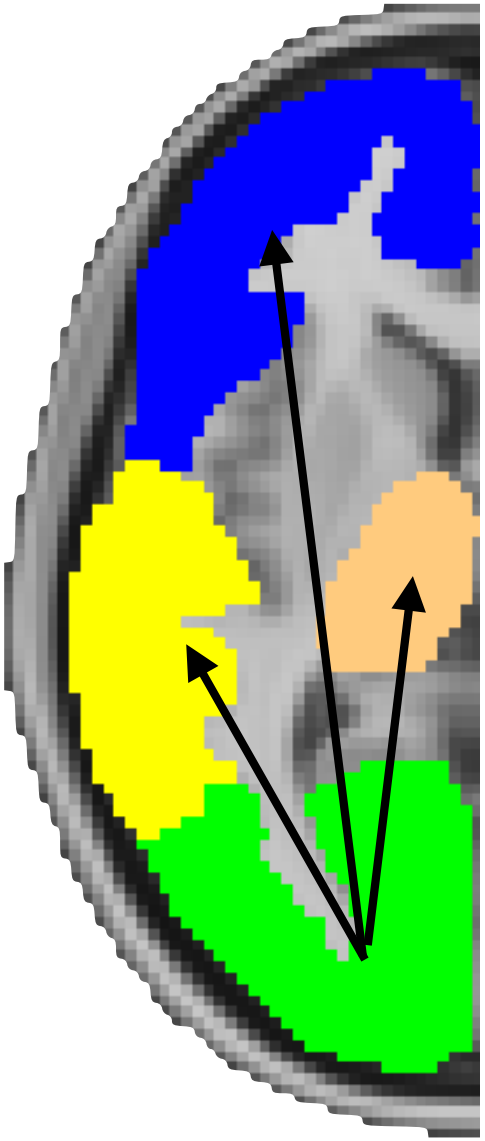


- Seed from yellow
- Other ROIs are waypoints
- Fill first row of matrix

Resulting matrix:

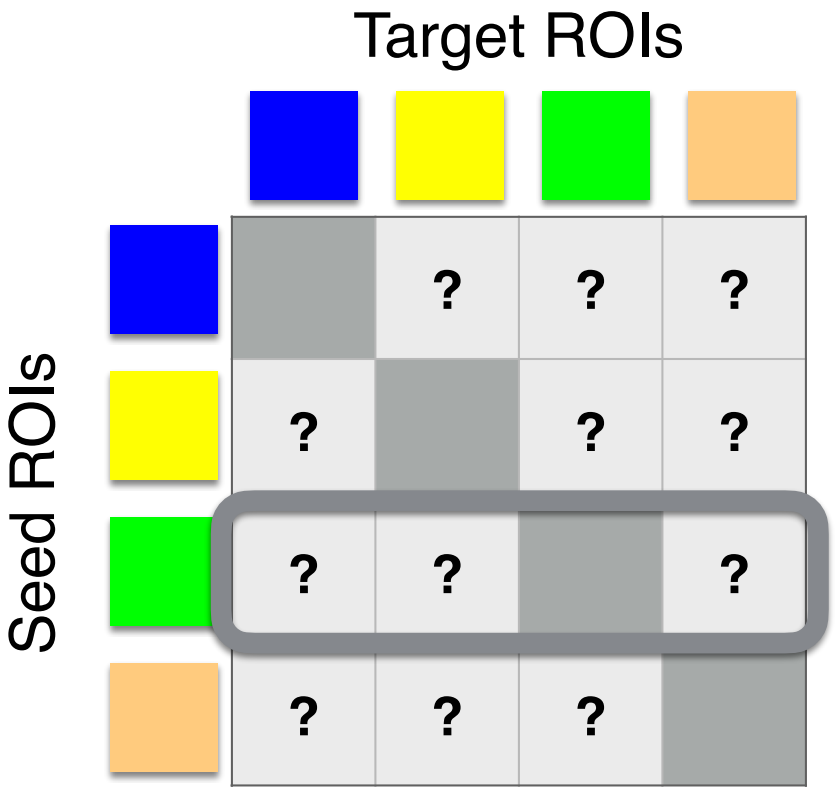


Connectivity between ROIs

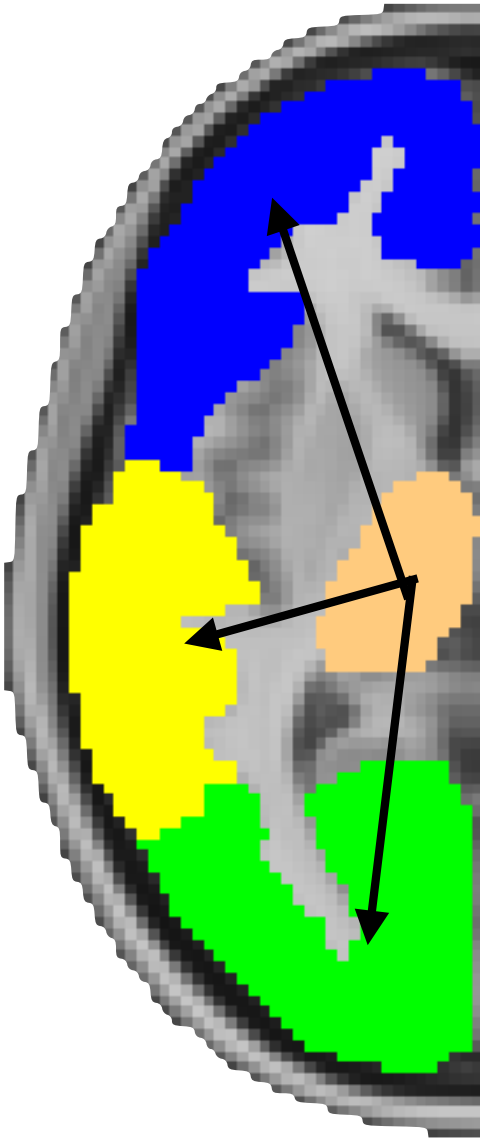


- Seed from green
- Other ROIs are waypoints
- Fill first row of matrix

Resulting matrix:

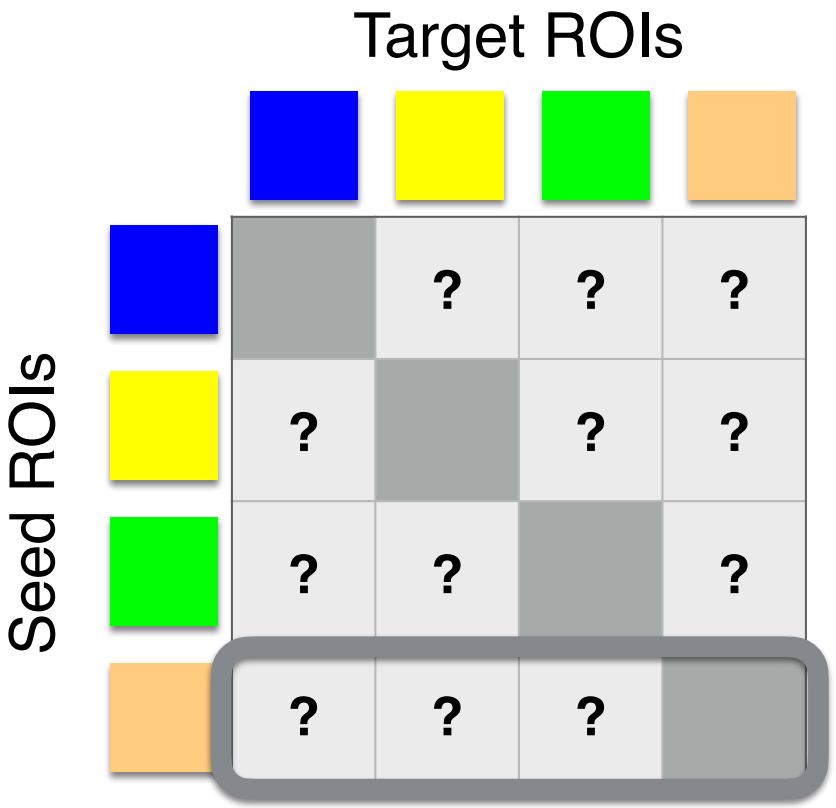


Connectivity between ROIs

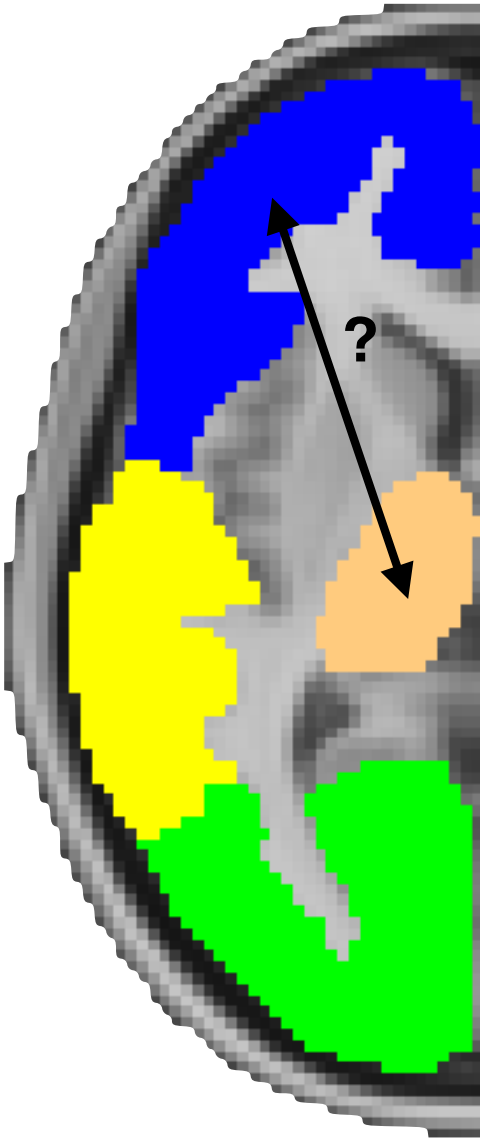


- Seed from copper
- Other ROIs are waypoints
- Fill first row of matrix

Resulting matrix:

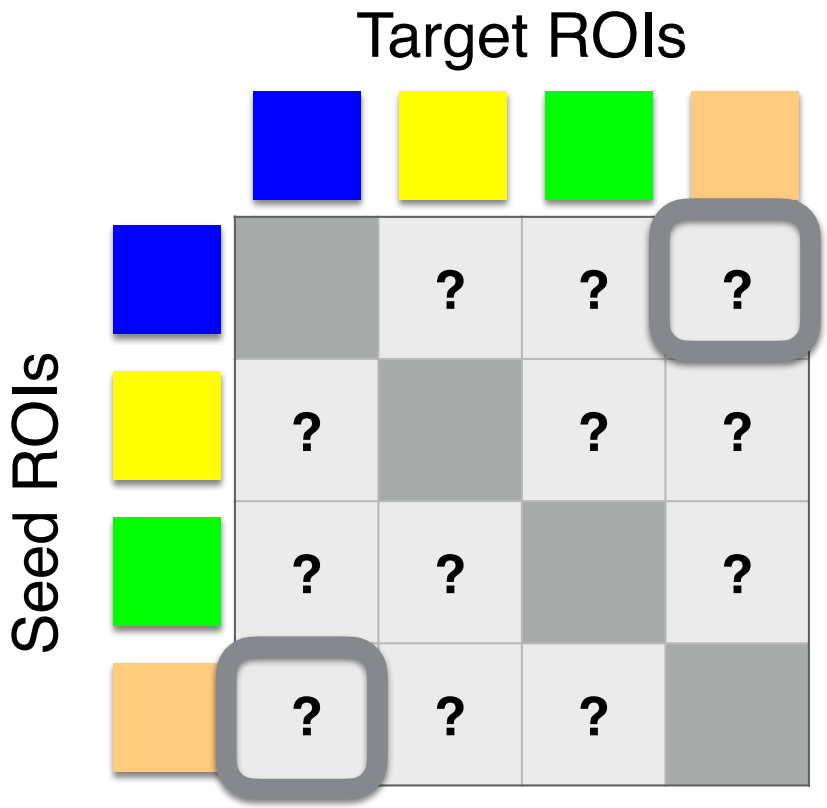


Connectivity between ROIs

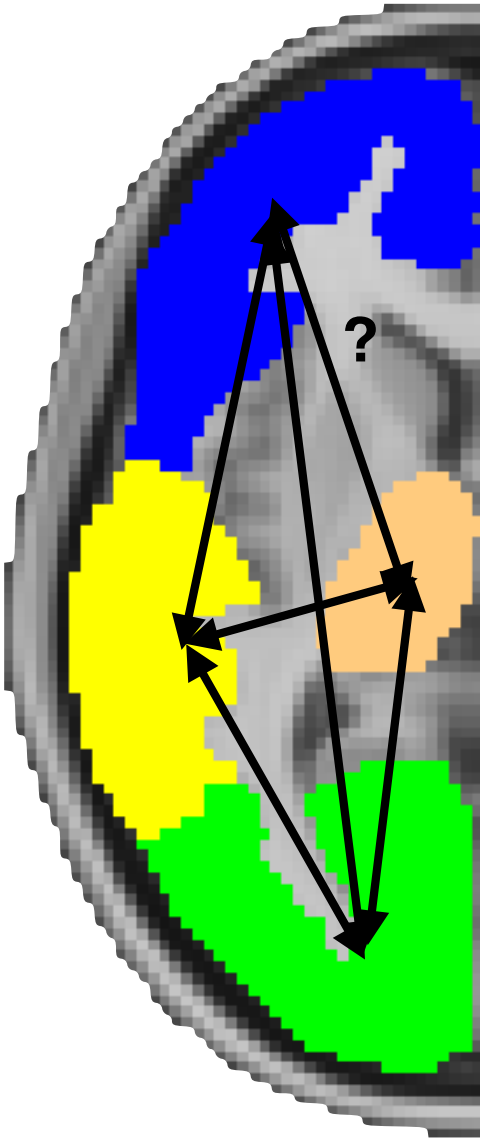


$$P(\blacksquare \leftrightarrow \blacksquare) = (P(\blacksquare \leftarrow \blacksquare) + P(\blacksquare \rightarrow \blacksquare))\,/2$$

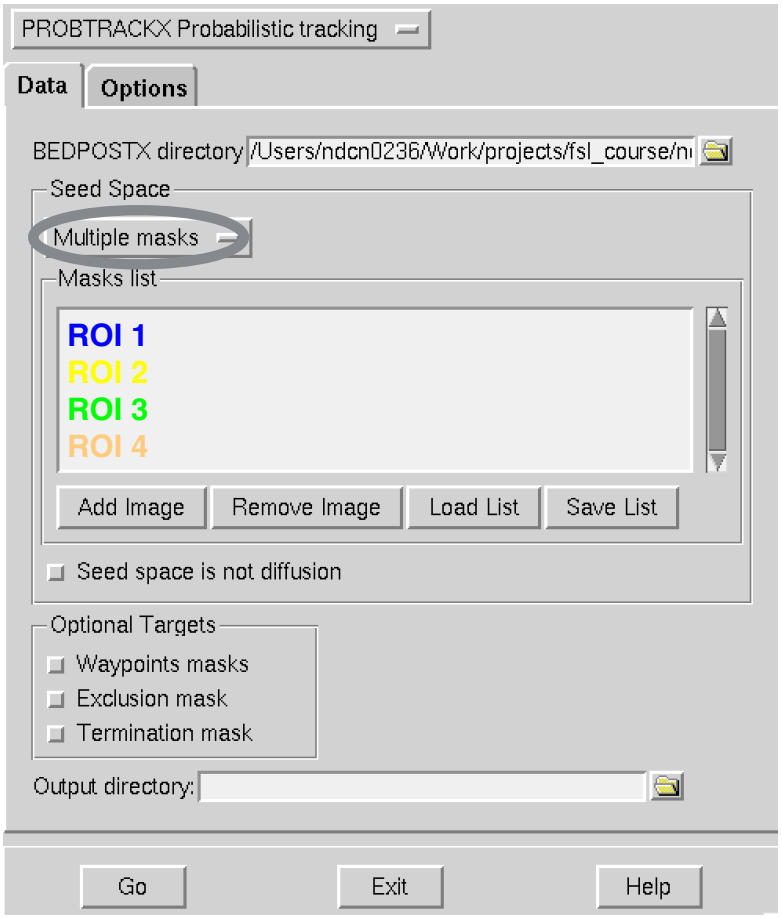
Resulting matrix:



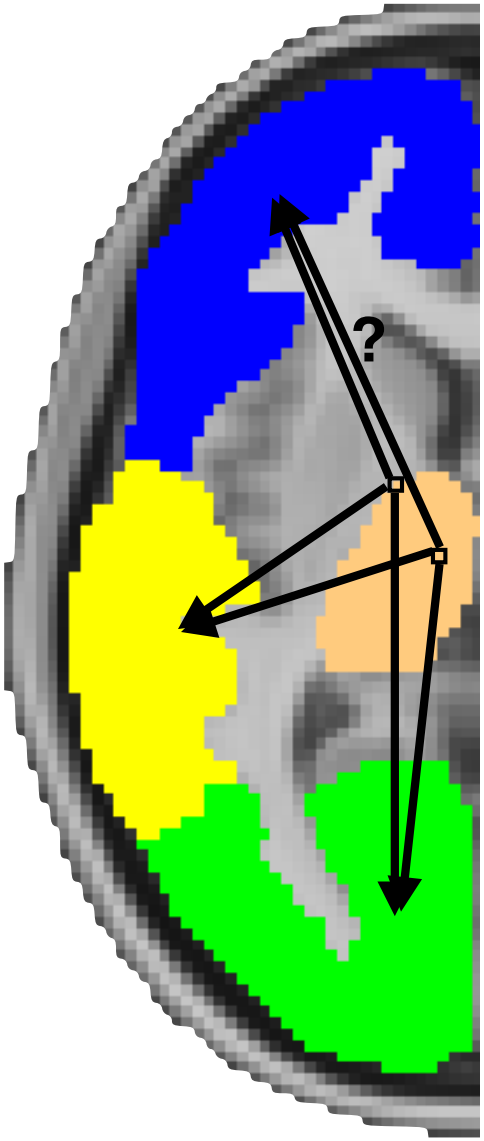
Connectivity between ROIs



Fdt GUI:



