FROM IMAGE RECONSTRUCTION TO CONNECTIVITY ANALYSIS: A JOURNEY THROUGH THE BRAIN'S WIRING

Francesca Pizzorni Ferrarese

Pipeline overview

WM and GM Segmentation

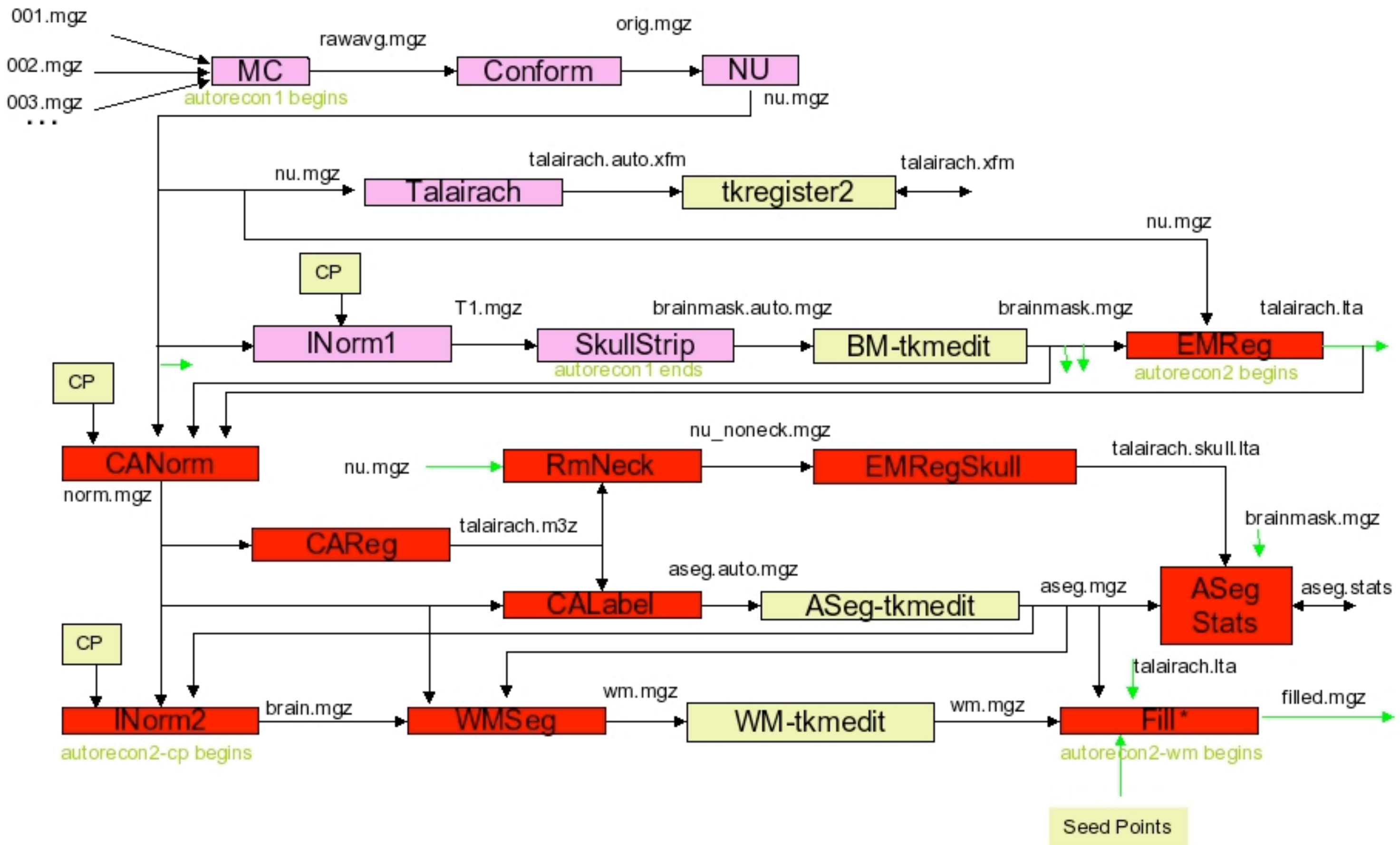
Registration

Data reconstruction
Tractography

Network construction

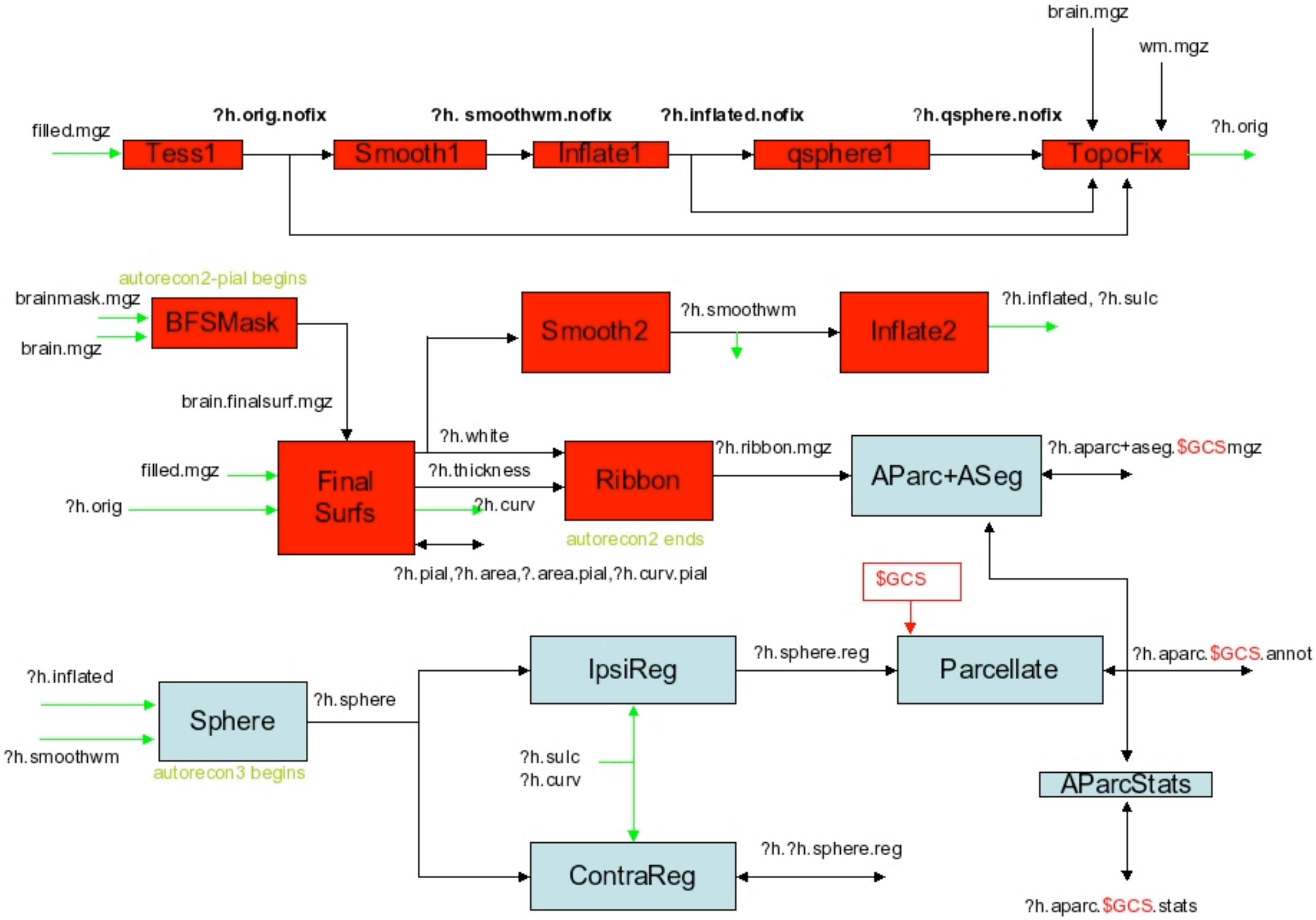
Morphological data - T1

Freesurfer overview



WMSeg includes mri_segment, edit_wm_with_aseg, and mri_pretess
CP = Control Points
Fill can have (aseg.mgz&tal.lta) or (tal.xfm,cutting planes) as input, but not both