Connectivity between voxels and ROIs



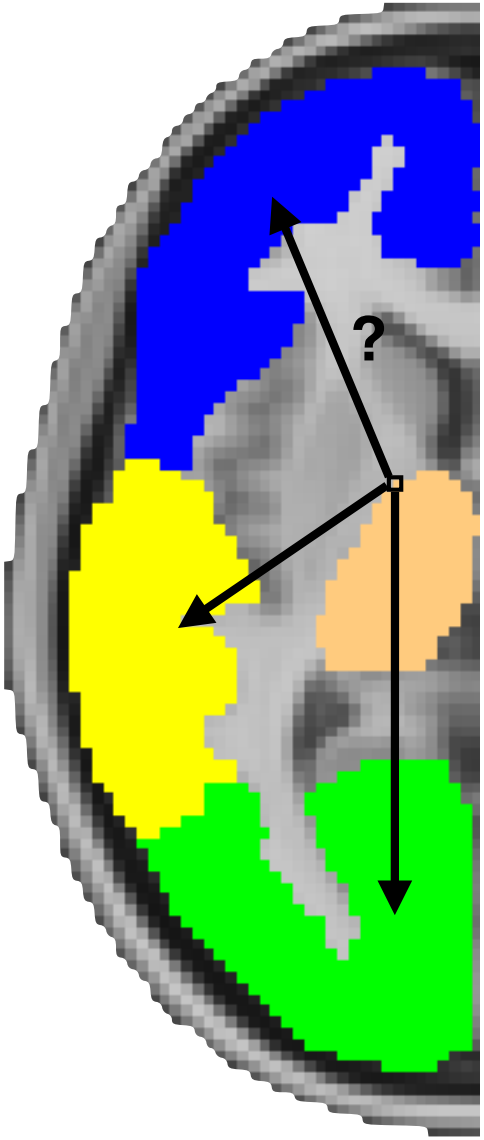
Resulting matrix:

Target ROIs

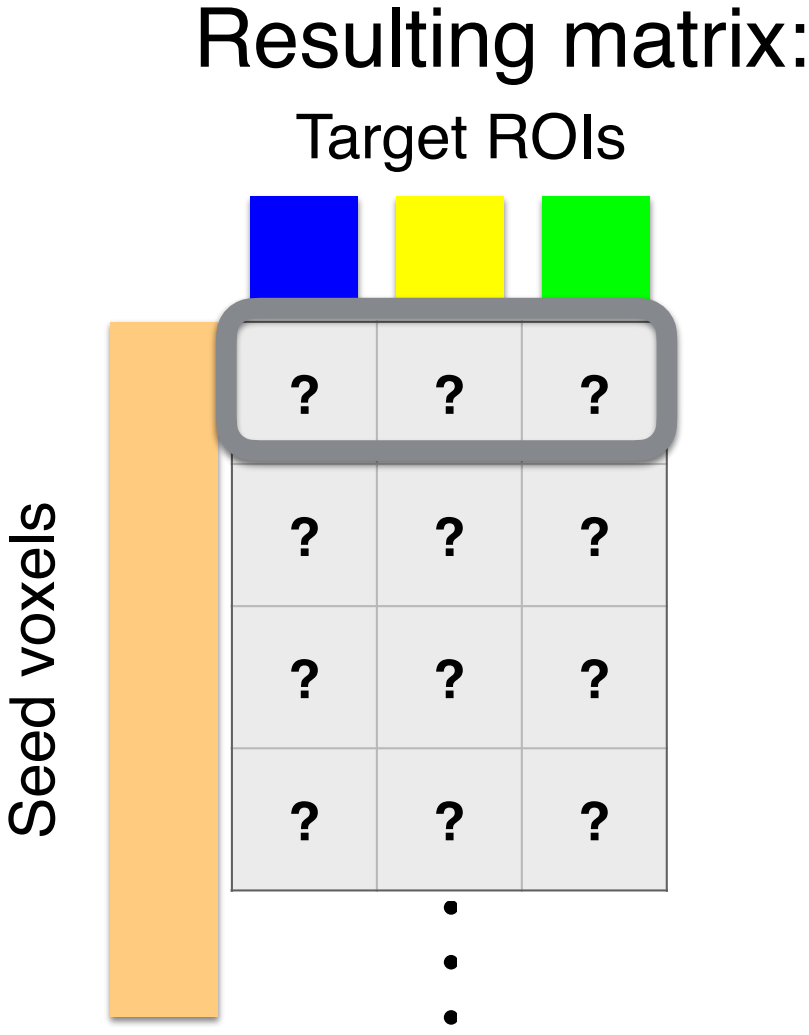
Seed voxels

?	?	?
?	?	?
?	?	?
?	?	?
•		
•		
•		

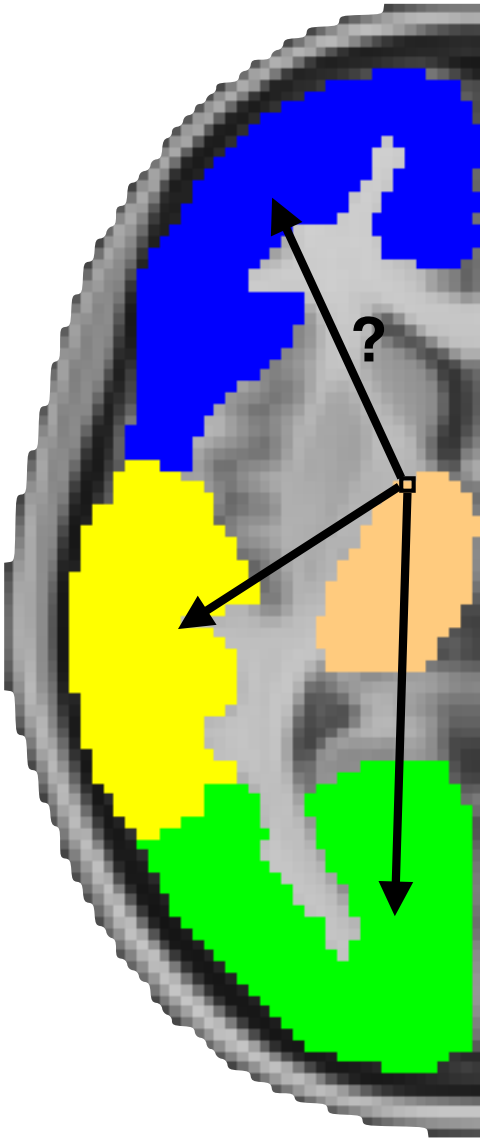
Connectivity between voxels and ROIs



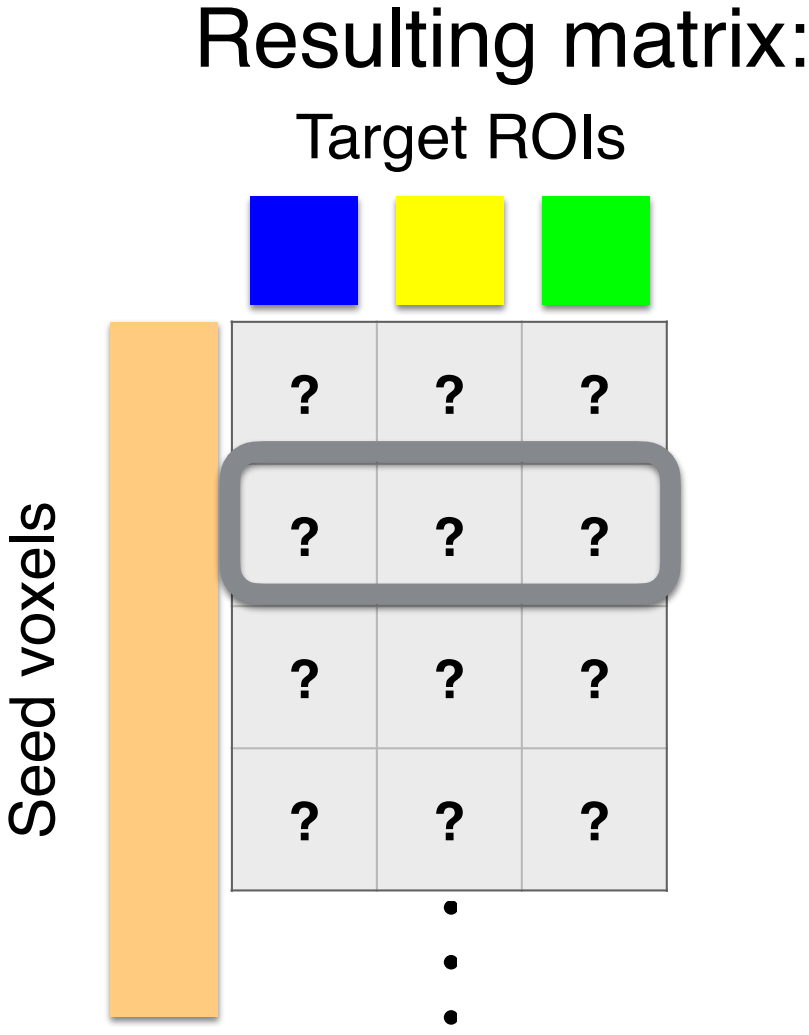
Resulting matrix:



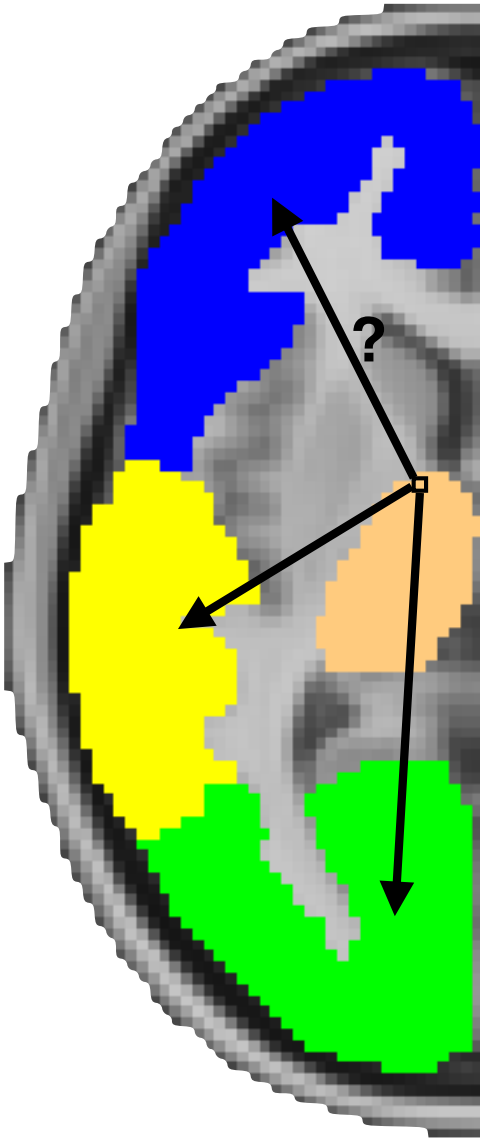
Connectivity between voxels and ROIs



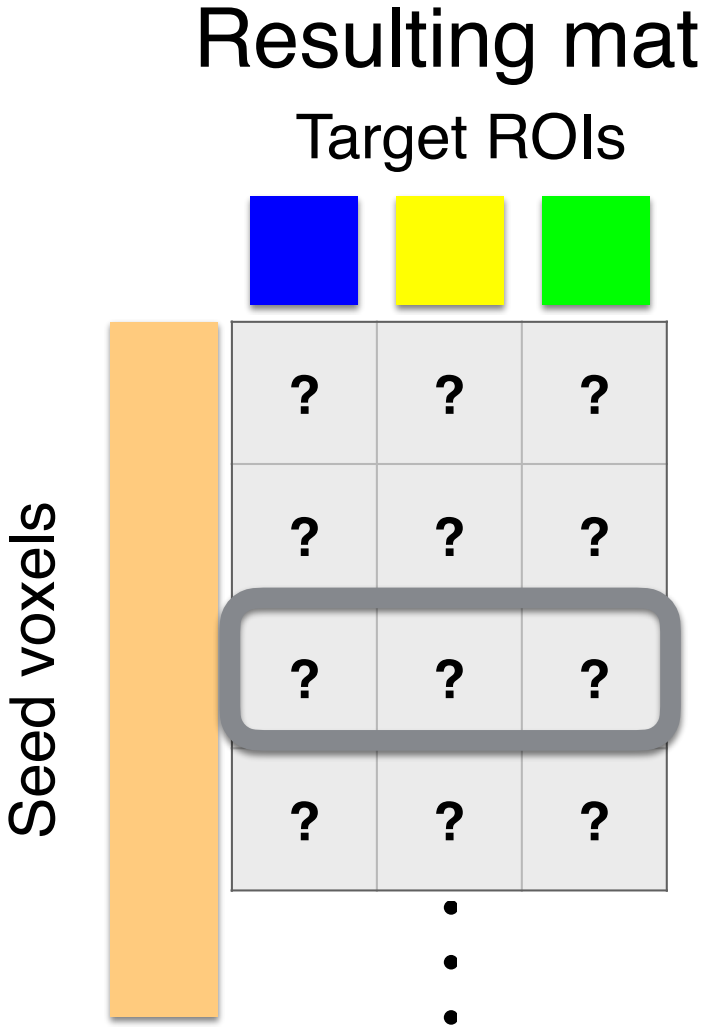
Resulting matrix:



Connectivity between voxels and ROIs

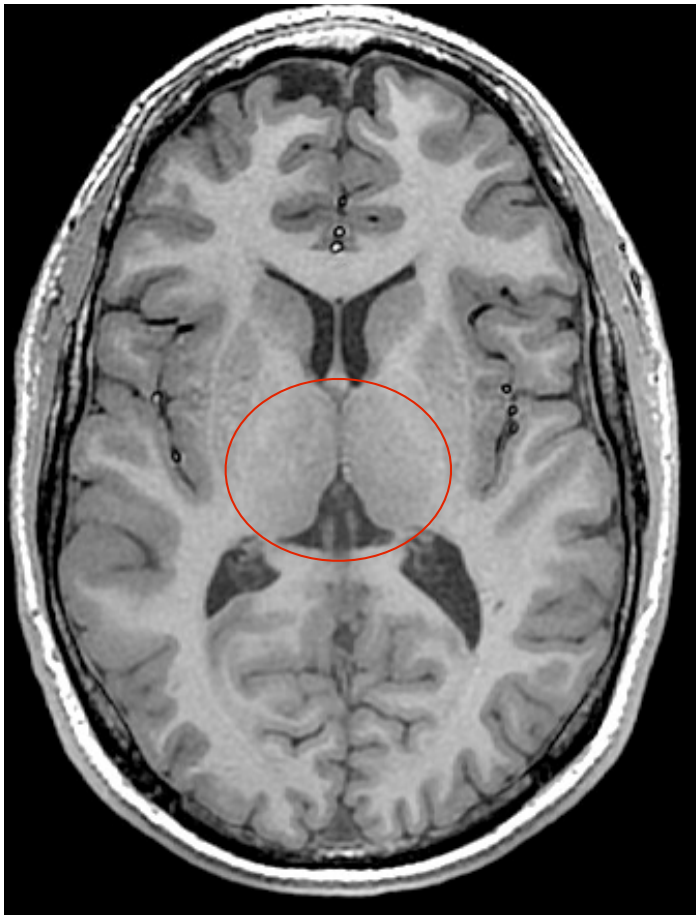


Resulting matrix:



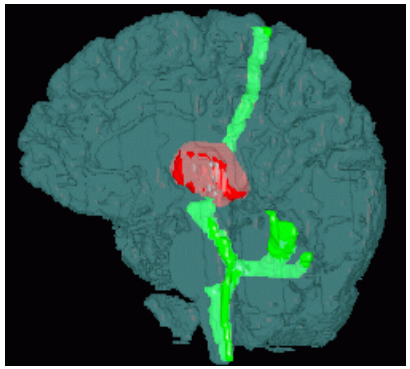
etc…

Segmenting the thalamus

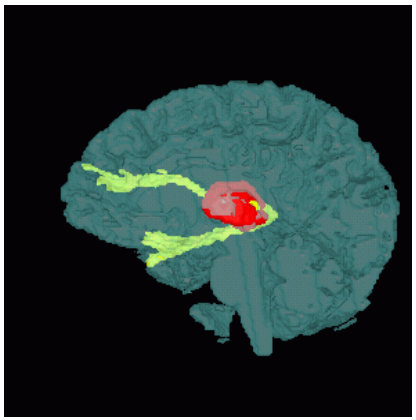


no contrast on conventional MRI

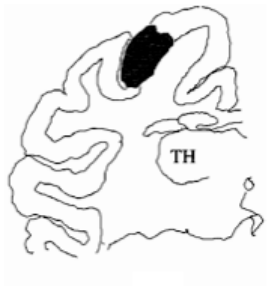
VL –> M1

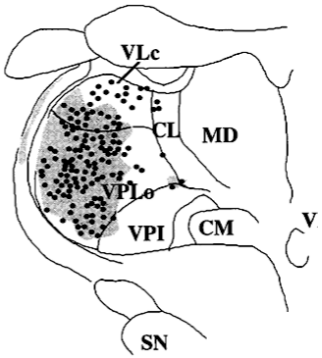


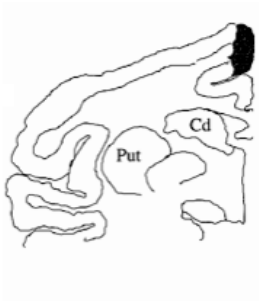
MD –> PFC

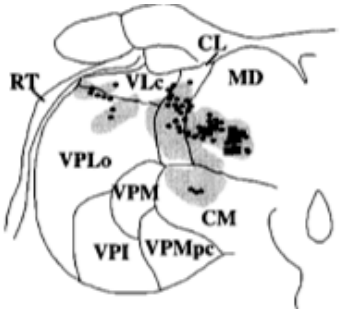


Behrens et al, 2003
(probabilistic tractography)