Freesurfer overview



Freesurfer - MGZ File Format

- mgz = compressed MGH file
- Can store 4D (like NIFTI)
- cols, rows, slices, frames
- Generic: volumes and Surfaces

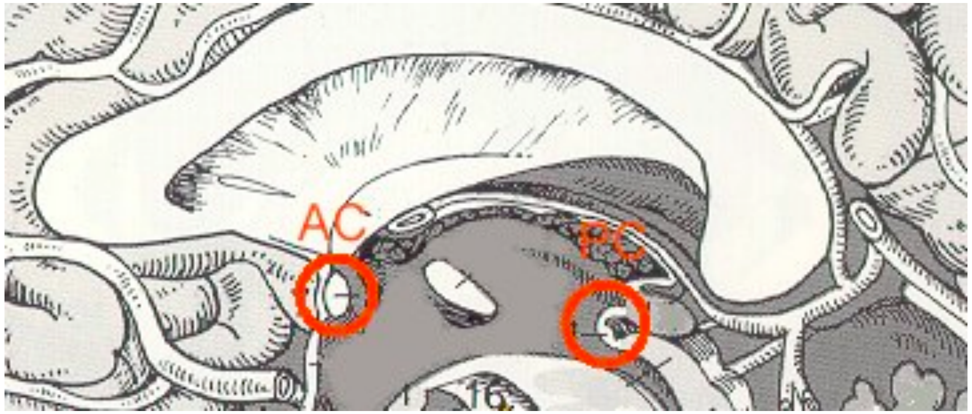
- Eg, Typical Anatomical volume: 256 x 256 x 128 x 1

"Volume-encoded" Surface Files

- nvertices, 1, 1, frames (eg, 163214 x 1 x 1 x 40)
- No geometry information

Freesurfer – Talairach coordinate system

- The Talairach coordinate system is defined by making two points, the anterior commissure and posterior commissure, lie on a straight horizontal line.
- Since these two points lie on the midsagittal plane, the coordinate system is completely defined by requiring this plane to be vertical.
- Distances in Talairach coordinates are measured from the anterior commissure as origin.
- Talairach atlas is based upon postmortem sections of a 60-year-old French female who had a smaller than average brain size.
  - This means that most individual brains must be considerably warped to fit the small size of the atlas, inducing some error.
  - Another disadvantage is the approximate method of labeling a tissue-specific Brodmann area based on gross visual inspection rather than histological examination.

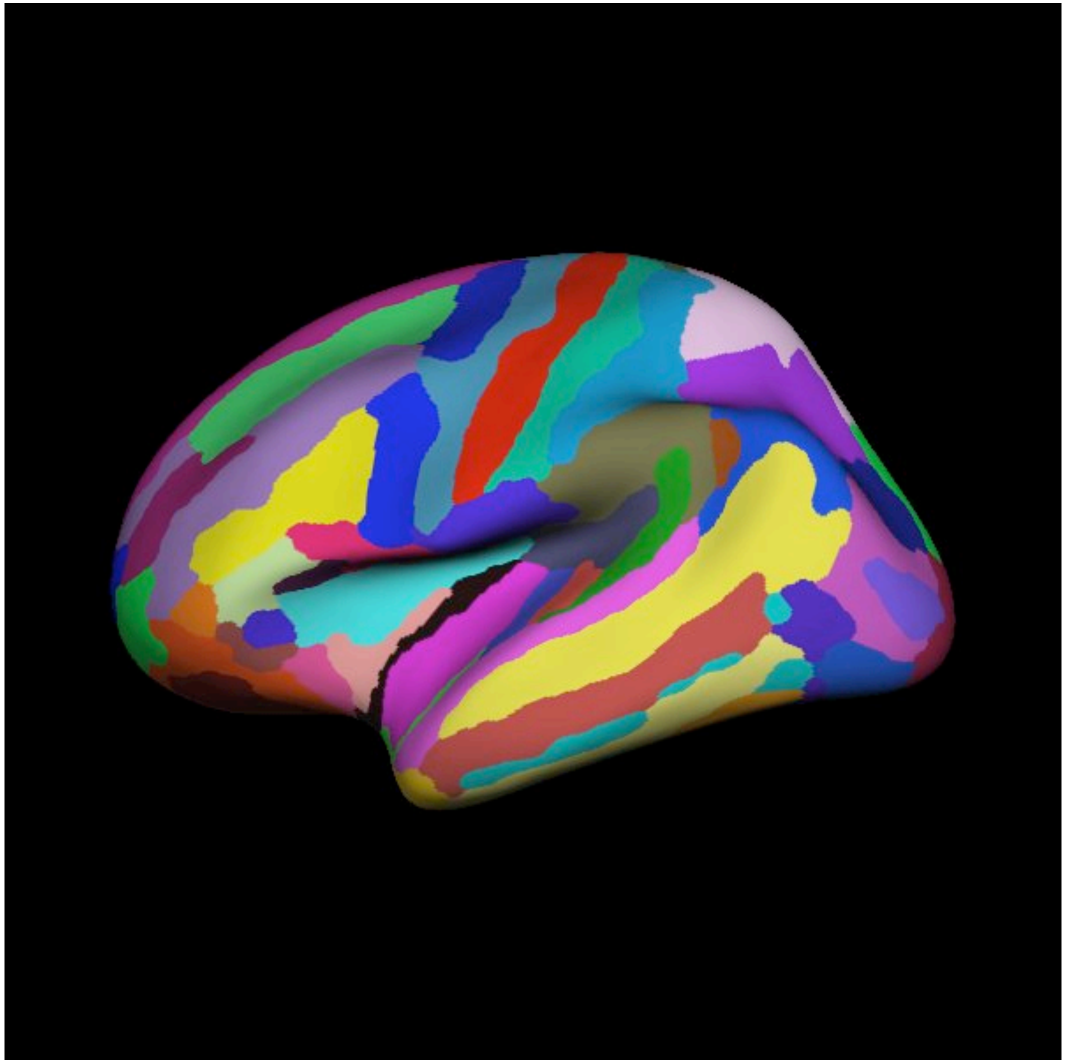


Freesurfer – MNI coordinate system

- The MNI defined a new standard brain by using a large series of MRI scans on normal controls.
- The MNI wanted to define a brain that is more representative of the population.
- They created a new template that was approximately matched to the Talairach brain in a two-stage procedure.
  - First, they took 250 normal MRI scans, and manually defined various landmarks, in order to identify a line very similar to the AC-PC line, and the edges of the brain. Each brain was scaled to match the landmarks to equivalent positions on the Talairach atlas. This resulted in the 250 atlas brain that is very rarely used.
  - They then took an extra 55 images, and registered them to the 250 atlas using an automatic linear registration method. They averaged the registered 55 brains with the 250 manually registered brains to create the MNI 305 atlas.
- The MNI 305 brain is made up of all right handed subjects, 239 M, 66 F, age 23.4 +/- 4.1.