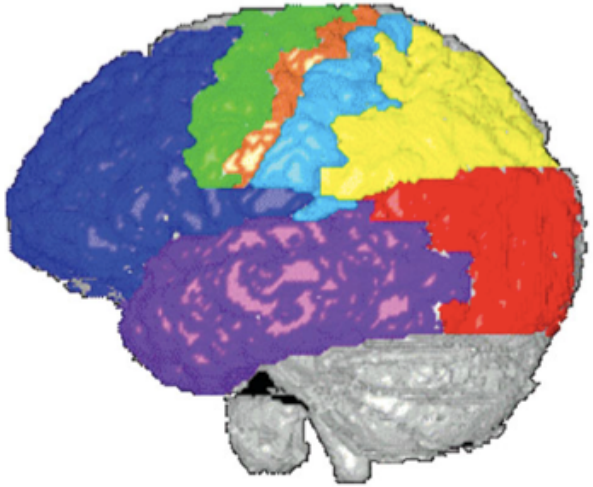


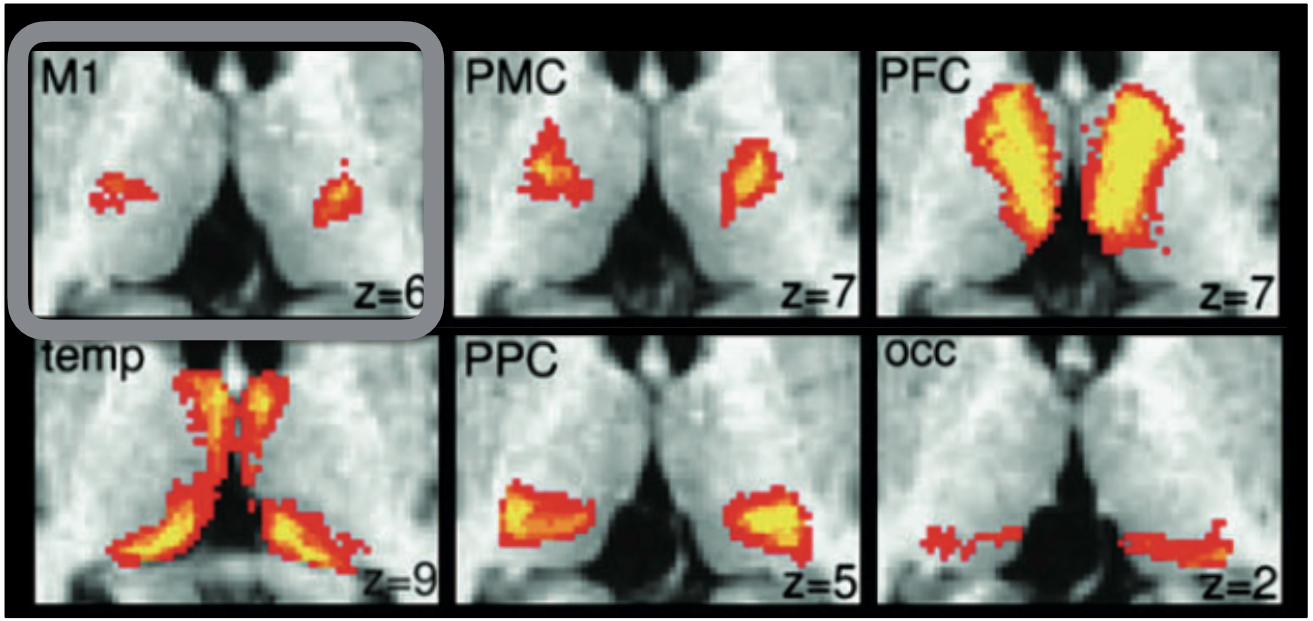


Rouiller et al, 1998
(BDA anterograde tracing)

Segmenting the thalamus

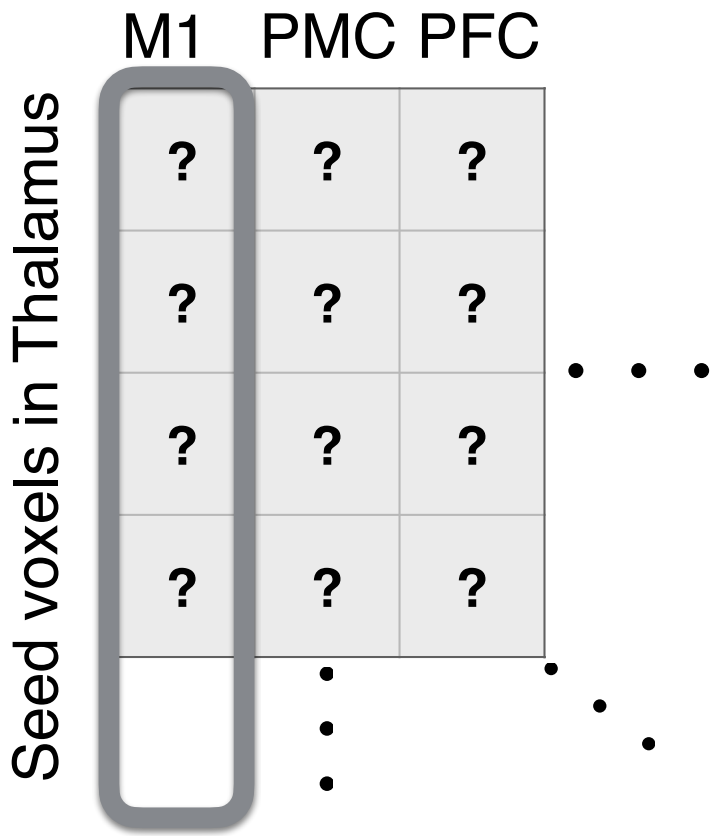
Prior cortical parcelaltion





Resulting matrix:

Target ROIs

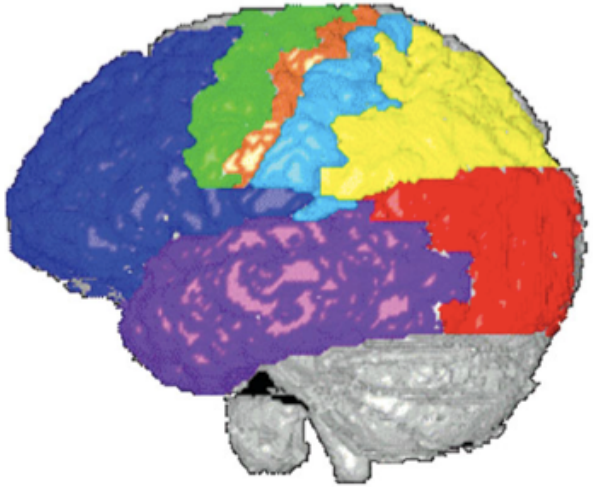


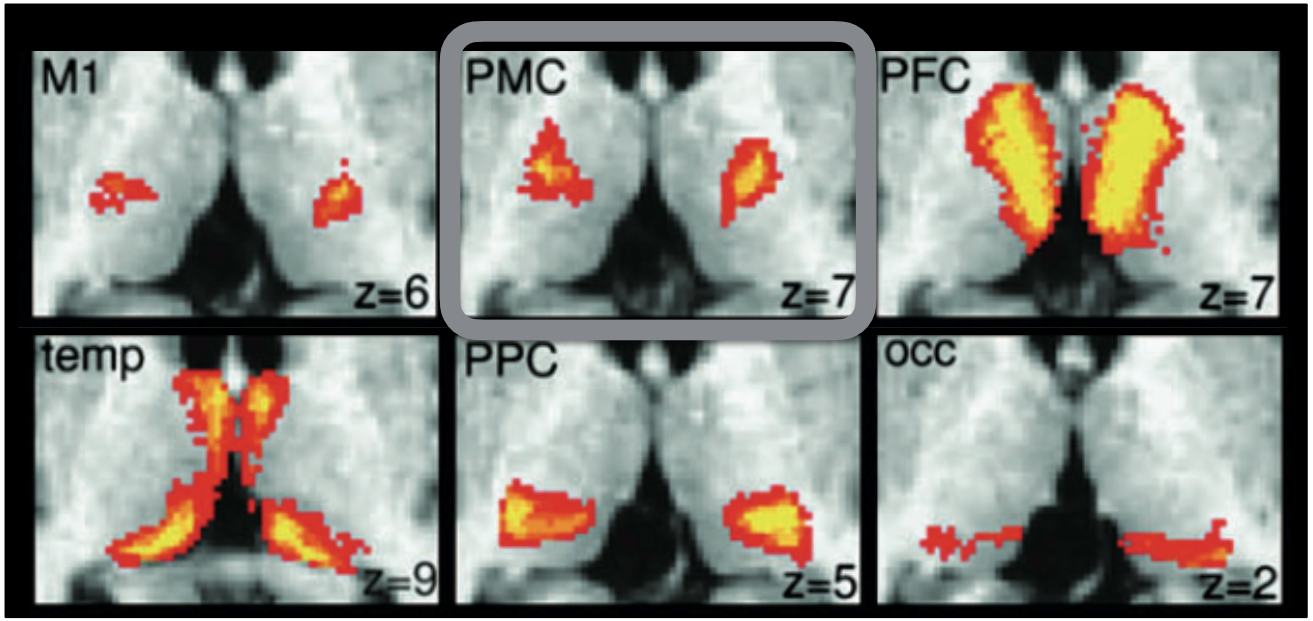
Behrens et al. Nat Neuro2003

Johansen-Berg et al. Cereb Ctx 2005

Segmenting the thalamus

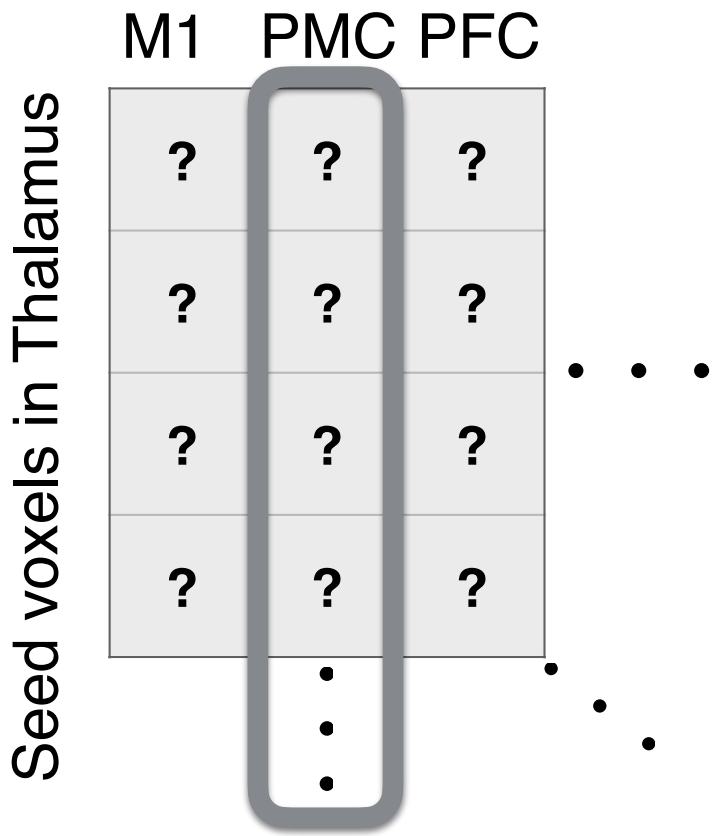
Prior cortical parcelaltion





Resulting matrix:

Target ROIs

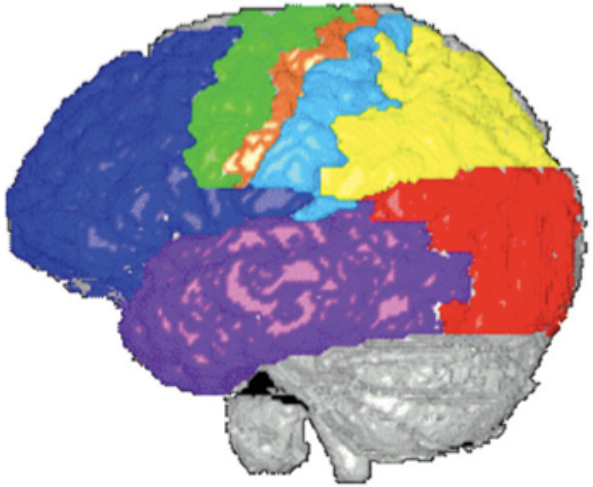


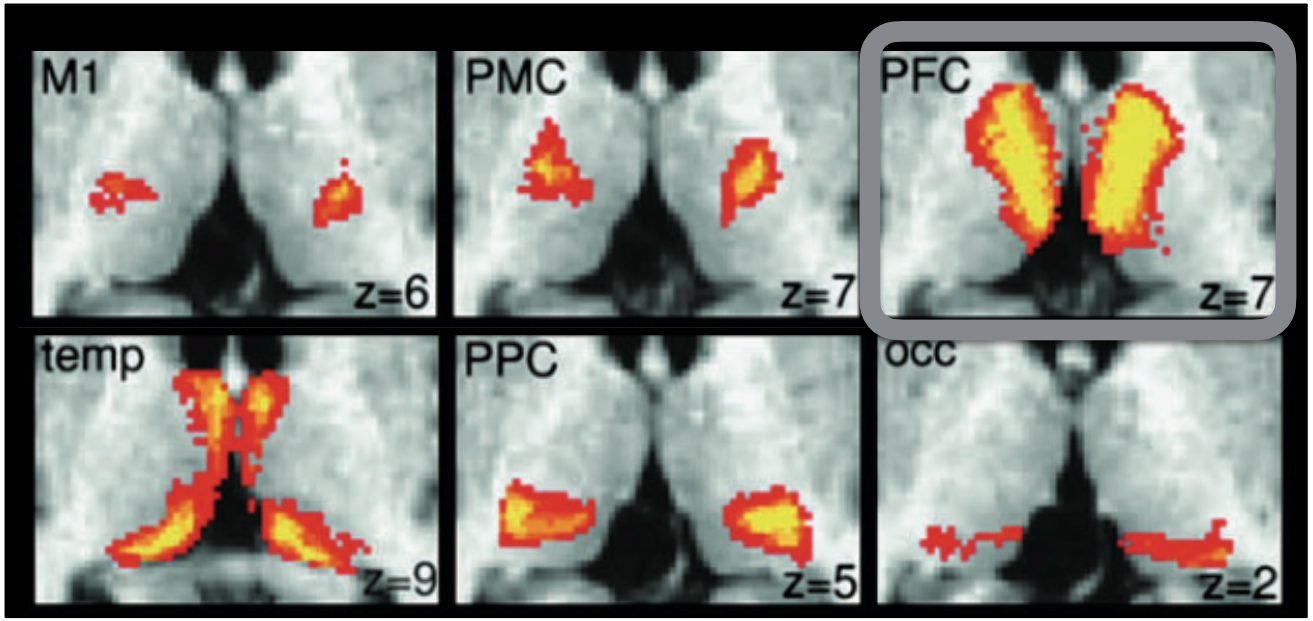
Behrens et al. Nat Neuro2003

Johansen-Berg et al. Cereb Ctx 2005

Segmenting the thalamus

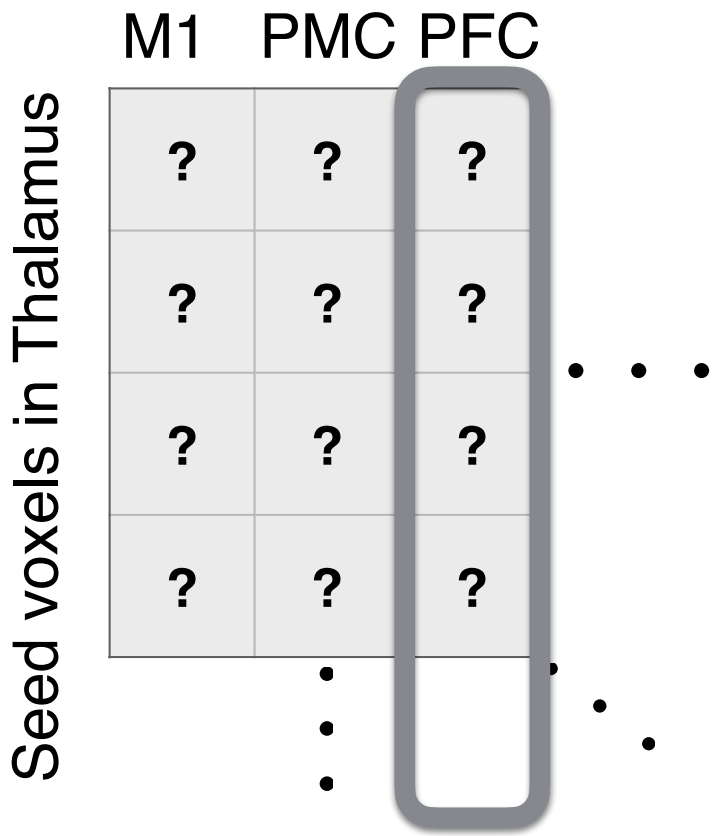
Prior cortical parcelaltion





Resulting matrix:

Target ROIs

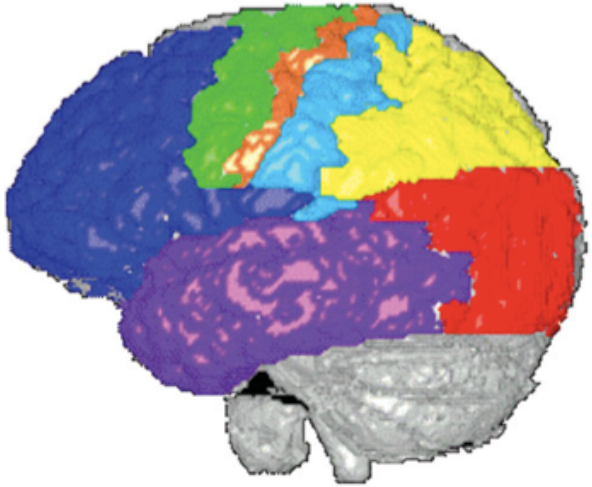


Behrens et al. Nat Neuro2003

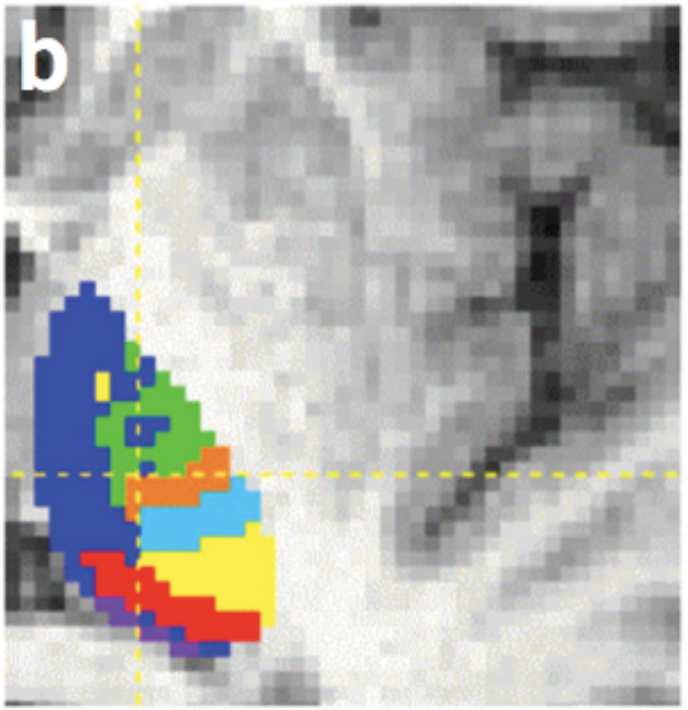
Johansen-Berg et al. Cereb Ctx 2005

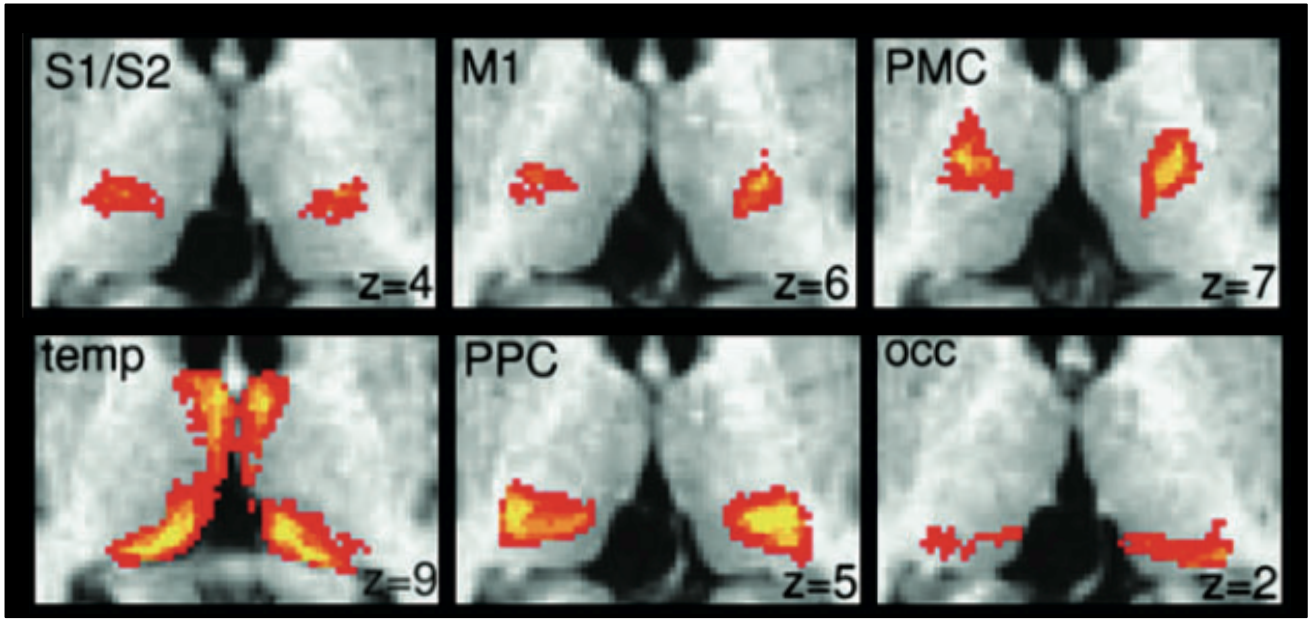
Segmenting the thalamus

Prior cortical parcelaltion



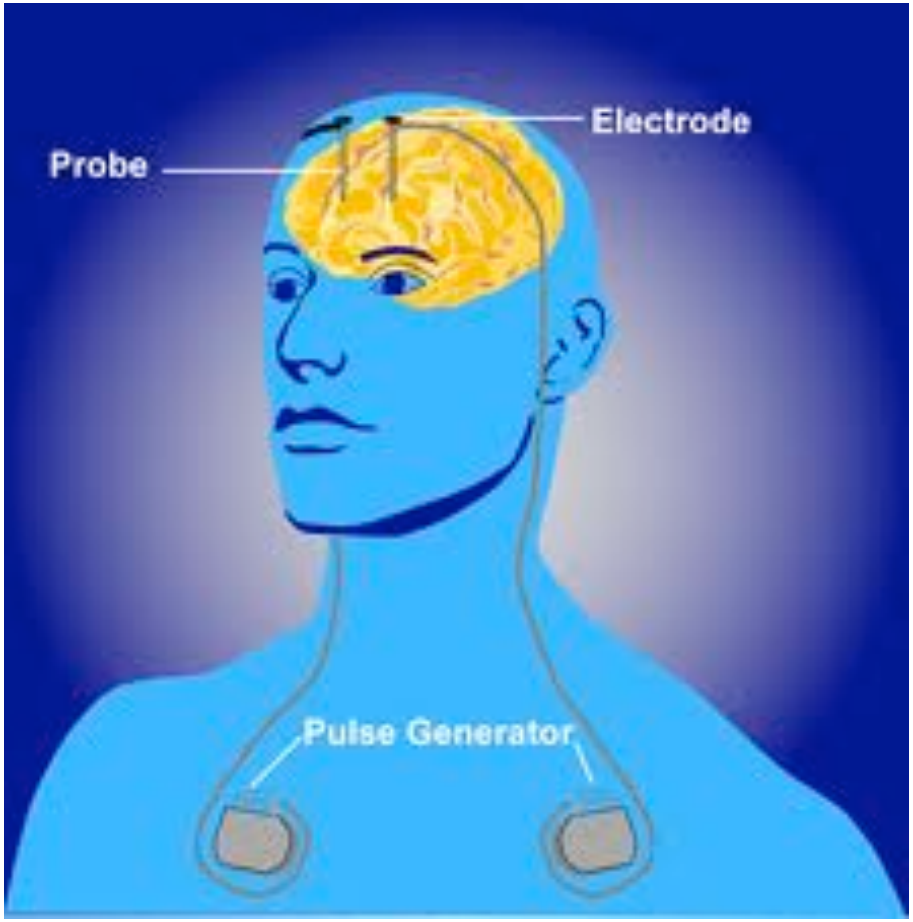
Hard thalamic parcellation

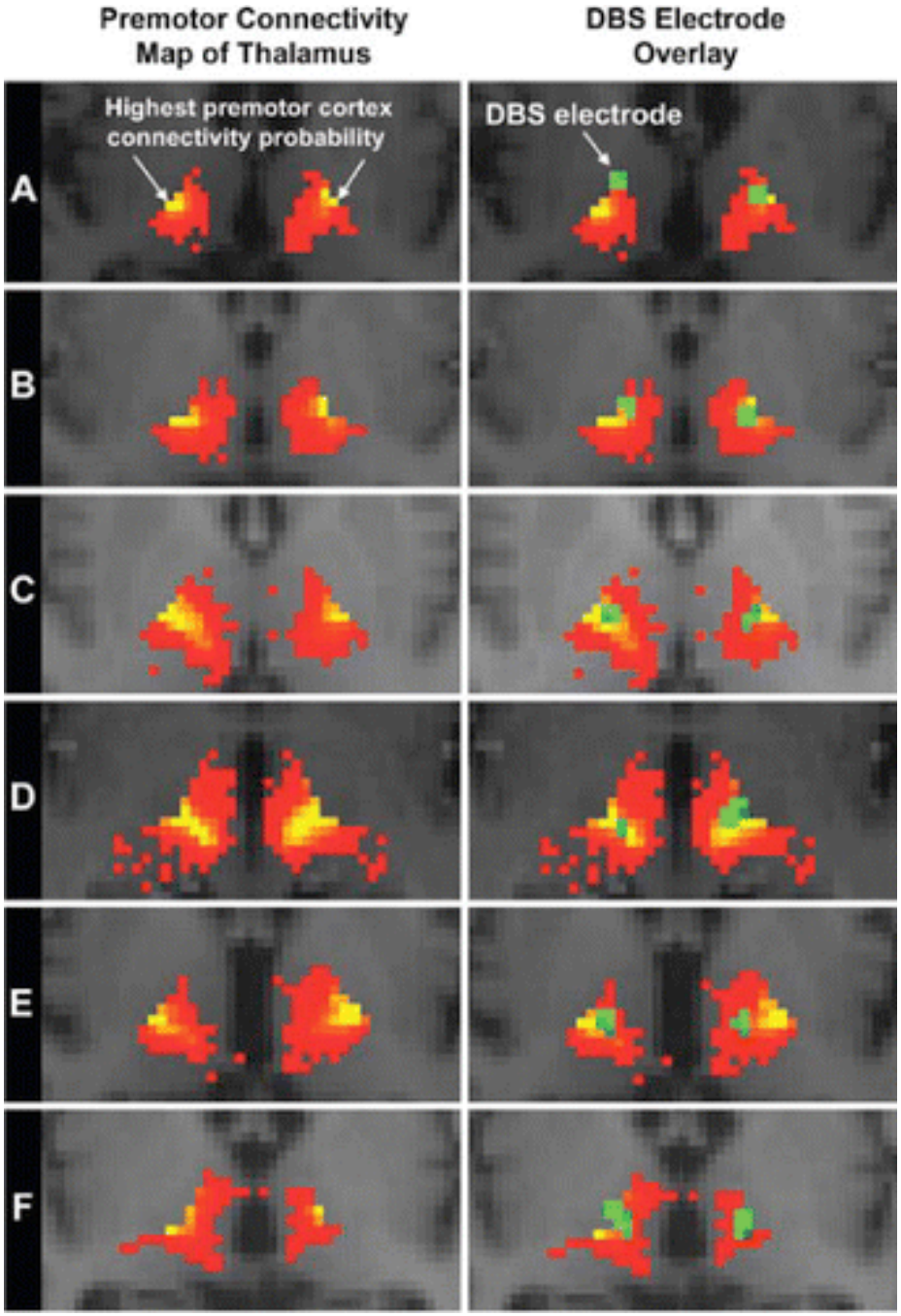




Behrens et al. Nat Neuro2003
Johansen-Berg et al. Cereb Ctx 2005

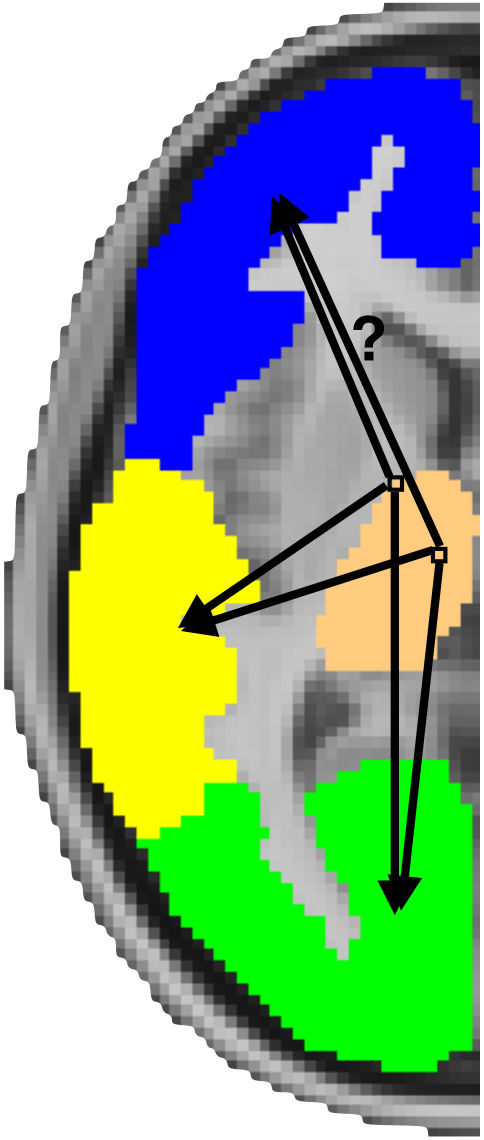
DBS for treatment of tremor in Parkinsons