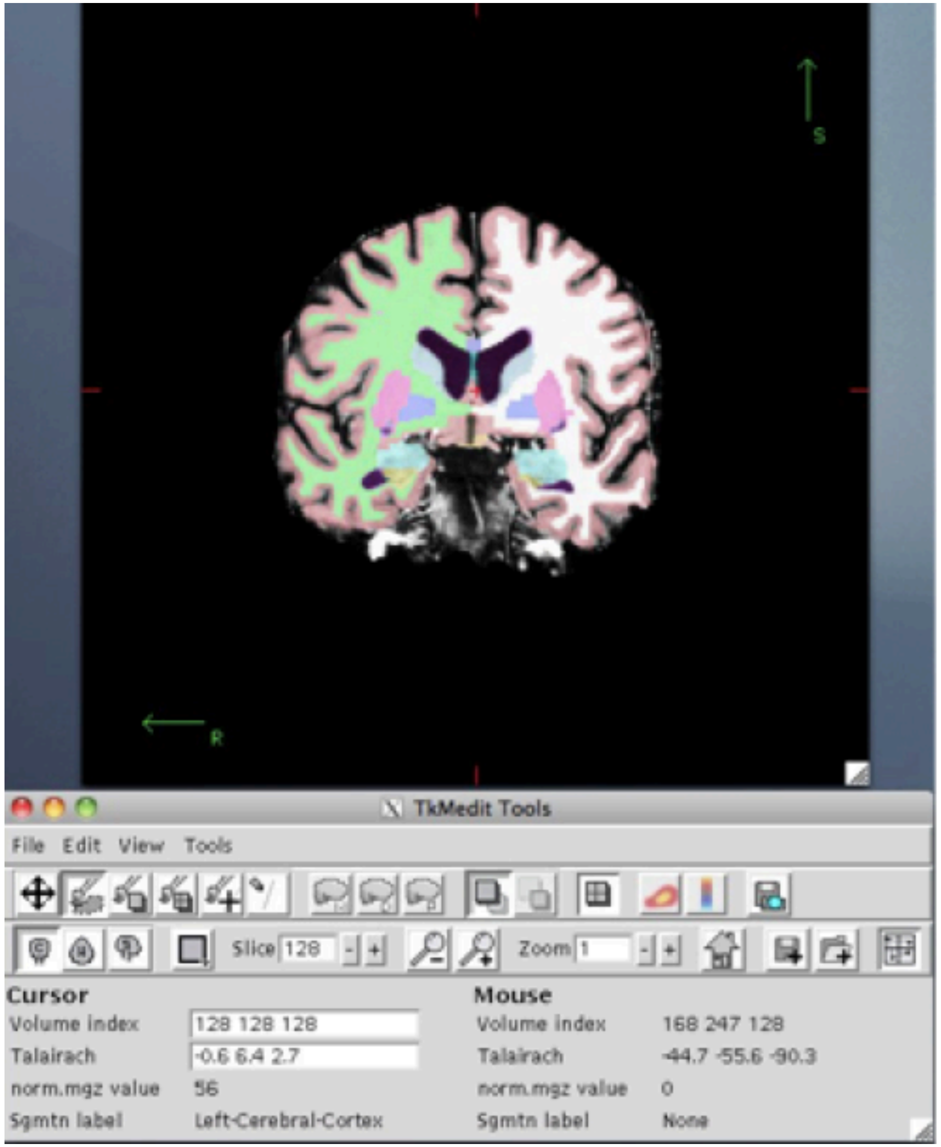
Freesurfer - GUI

- Tksurfer



Freesurfer - GUI

- Tkmedit

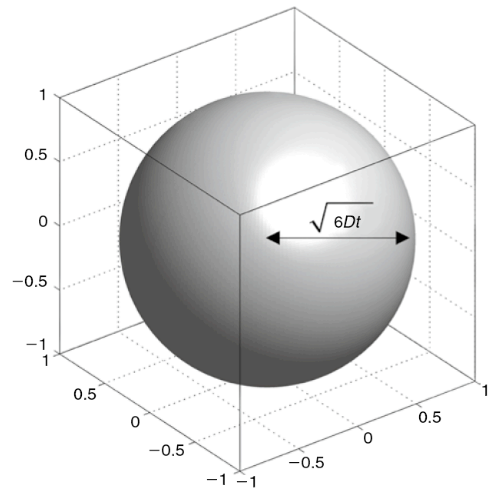


Diffusion Weighted MRI (DWI)

Diffusion MRI

- Molecular diffusion, or brownian motion, was first formally described by Einstein in 1905.
- The term *molecular diffusion* refers to the notion that any type of molecule in a fluid (eg. water) is randomly displaced as the molecule is agitated by thermal energy

$$\langle r^2 \rangle = 6Dt$$



Diffusion Weighted Imaging

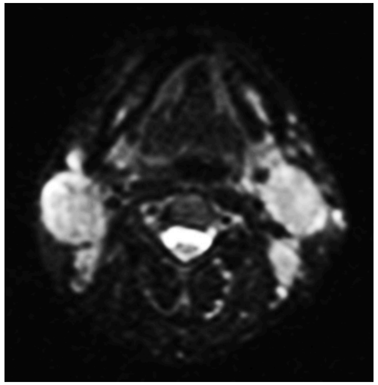
- When the PDF of the displacement of water molecules is Gaussian and behaves according to the Einstein equation, the attenuation of the MR signal due to diffusion is

$$\frac{I_2}{I_1} = \exp(-b \cdot ADC)$$

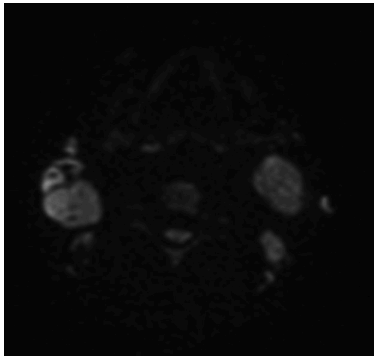
where

$$b = \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$$

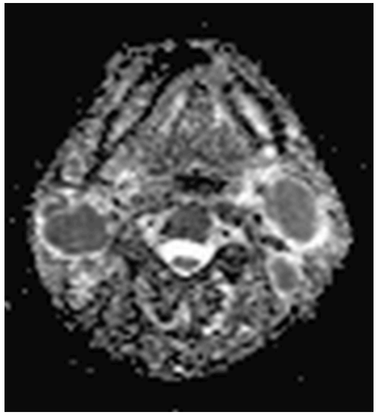
b=0



b=1000



ADC



Diffusion Tensor MRI (DTI)

DTI

- Assumption: the diffusion pdf is an anisotropic Gaussian (influenced by the tissue architecture).
- It is fully characterized by its covariance matrix, a 3x3 symmetric matrix called the Diffusion Tensor (6 degrees of freedom)

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

- The diffusion tensor can be estimated by the acquisition of diffusion images in 6 different directions of the diffusion gradient

DTI segmentation

- The necessity of developing new methods for the segmentation of tensor images arises from the fact that traditional segmentation techniques operate with scalars or vectors, and therefore cannot be directly applied to tensors.
- Initially, most of the methods intended for the analysis of tensor fields were based on scalar or vector values extracted from the tensors.

DTI segmentation

Technique	Application	Tensor Distance	Segmentation Type	Pros	Cons
Peled *et al.*, 1998 [57]	DTI (corpus callosum, internal capsule)	Linear, planar and spherical components	Quantitative analysis (not really segmentation)	Easy implementation	Computational cost (computing eigenvalues/eigenvectors); Noise affecting eigenvalues
Zhukov *et al.*, 2003 [89]	DTI (regions with high diffusivity/ anisotropy)	Diffusivity measure I_1 Anisotrpy measure C_a	GAC (level sets)	Faster and less sensitive to noise than [57]	GAC needs close inizialization Only scalar values employed Needs to adjust parameters and to combine results heuristically
Rousson *et al.*, 2003 [16, 66, 65]	LST (unsupervised segmentation)	Euclidean distance tensor components as vector	GAR(level sets)	Introduces statistical modeling of data Uses all tensor components	Does not take into account the tensor nature of the data
Feddern *et al.*, 2003 [26]	DTI	LST of the tensor data	GAC		Only segmented brain contour in 2D
Wiegell *et al.*, 2003 [87]	DTI (talamic nuclei)	Combination of Frobenius tensor distance and Mahalanobis voxel distance	k-means	Simple method	Frobenius distance is not best option
Jonasson *et al.*, 2003 [38, 37]	DTI (corpus callosum, corticospinal tract	Normalized tensor scalar product (NTSP)	Level set, curve propagation based on tensor distance	Tensor distance specifically designed	Tensor distance appropriate for other structures?
Wang & Vemuri, 2004 [78]	LST	Frobenius	Mumford-Shah functional (level sets)	First method to combine curve evolution and tensor distances	Frobenius distance