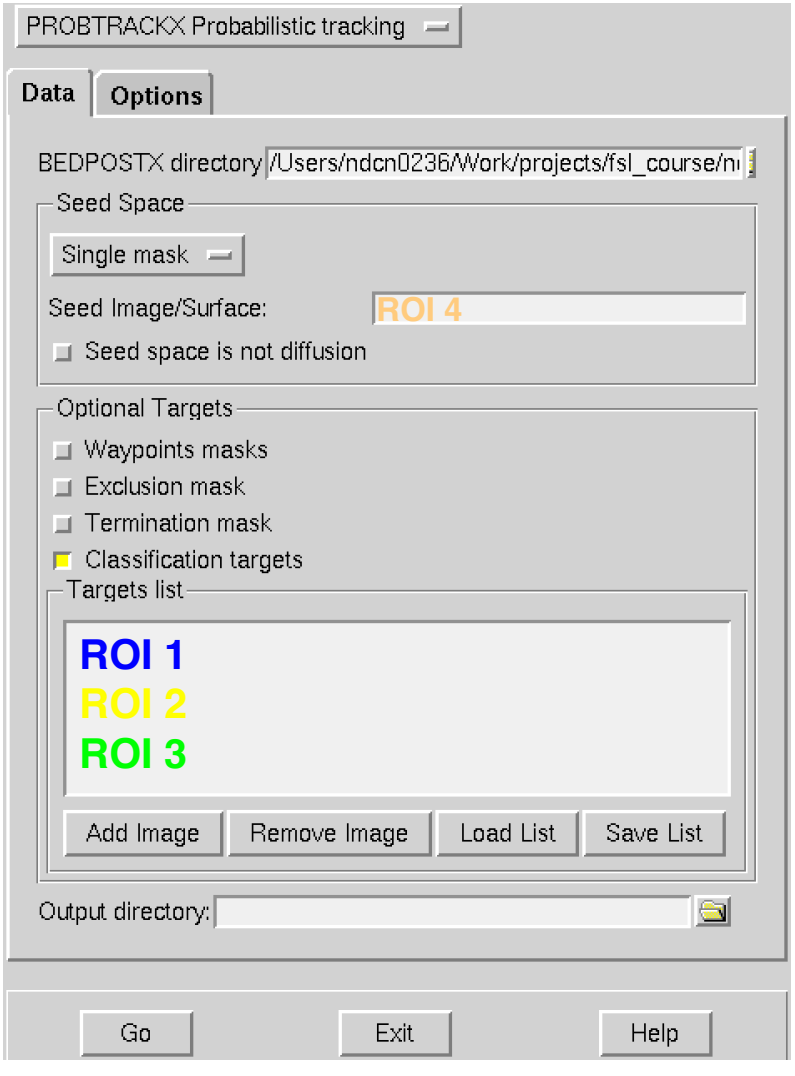


Pouratian et al. JNS 2011

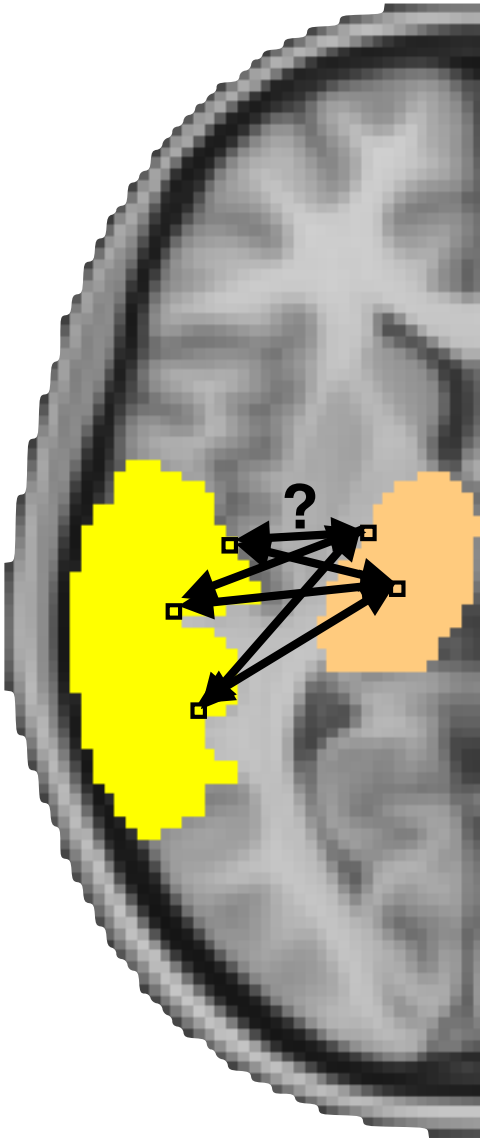
Connectivity between voxels and ROIs



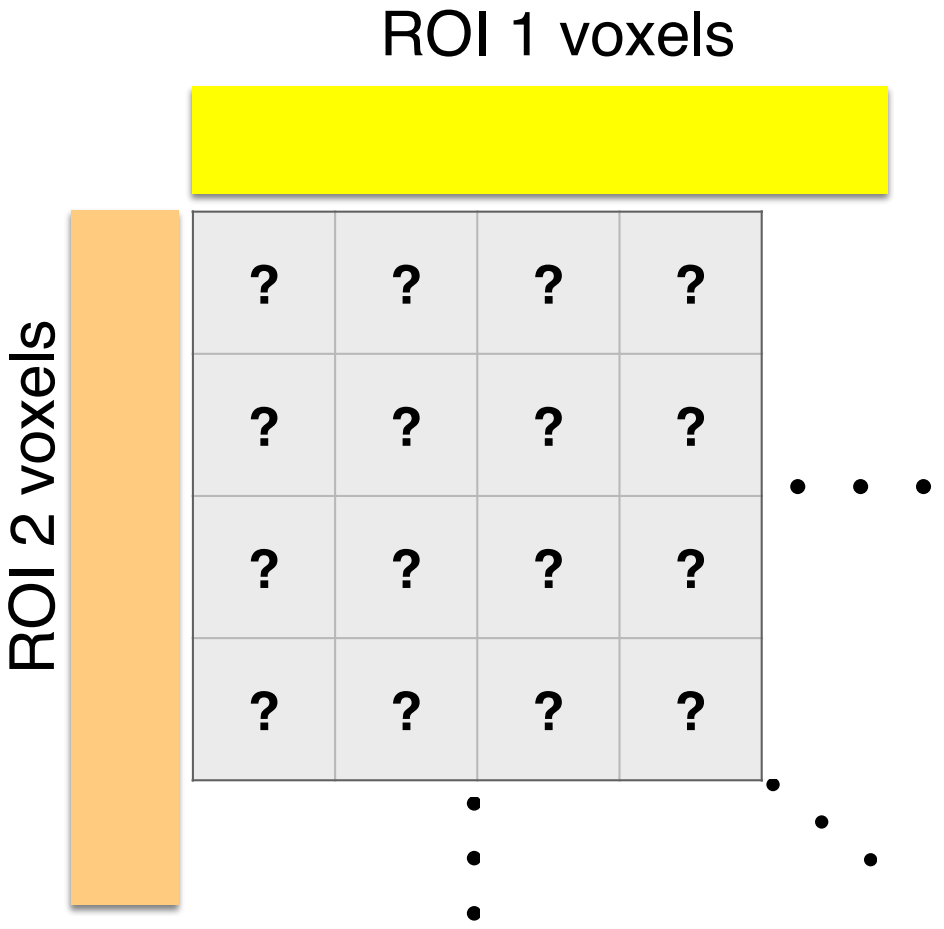
Fdt GUI:



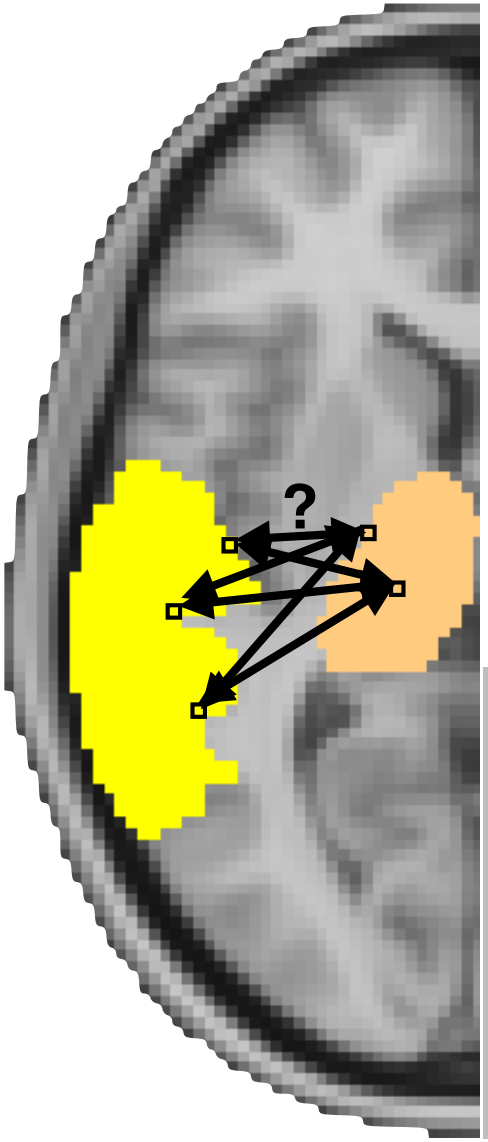
Connectivity between voxels



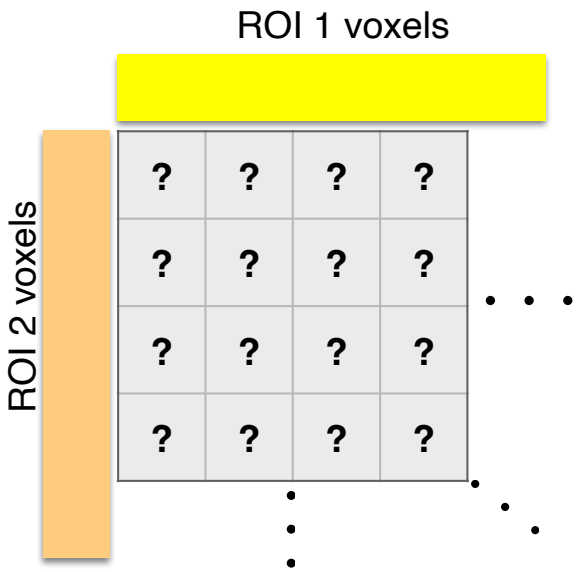
Resulting matrix:

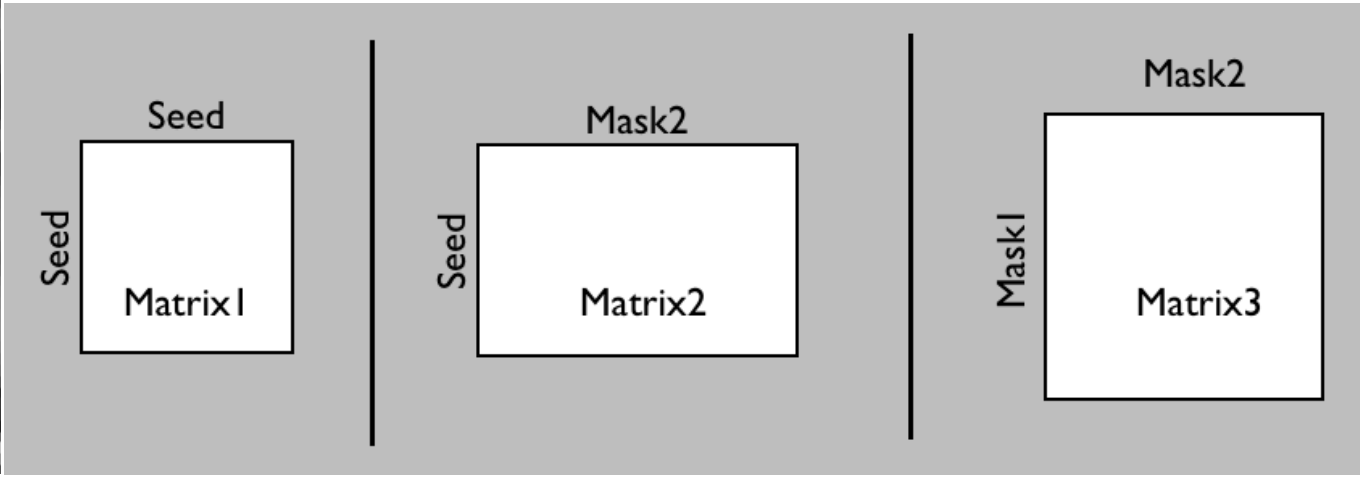


Connectivity between voxels

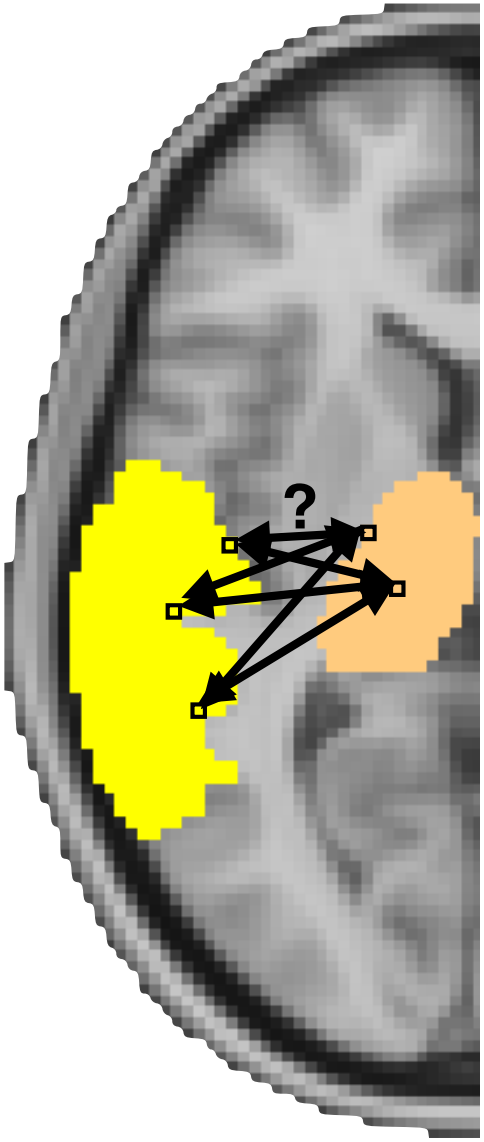


Resulting matrix:

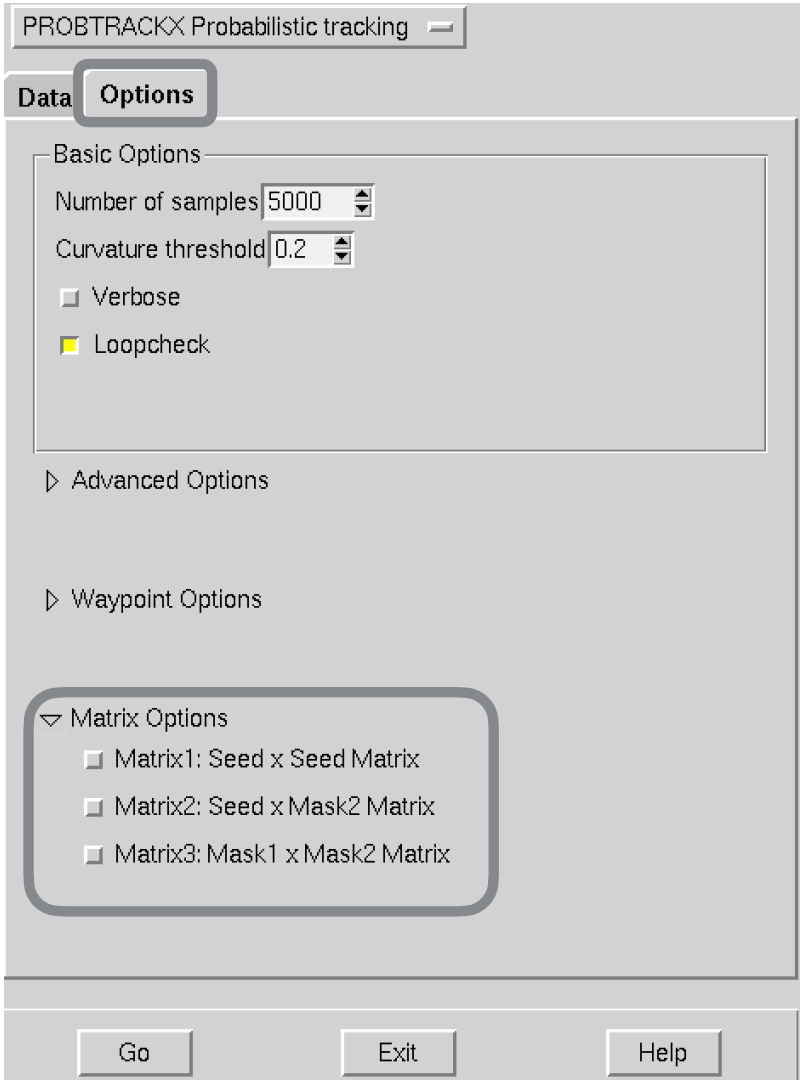




Connectivity between voxels

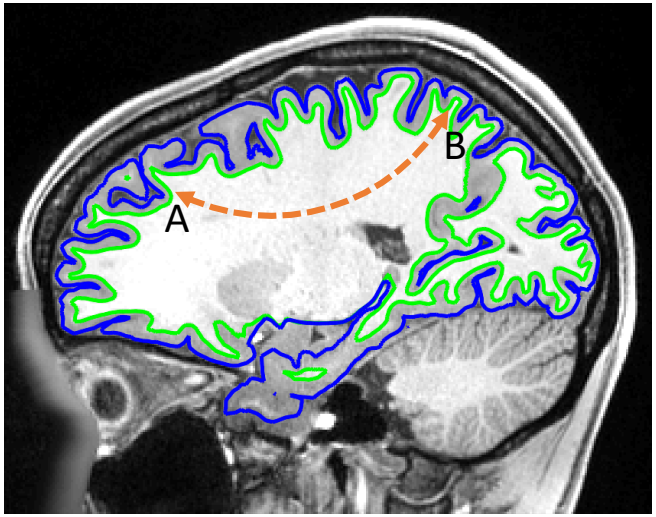


Fdt GUI:

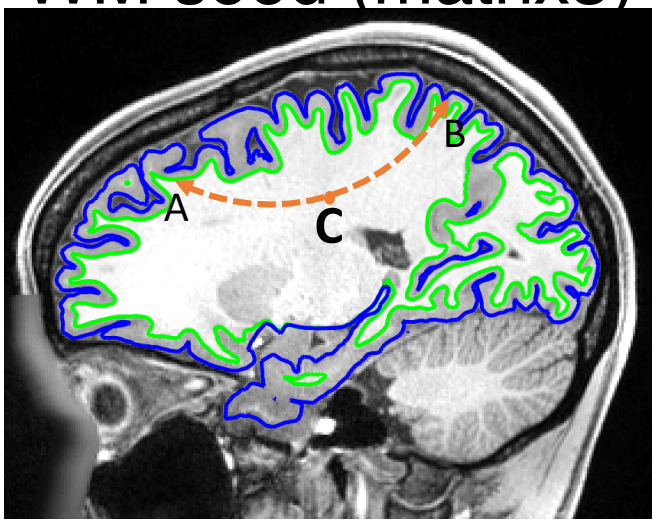


Dense connectome

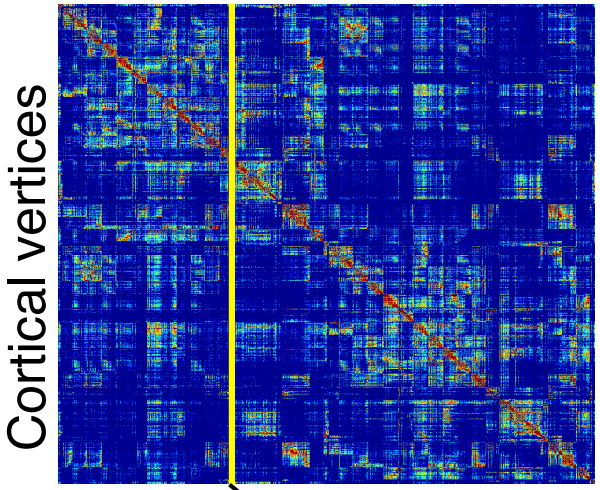
Cortical seed (matrix1)