DTI segmentation

Technique	Application	Tensor Distance	Segmentation Type	Pros	Cons
Wang & Vemuri, 2004 [77]	DTI LST	K-L distance	Chan andVese model (level sets)	Better tensor distance than Frobenius	Piecewise constant model
Lenglet *et al.*, 2004 [43, 47]	DTI	K-L distance geodesic distance	GAR on the distance to the mean tensor	Incorporates statistical model	Does not directly model the data, but the distances
Lenglet *et al.*, 2006 [48, 44, 45]	DTI	Euclidean distance K-L distance Geodesic distance	GAR with Gaussian distribution over tensor fields	Incorporates statistical model directly on the tensor domain	Complicated formulation Needs manual initialization
Ziyan *et al.*, 2006 [90]	DTI (thalamus nuclei)	Frobenius distance K-L distance Eigenvectors angular diff.	Spectral clustering with Markovian relaxation	Accurate segmentation	Needs careful delineation of thalamus for initialization
de Luis-Garcia & Alberola, 2007 [25]	DTI (corpus callosum)	K-L distance Geodesic distance	GAR with mixtures of Gaussians on tensors	More flexible than [48, 44, 45] Accurate results	Complicated model Needs initialization
Weldeselasie & Hamarneh, 2007 [83]	DTI (corpus callosum and cardiac)	Log-Euclidean K-L distance	Graph-cuts	Allows for interactive segmentation	Results only in 2D slices
Awate *et al.*, 2007 [9, 8]	DTI (cingulum, corticospinal tract)	Log-Euclidean	Fuzzy C-means with nonparametric statistical models	Overcomes Gaussian limitations on bending fiber bundles	Need some manual initialization

[LuisGarcia_2009]

Initial goal: LGN identification

1. We wanted to find an automated way to identify LGN
2. Clustering had initially being used in the thalamus.

Behrens *et al.* 2003

- Use thamalic-cerebral connections to segment the thalamic nuclei

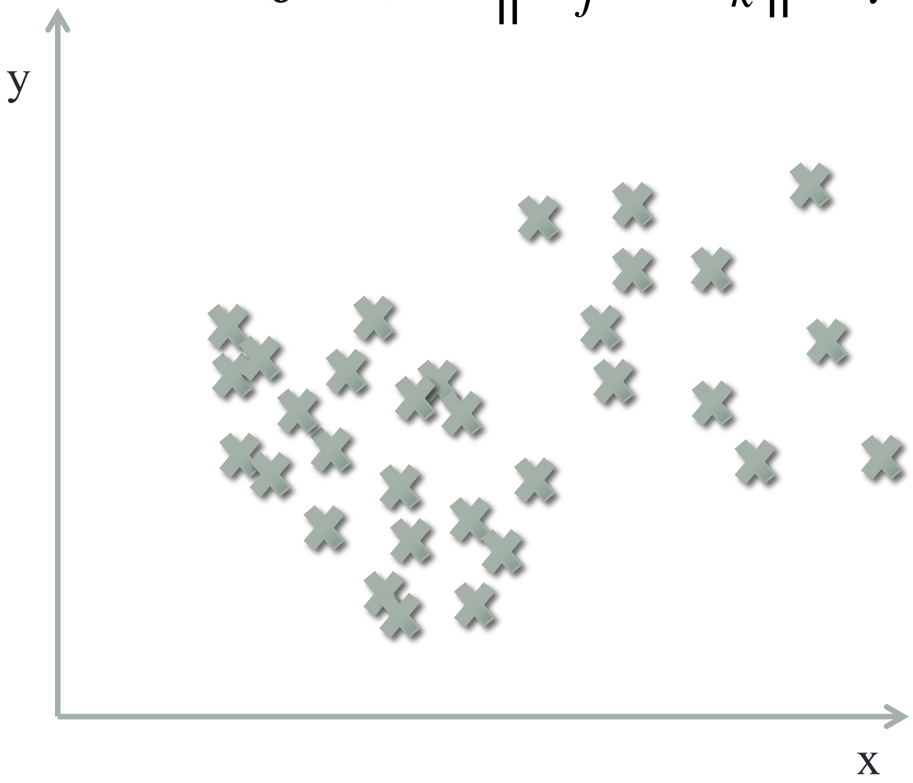
Wiegell *et al.* 2003

- Use similarity between tensor and coordinates information to identify clusters

First paper to use coordinate + diffusion

- Wiegell *et al.* 2003

$$E(j,k) = \left\| \mathbf{x}_j - \bar{\mathbf{x}}_k \right\| + \gamma \left\| \mathbf{D}_j - \bar{\mathbf{D}}_k \right\|$$



Where

- $\mathbf{x}$ is the coordinate vector
- $\mathbf{D}$ is the diffusion tensor
- j is the pixel under investigation
- k is the centroid of the cluster
- γ is a weighting factor

First paper to use coordinate + diffusion

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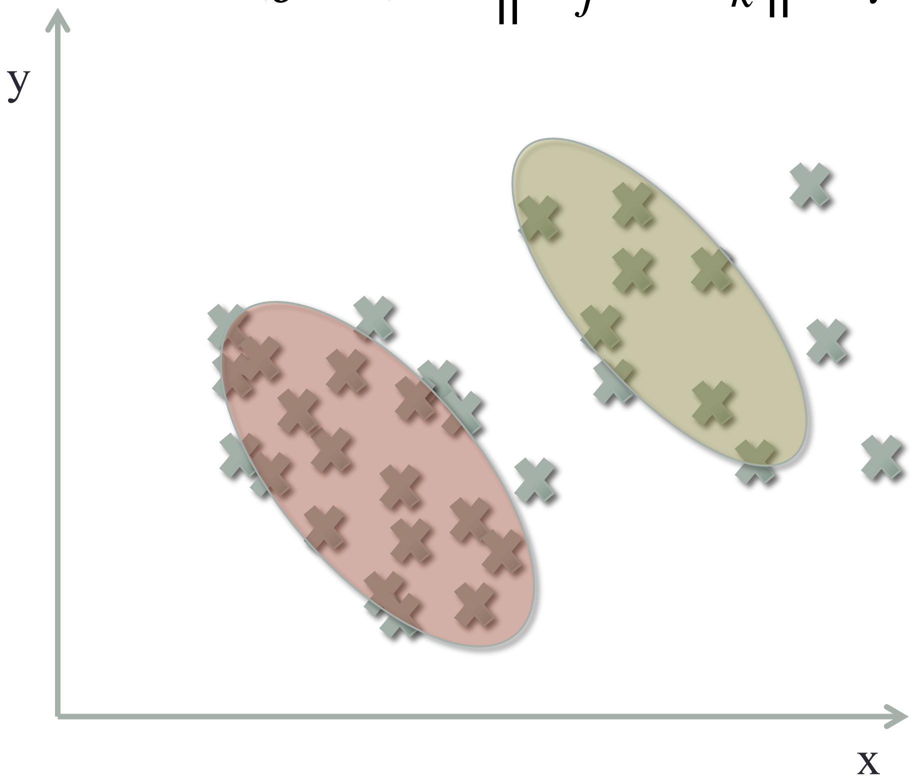