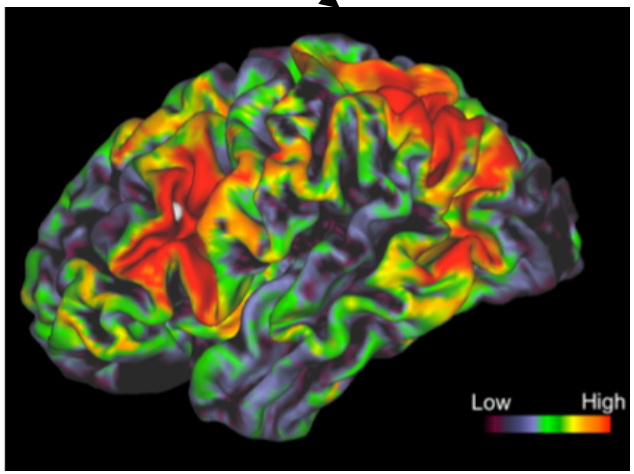


WM seed (matrix3)

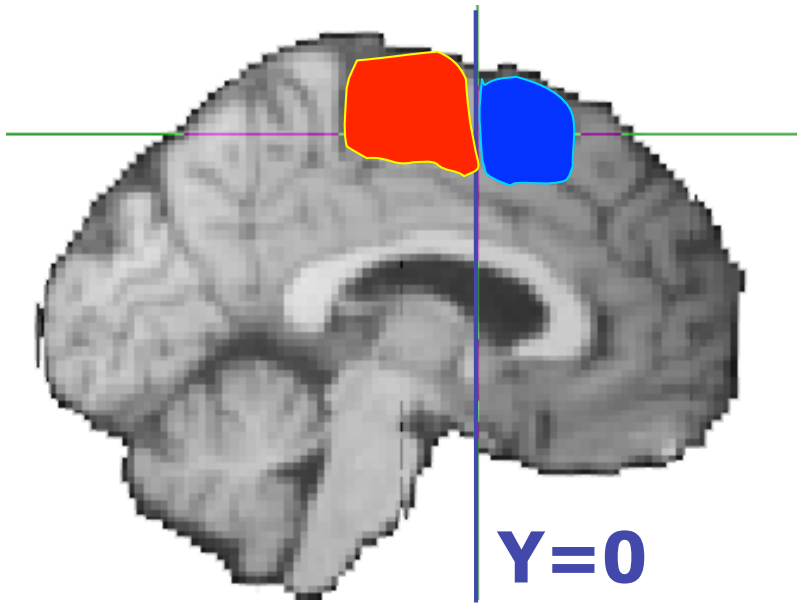


Cortical vertices





Changes in connectivity profiles
Medial Frontal Cortex

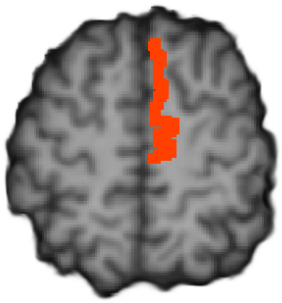


Medial area 6 contains two distinct regions with very different connectivity:

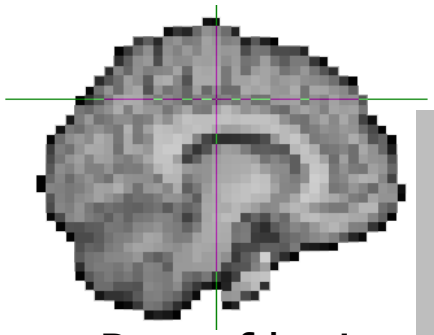
SMA and Pre-SMA

Can we define a border based on a change in connectivity profile?

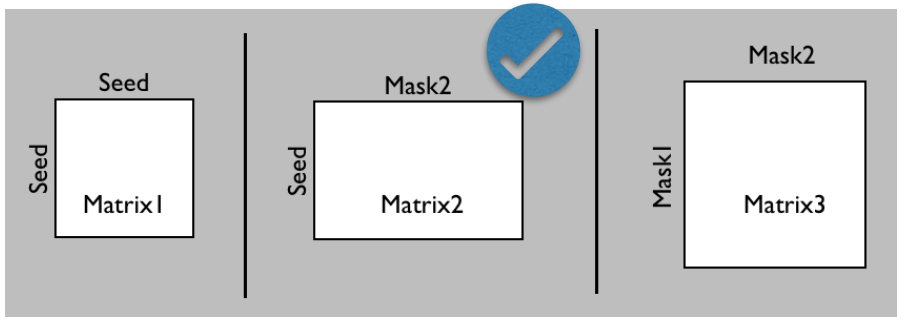
Changes in connectivity profiles
Medial Frontal Cortex

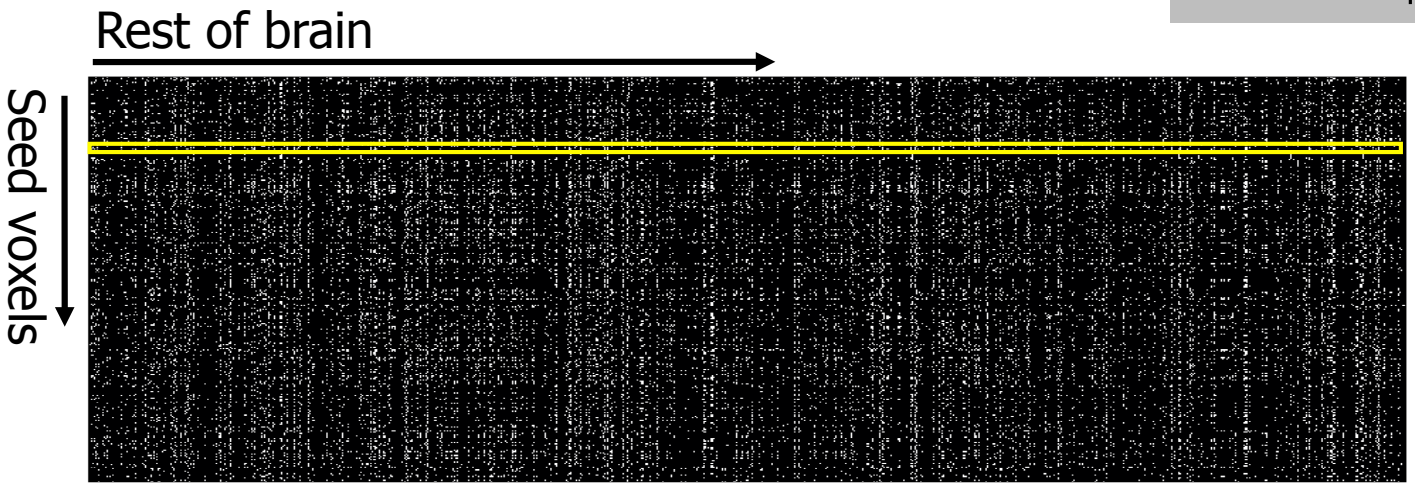


Seed voxels

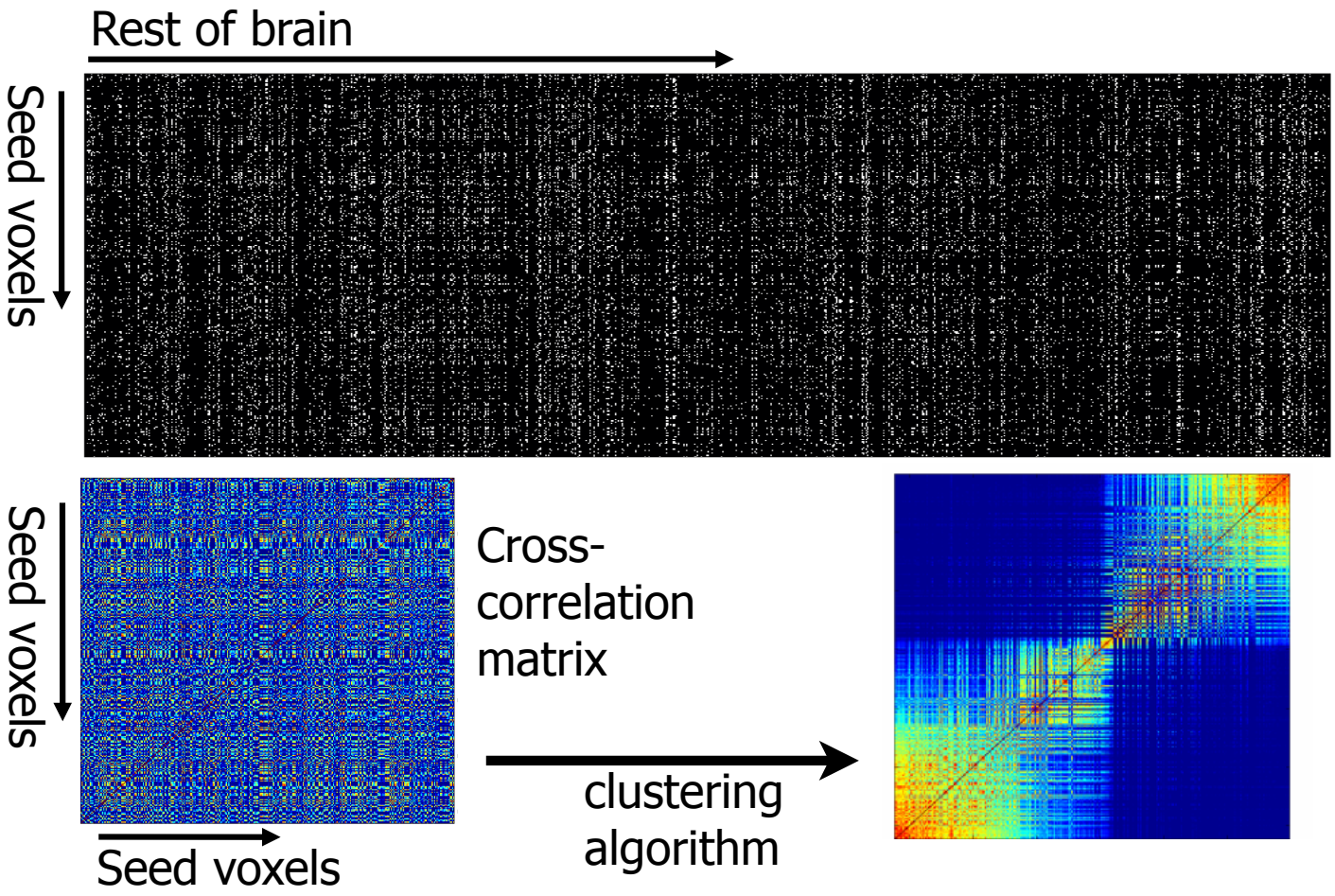


Rest of brain

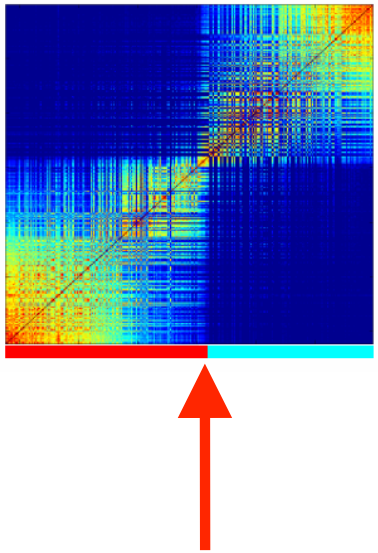




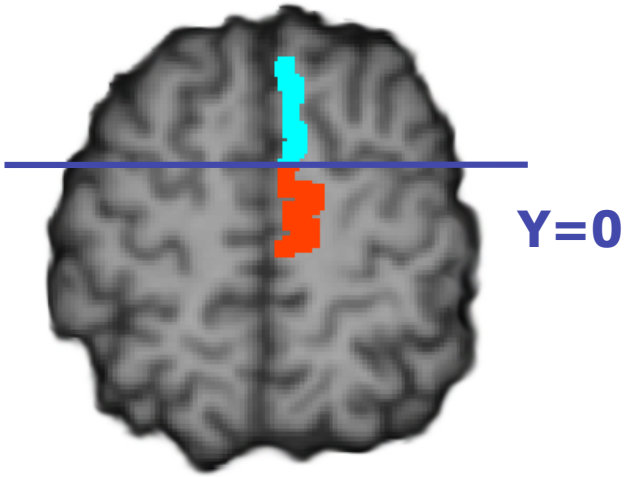
Changes in connectivity profiles
Medial Frontal Cortex



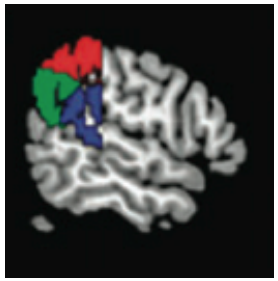
Changes in connectivity profiles Medial Frontal Cortex



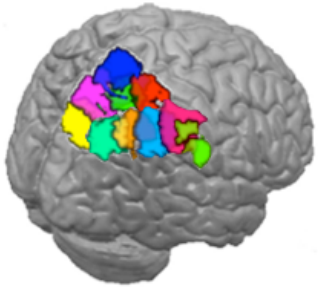
- Clusters in the re-ordered matrix represent seed voxels with similar connectivity
- Breaks between clusters represent where connectivity patterns change