Given a set of pixels in a ROI

Prior knowledge of clusters #

First paper to use coordinate + diffusion

- Wiegell *et al.* 2003

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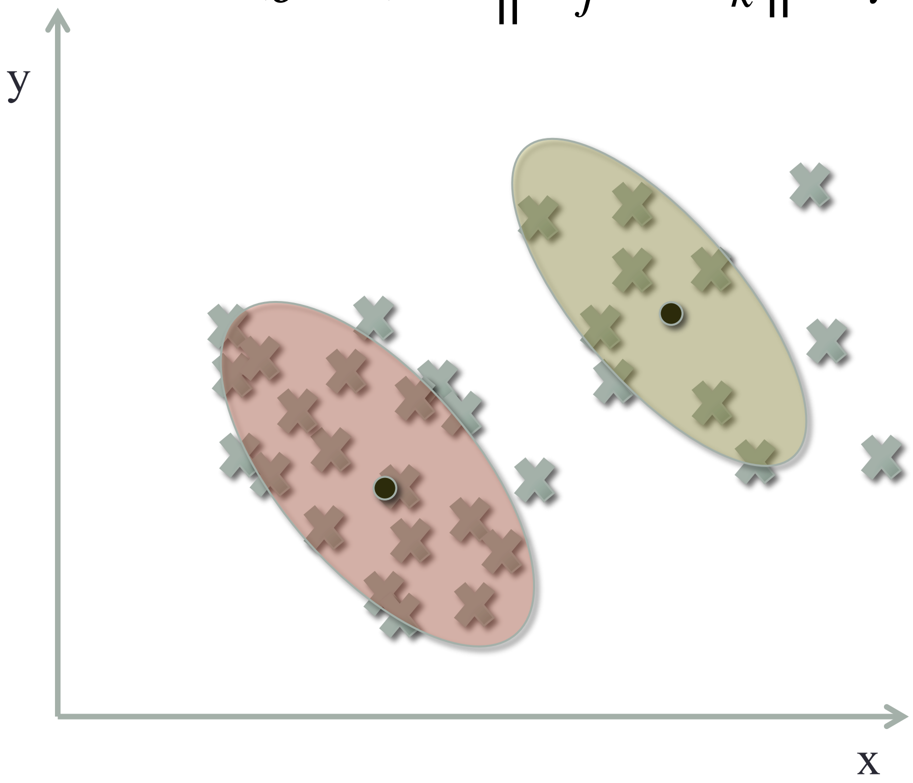

Given a set of pixels in a ROI

Prior knowledge of clusters #

Manual cluster initialization

First paper to use coordinate + diffusion

- Wiegell *et al.* 2003

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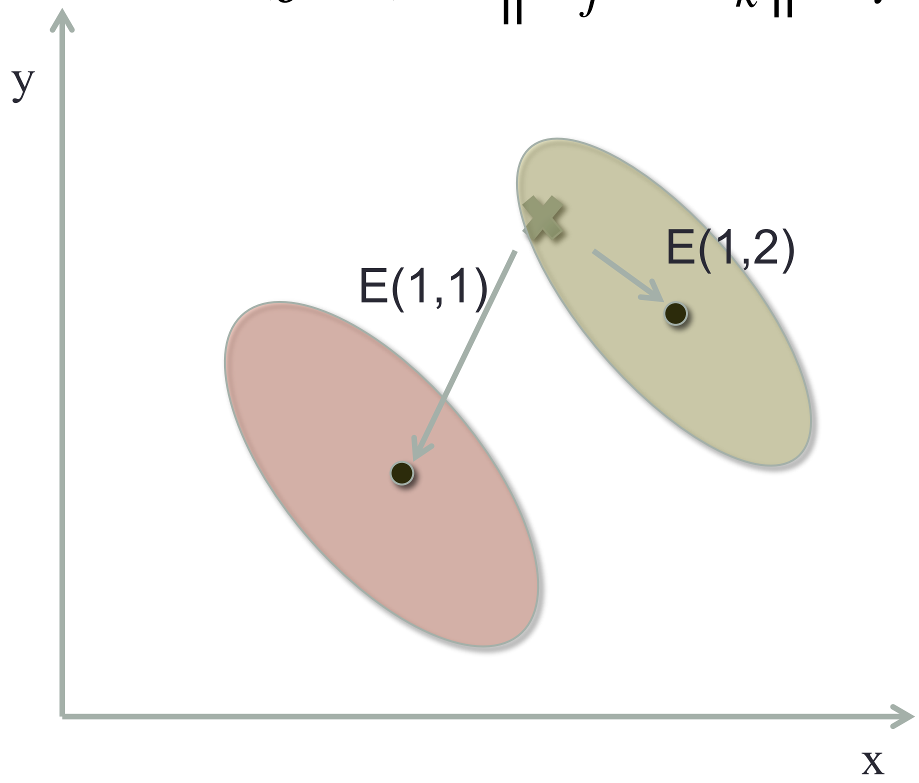


Given a set of pixels in a ROI

Prior knowledge of clusters #

Manual cluster initialization

Distance voxel-centroids

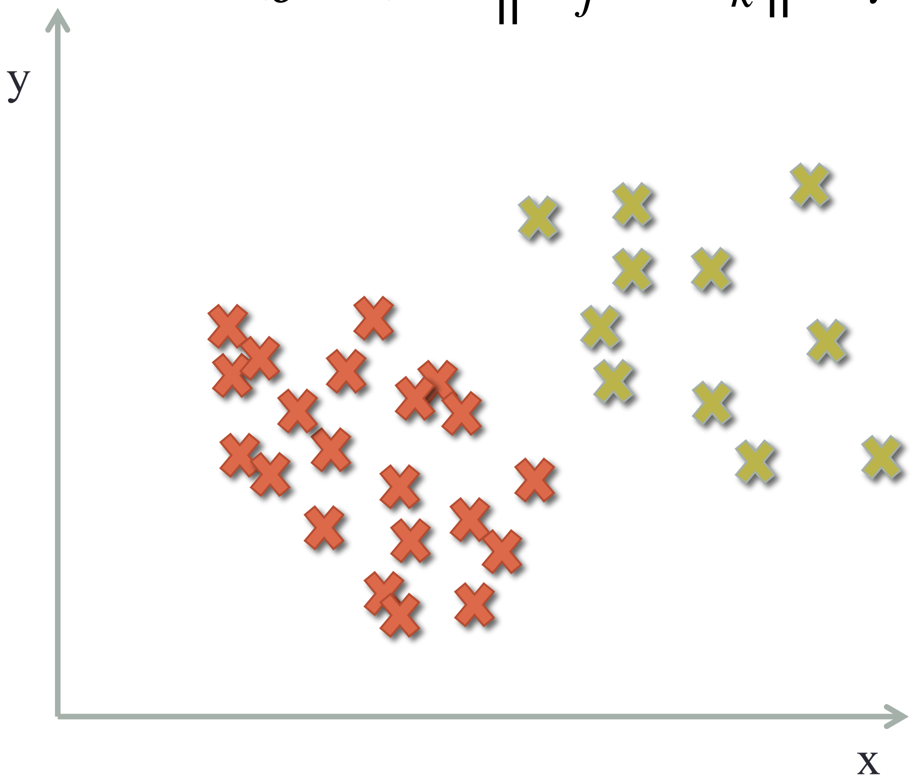
k-means clustering

New centroids calculation

First paper to use coordinate + diffusion

- Wiegell *et al.* 2003

$$E(j,k) = \left\| \mathbf{x}_j - \bar{\mathbf{x}}_k \right\| + \gamma \left\| \mathbf{D}_j - \bar{\mathbf{D}}_k \right\|$$



Given a set of pixels in a ROI

Prior knowledge of clusters #

Manual cluster initialization

Distance voxel-centroids

k-means clustering

New centroids calculation

Pixels labeling

Improvements from previous work

- Previous work relied heavily on **manual initialization by an expert, had a fixed # of clusters and used only space and diffusivity information**
- We wanted to create an automatic and scalable segmentation method and run it on a set of subjects

- We modified the Wiegell algorithm:
  - Automatic: no manual initialization needed
  - Scalable: to scale up different measurements, not constrained to space and diffusion information

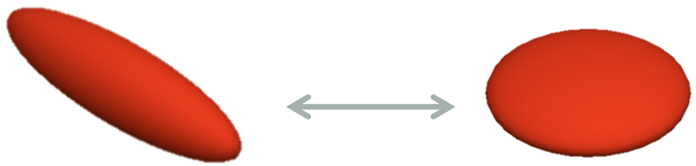
A scalable distance measure

Coords distance (mm)