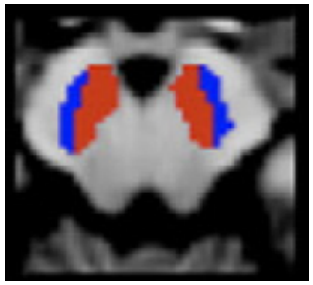
Johansen-Berg et al. 2004



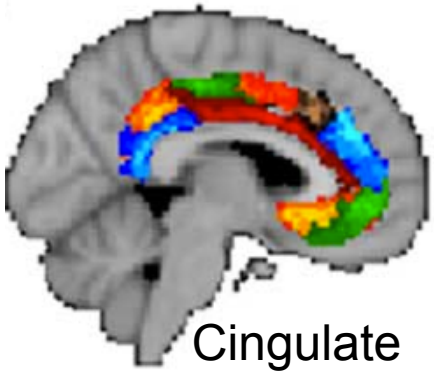
Temporo-parietal junction
Mars 2012



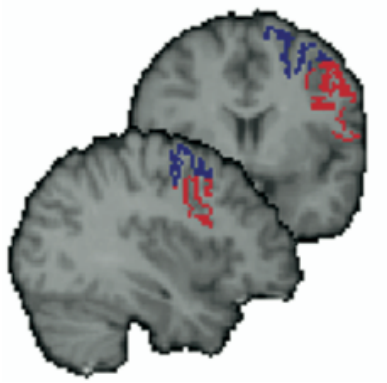
Lateral Parietal
Mars 2011



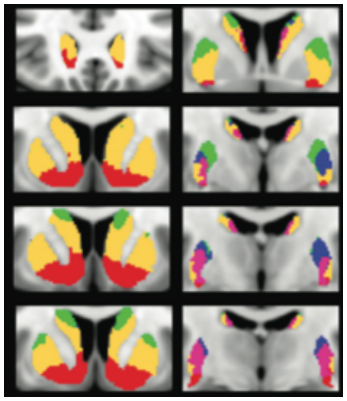
Substantia Nigra
Menke 2010



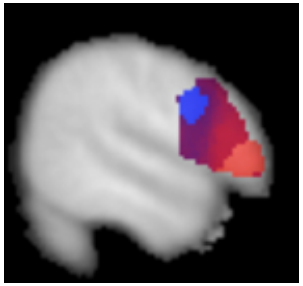
Cingulate
Beckmann 2009



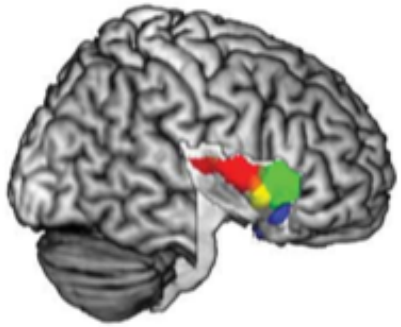
Lateral pre-motor
Tomassini 2007



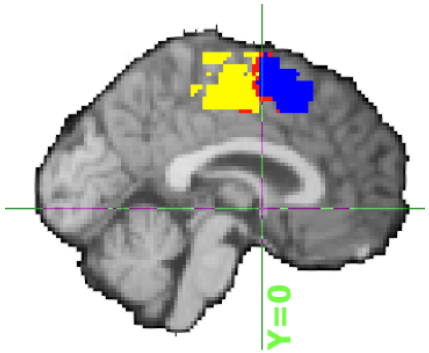
Striatum
Tziortzi 2013



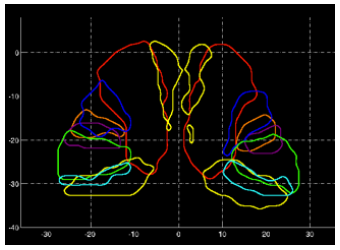
Broca's area
Klein 2007



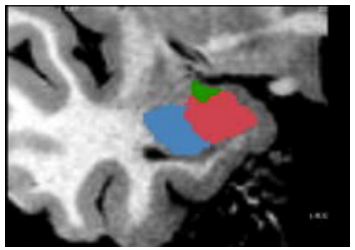
Insular cortex
Cerliani 2012



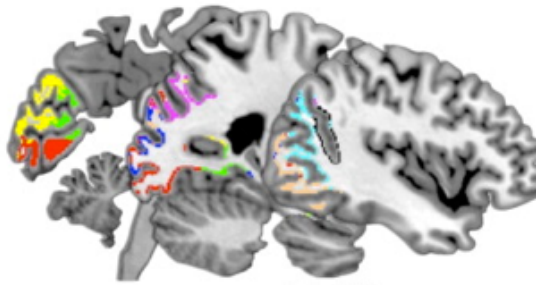
Medial prefrontal
Johansen-Berg 2004



Thalamus
Behrens 2003



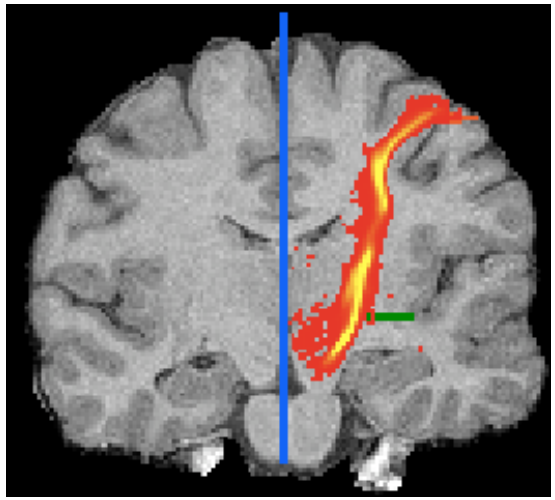
Amygdala
Saygin 2011

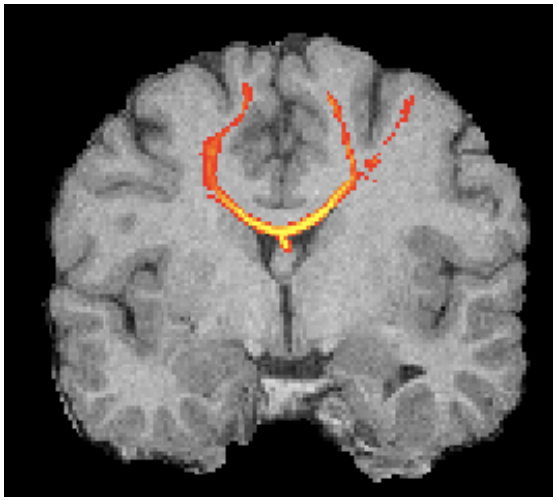


Occipital cortex
Thiebaut de Schotten 2013

ProbtrackX outputs

Known white matter tracts



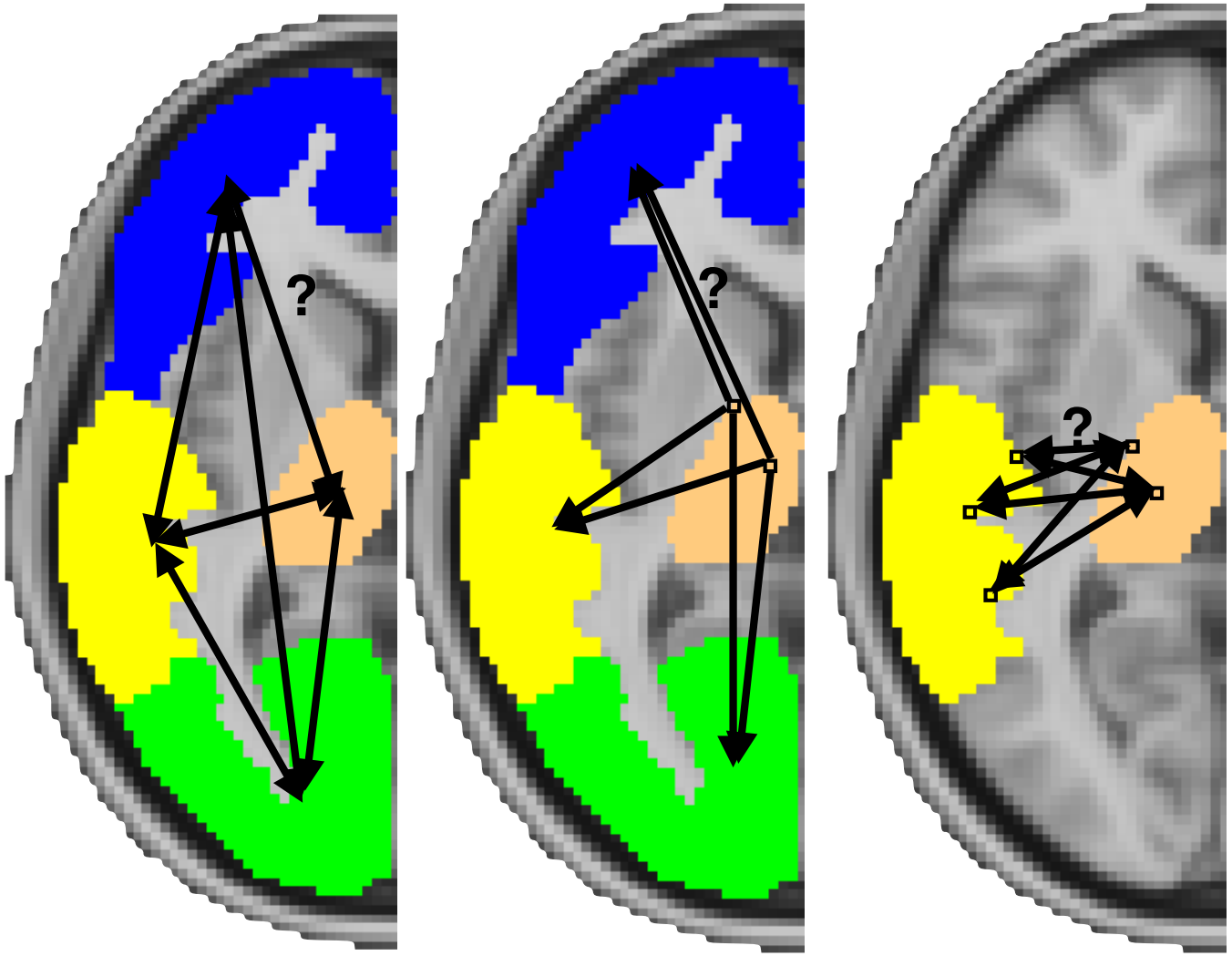


Connectivity matrices

ROI by ROI

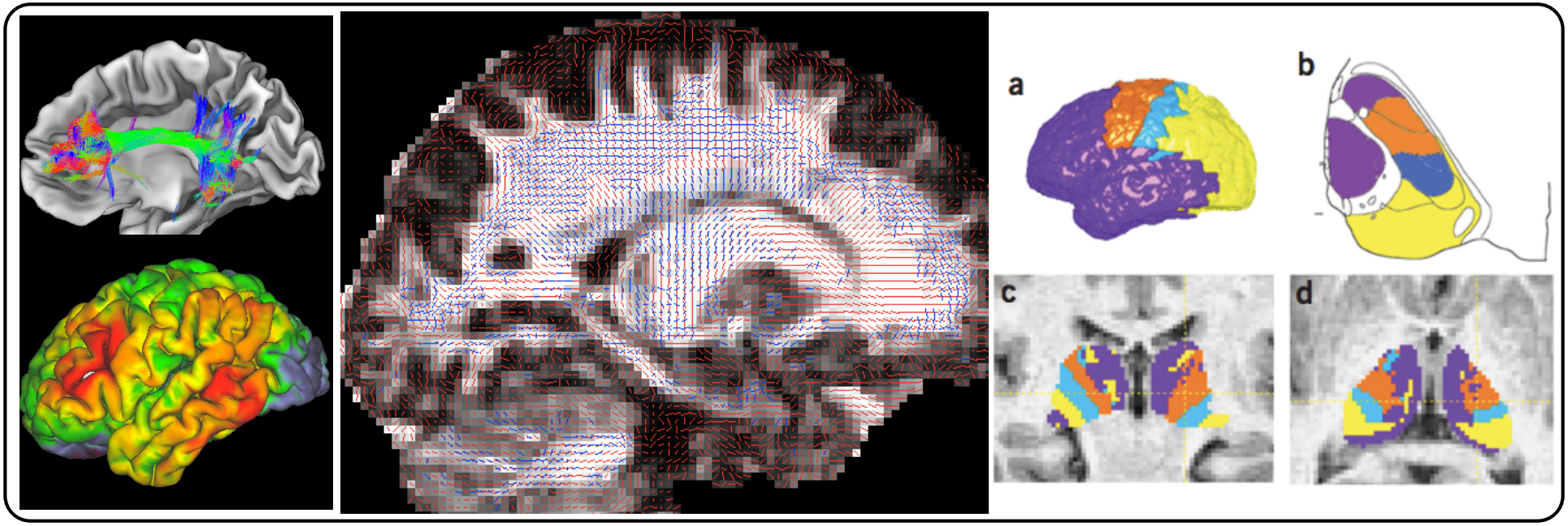
voxel by ROI

voxel by voxel



Overview

- Goal of tractography
- Estimating Fibre Orientations - BEDPOSTX
- Probabilistic Tractography - PROBTRACKX
- ProbtrackX outputs
- Tractography limitations



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:

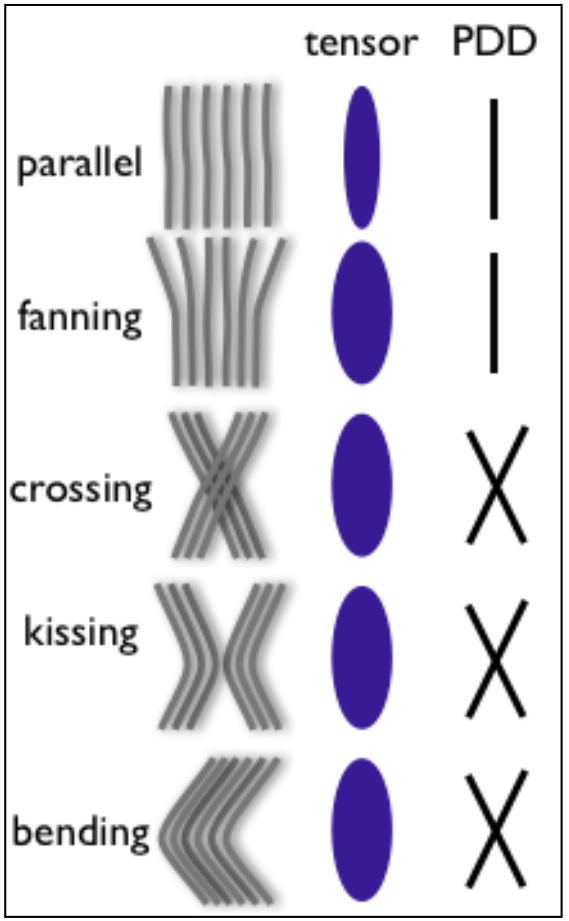
  Connection length: Longer connections have smaller probability than shorter ones

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

- Cross-subject comparison of the same tract is more meaningful than comparing different tracts

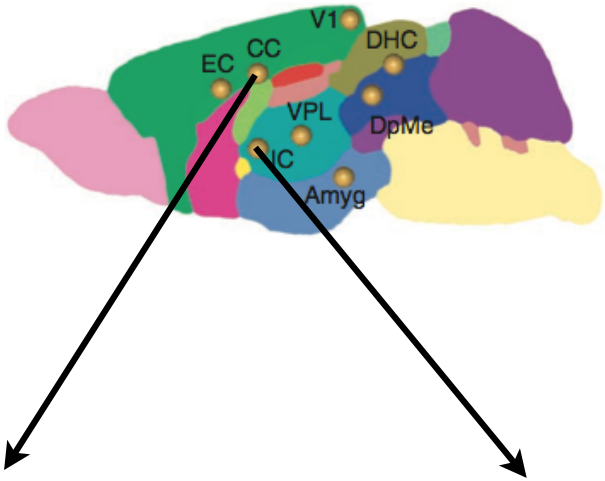
Can we trust tractography?

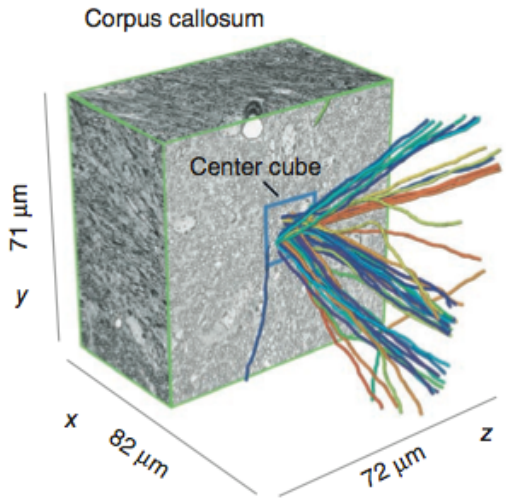
Is the direction of least hindrance to diffusion a good proxy for fibre orientation?

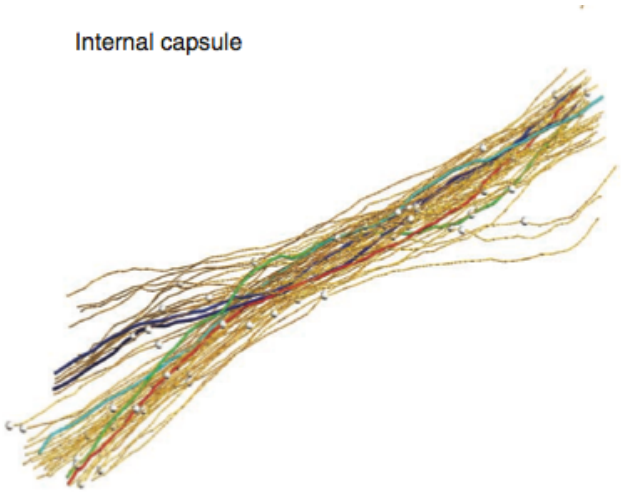


mapping between axon geometry and diffusion profile can be ambiguous

White matter organisation can be surprising

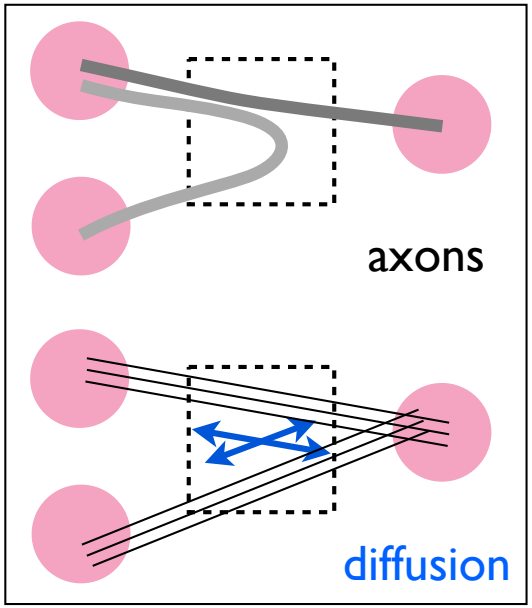




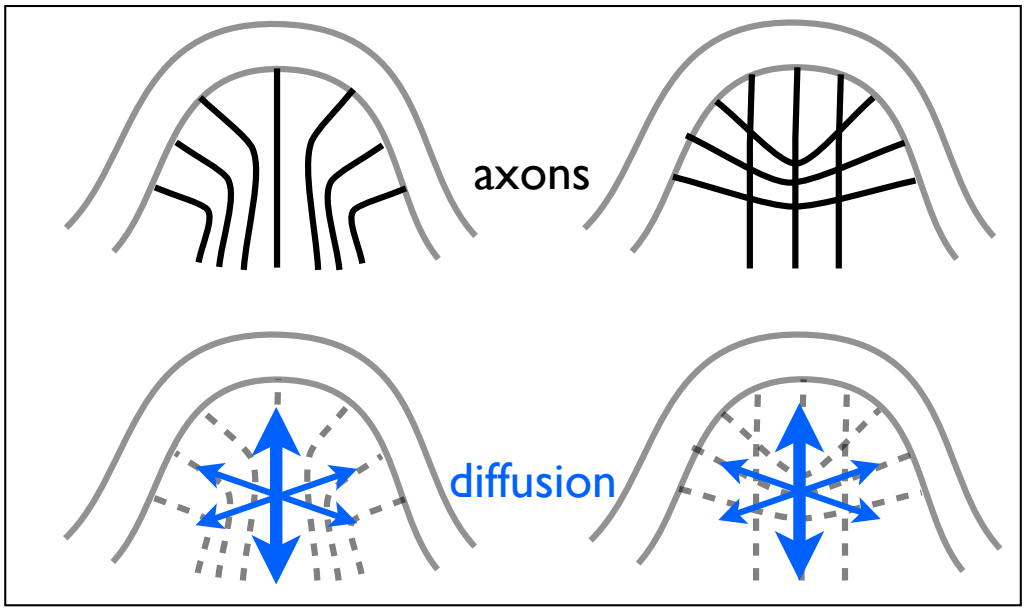


Whole mouse brain Electron Microscopy!
Mikula Binding Denk, Nature Methods 2012

Can we trust tractography?