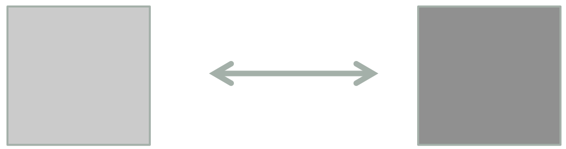
$\mathbf{x}_j \longleftrightarrow \mathbf{x}_k$

$$E(j,k) = \frac{1}{n}\sum_{i=1}^{n} d_i(j,k)$$

Tensors elements similarity



T1 pixel intensity



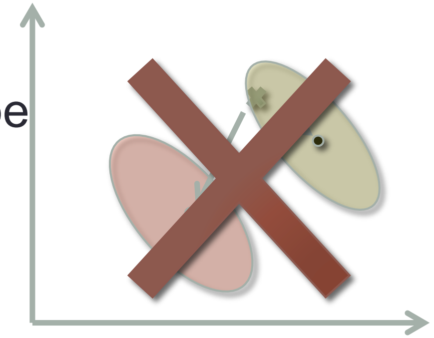
…

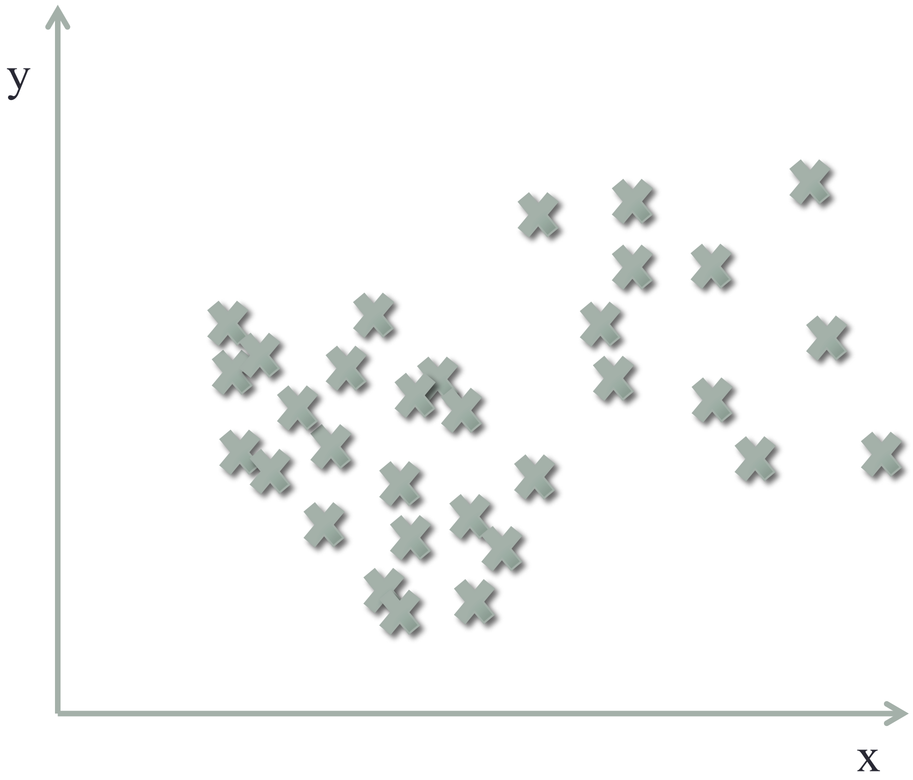
Where

- j is the pixel under investigation
- k is the centroid of the cluster
- n is the number of measures considered

Avoid manual initialization

Data driven approach: voxels' dissimilarity is used to describe the distances of one voxel j to all the other voxels in the ROI.





Dissimilarity matrix representation (DMR)

$$E'(j,j) = \frac{1}{n}\sum_{i=1}^{n} d_i(j,j)$$

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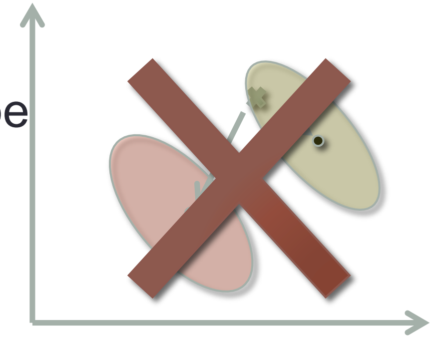

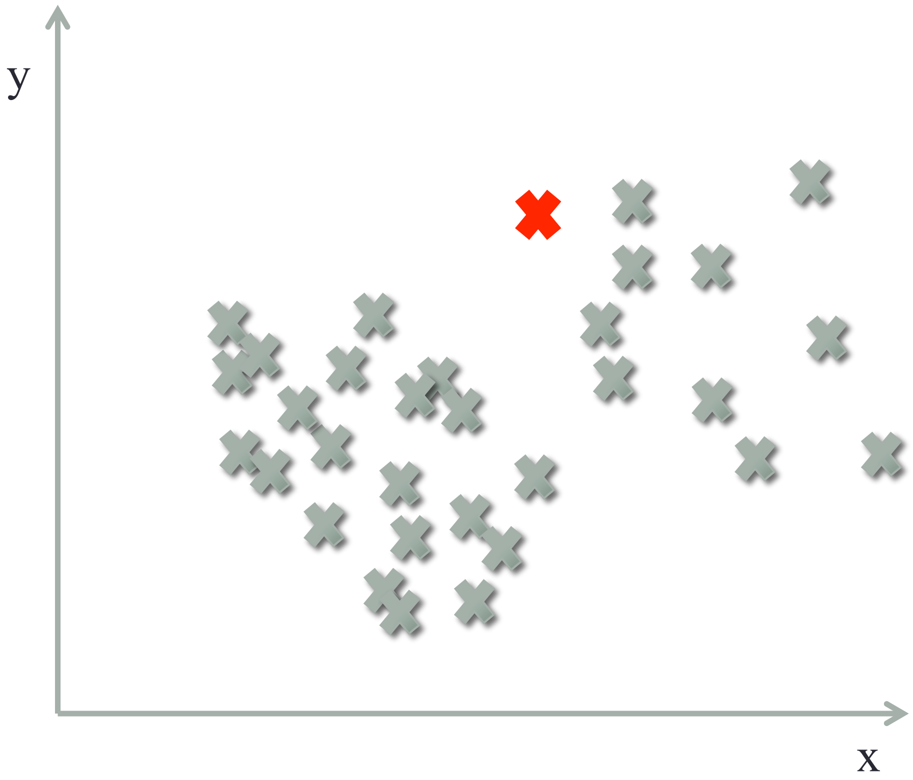

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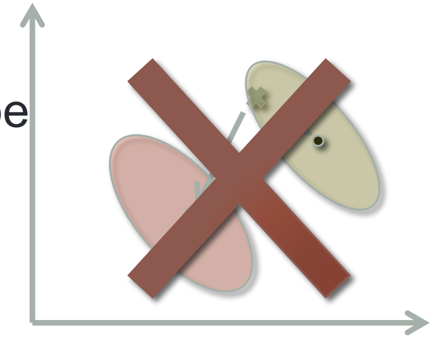

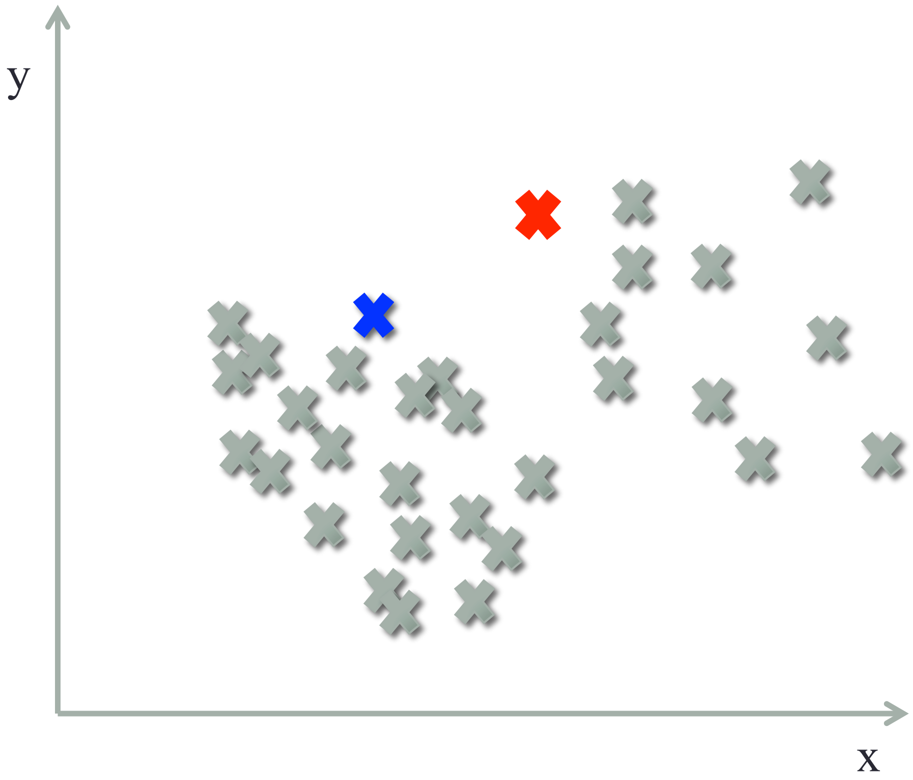

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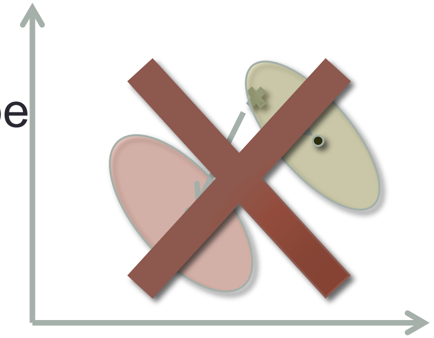

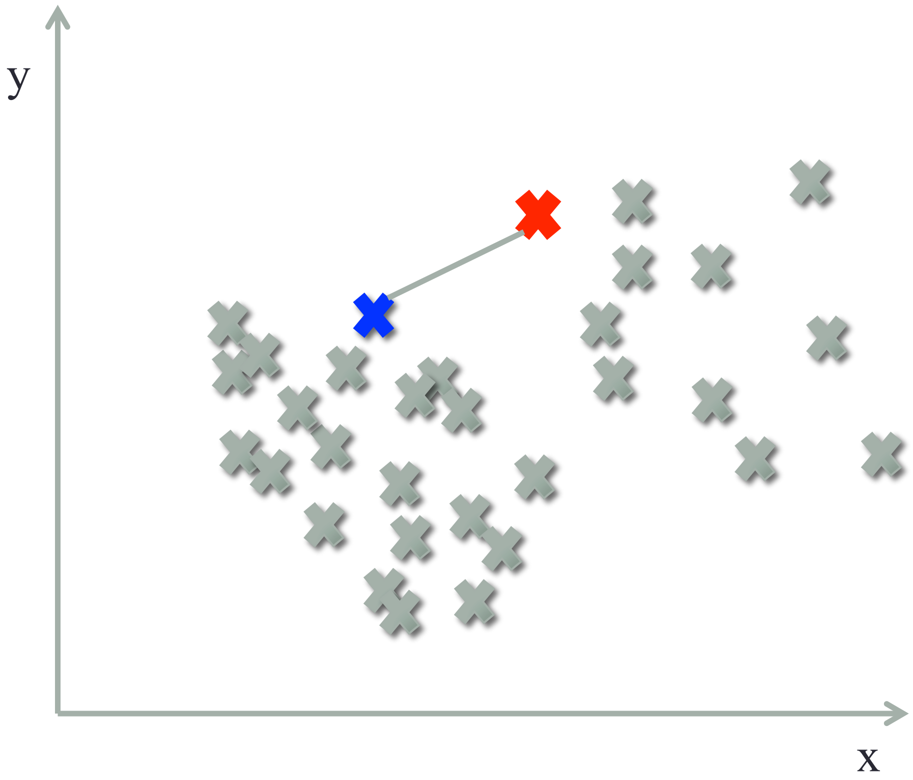

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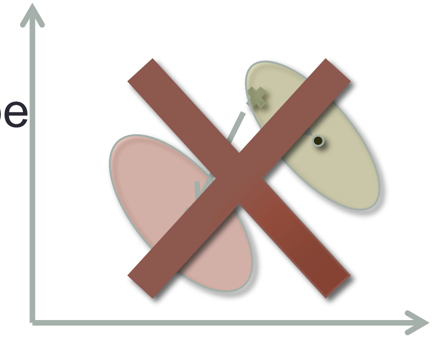

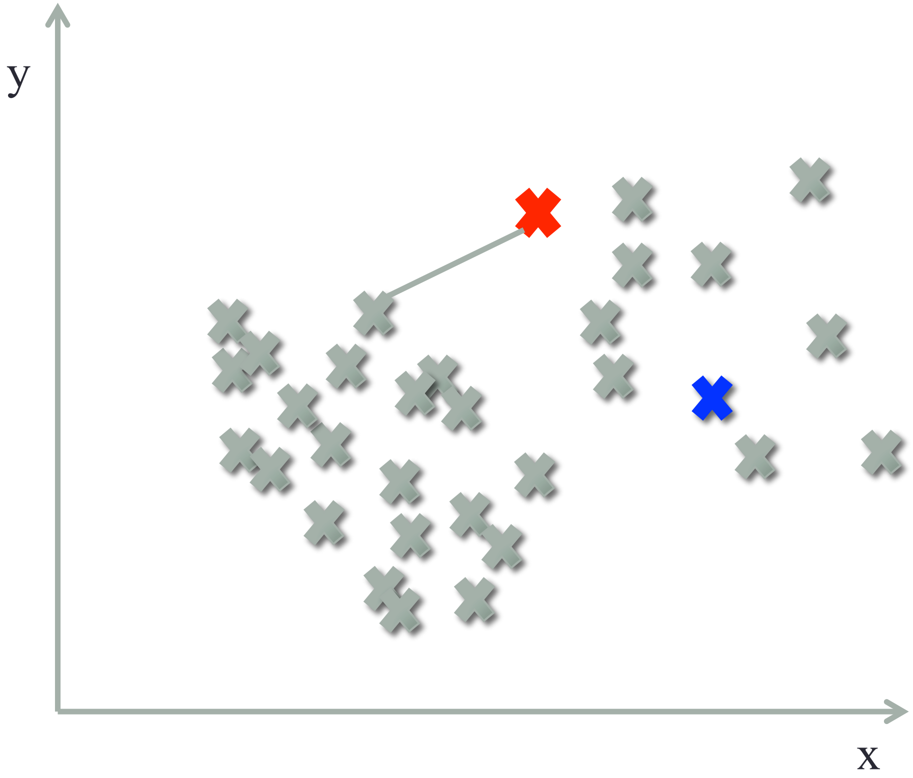

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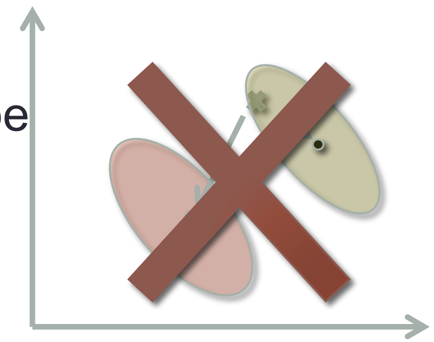