In the white matter:
jumping between tracts



Near the cortex
ambiguities/biases

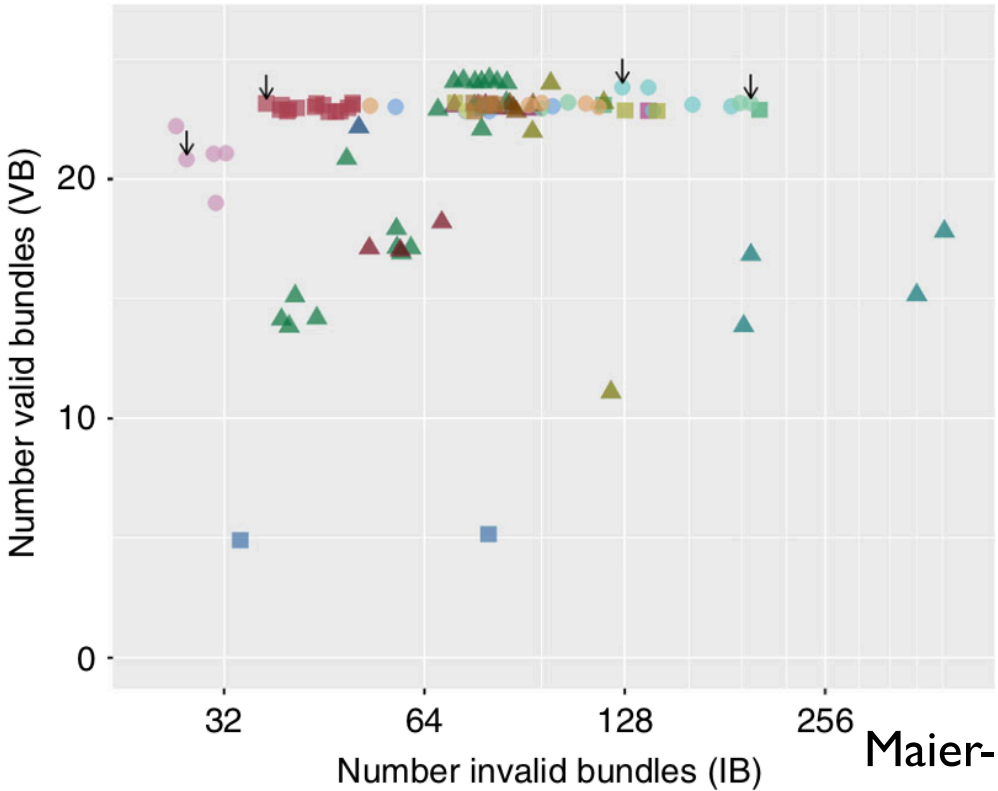
Jbabdi & Johansen-Berg (2011)

Many false positives in tractography

25 synthetic WM tracts (based on real data)

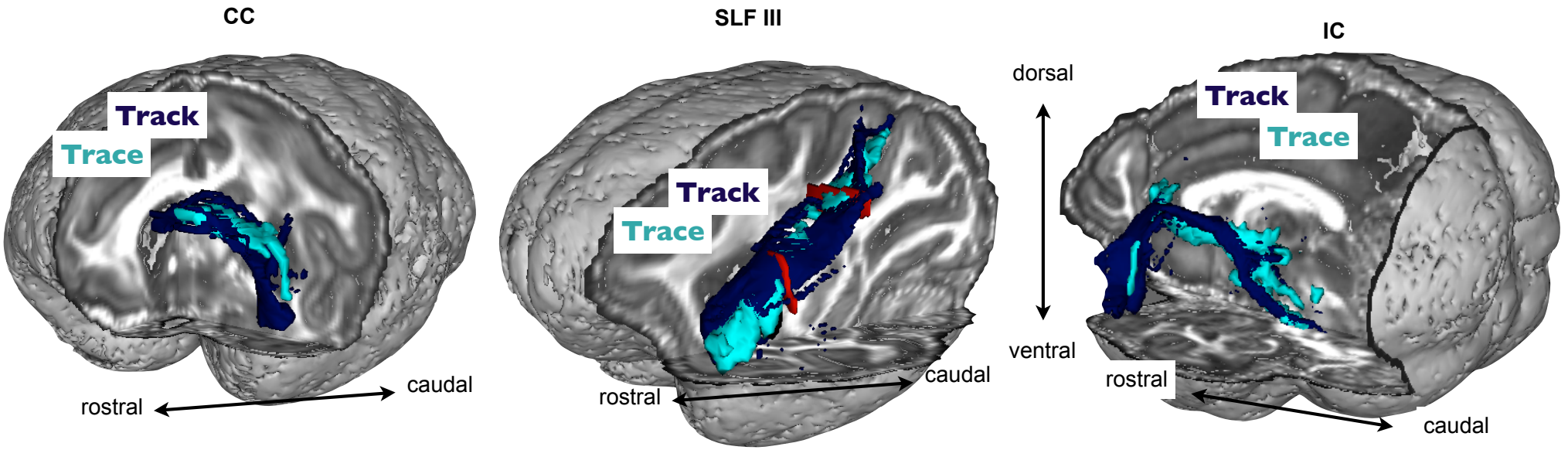
Simulated diffusion data

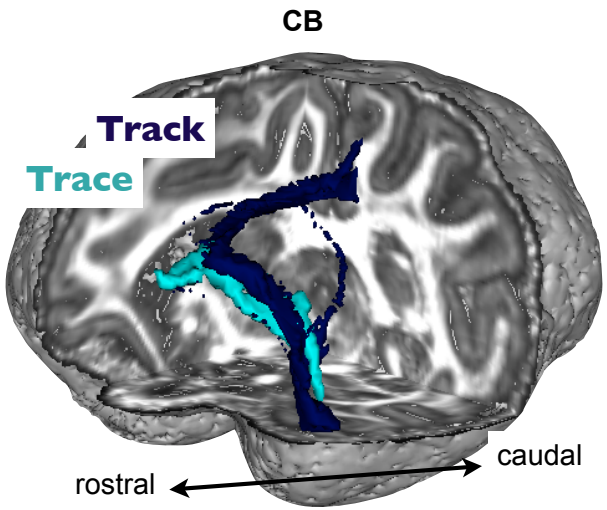
Bundle detection

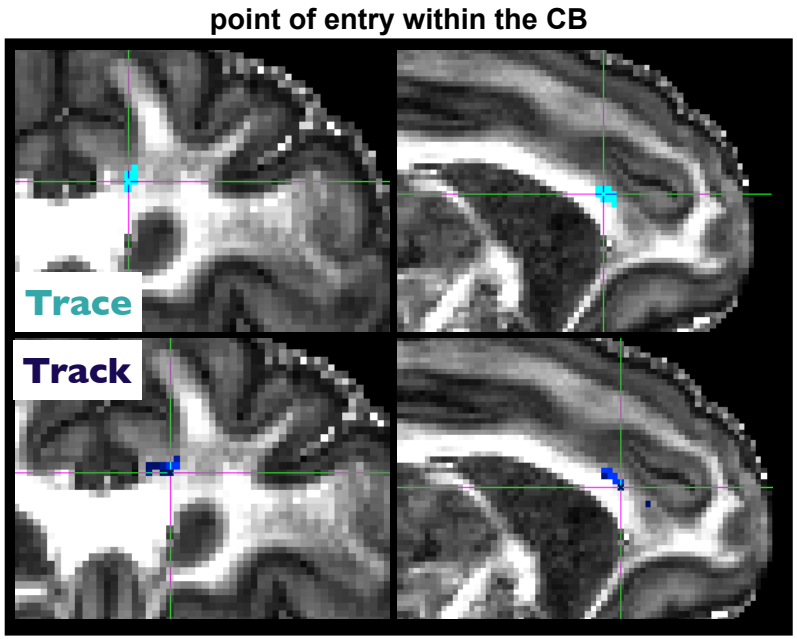


Maier-Hein et al. (Nat. Comm., 2017)

Validation: comparison with classical chemical tracing

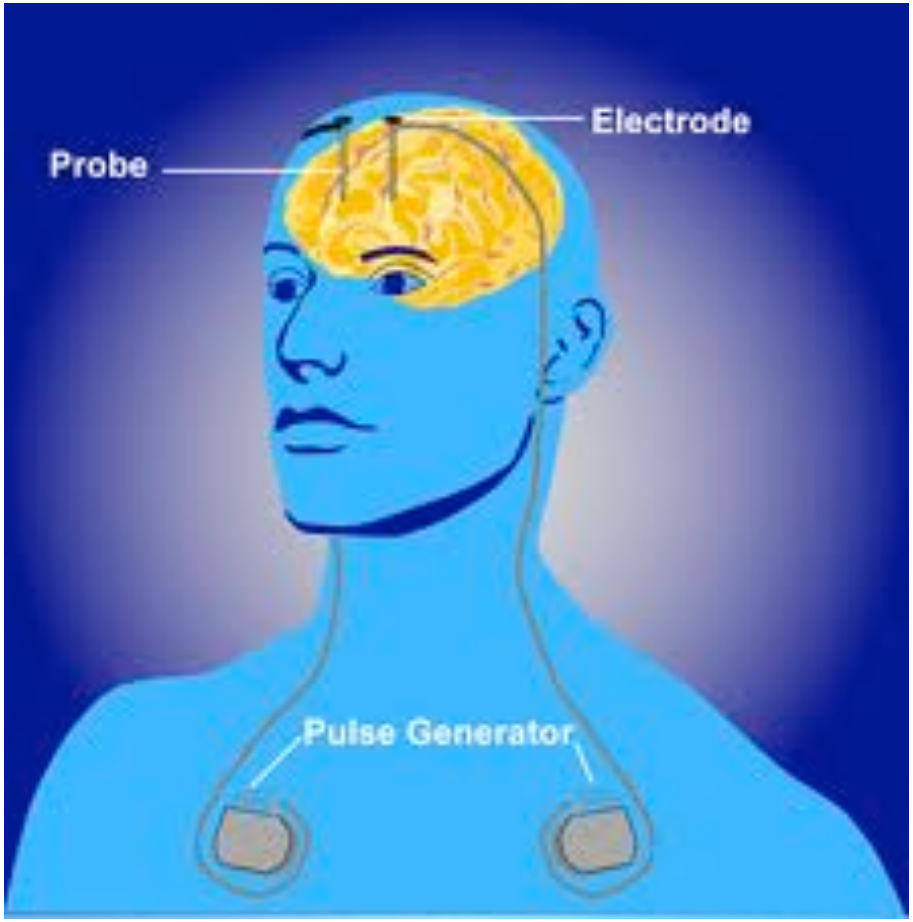


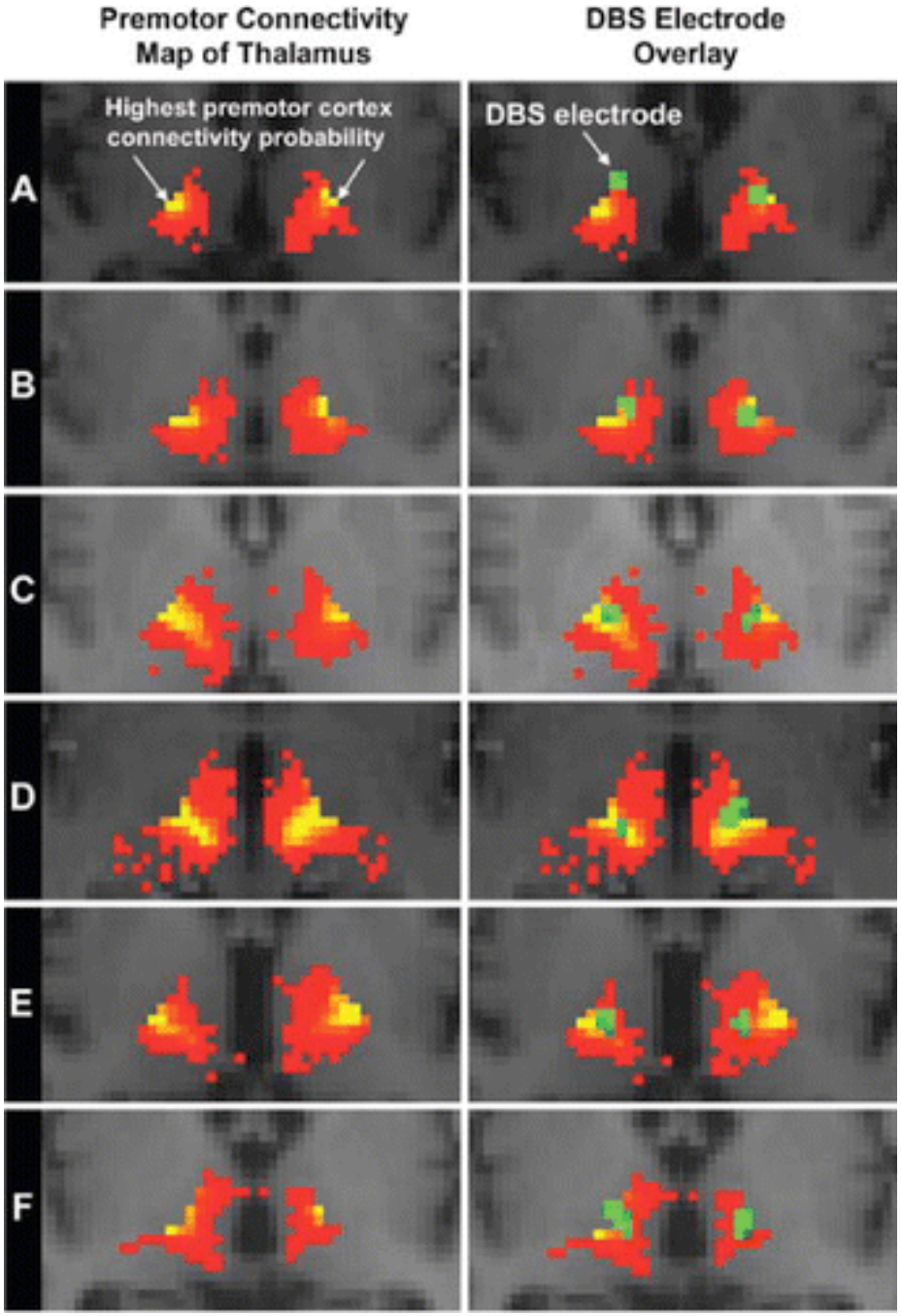




Jbabdi et al, Journal of Neuroscience, 2013

DBS for treatment of tremor in Parkinsons

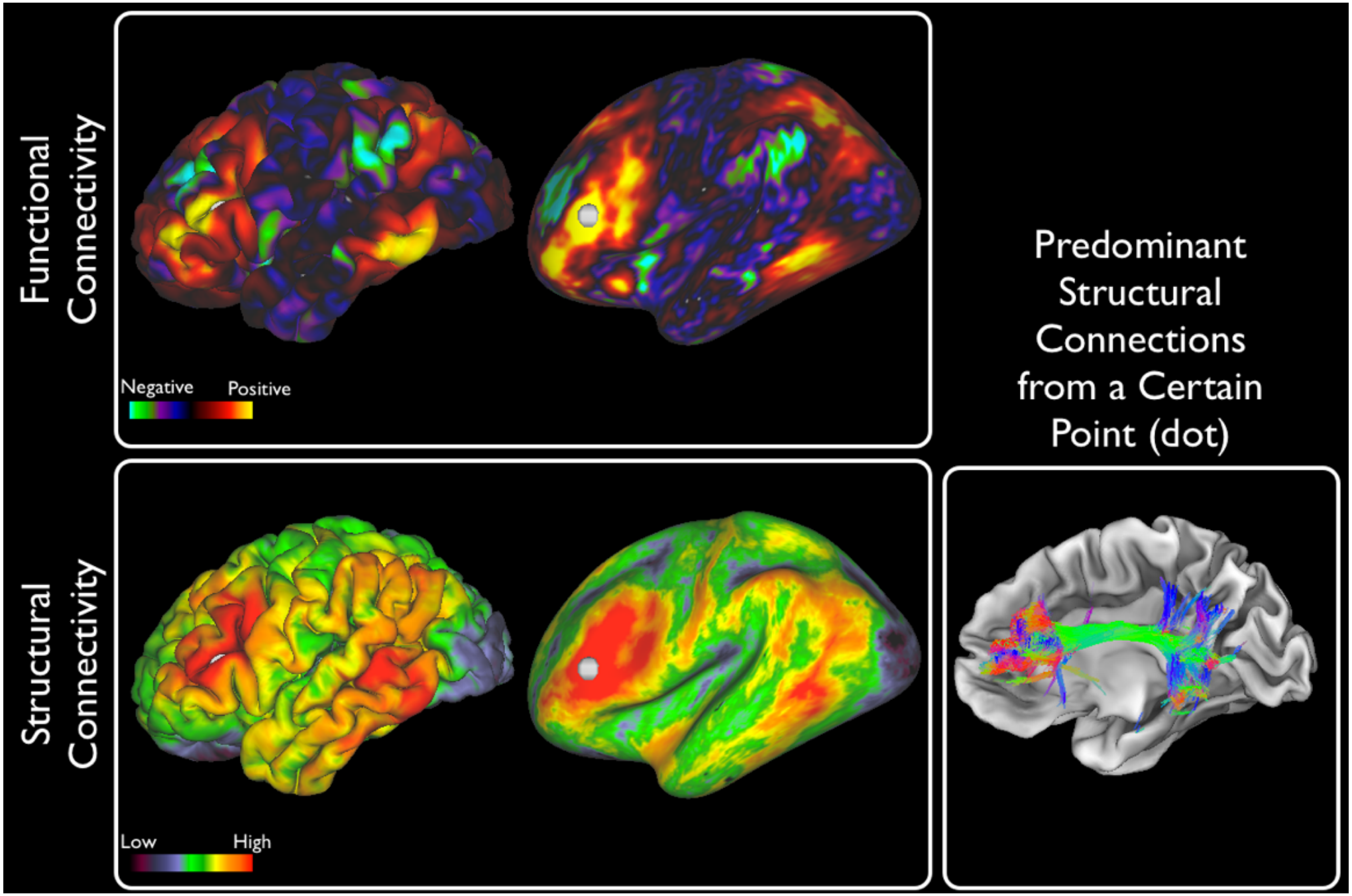




Pouratian et al. JNS 2011

The Human Connectome Project

www.humanconnectome.org



That's all folks