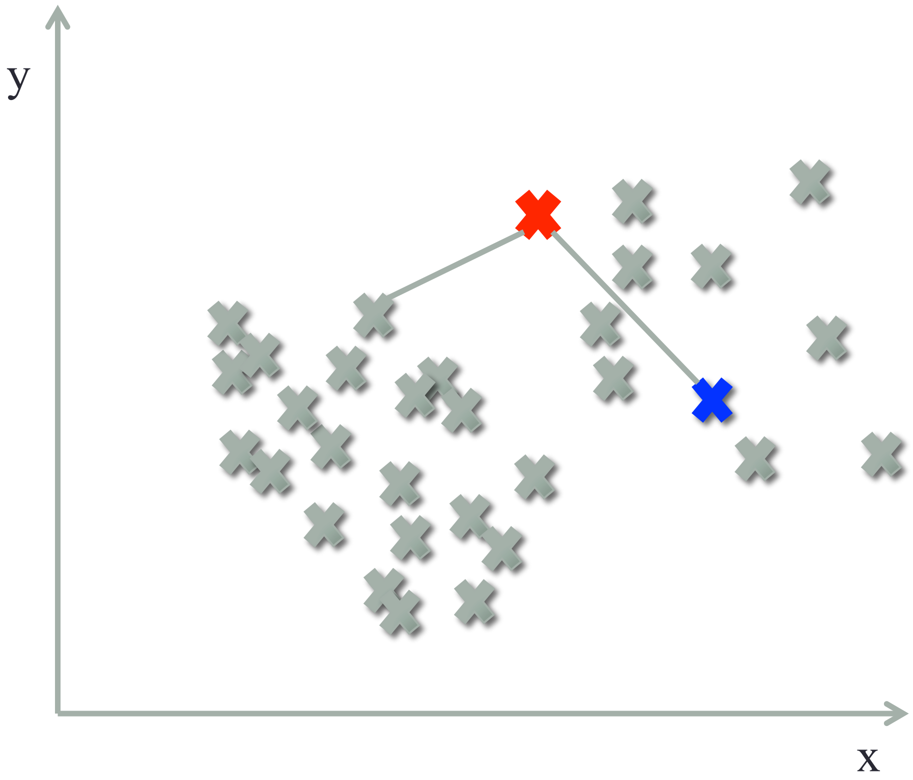

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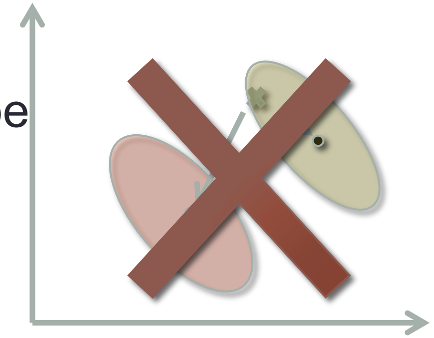

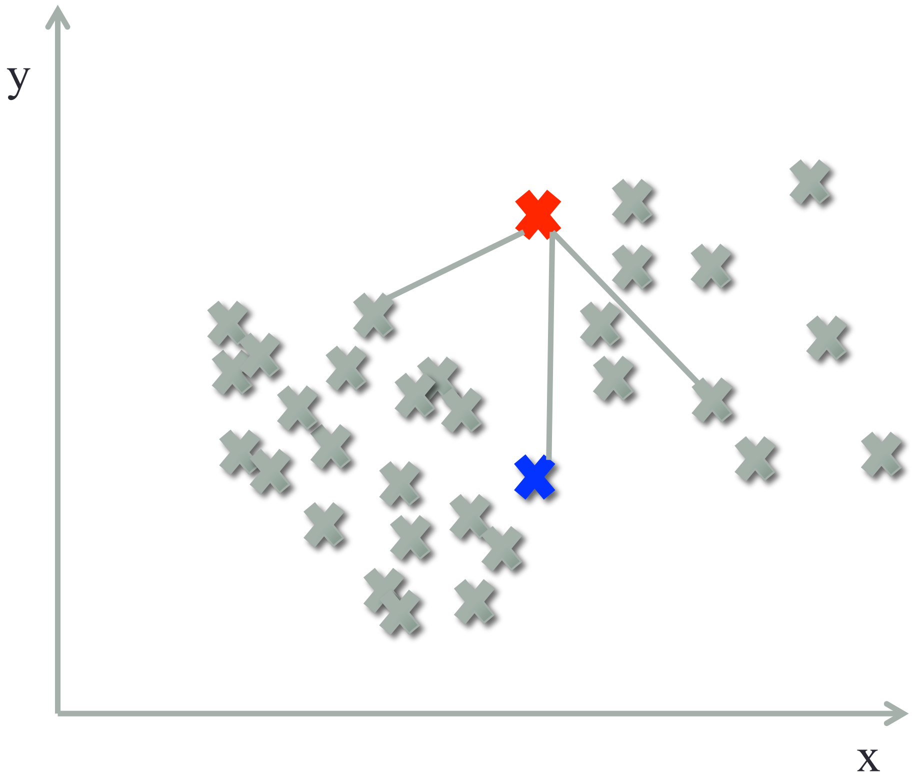

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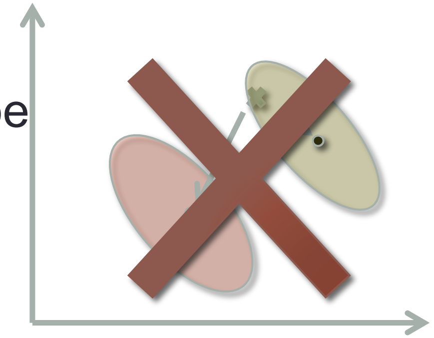

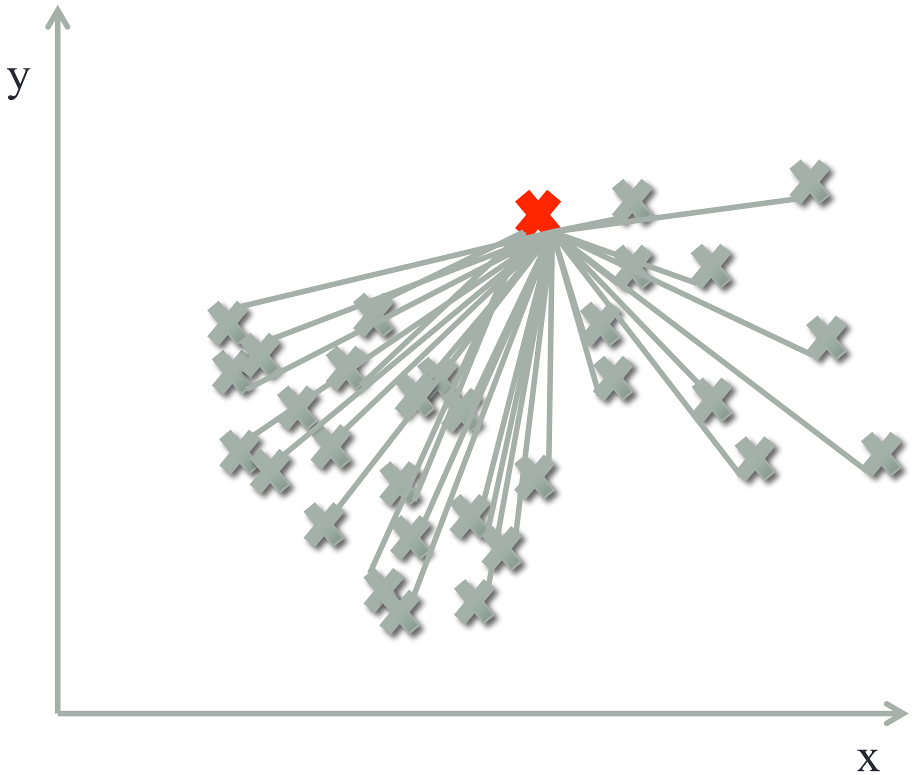

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Thalamus: clustering results

Load Freesurfer Thalamus ROI

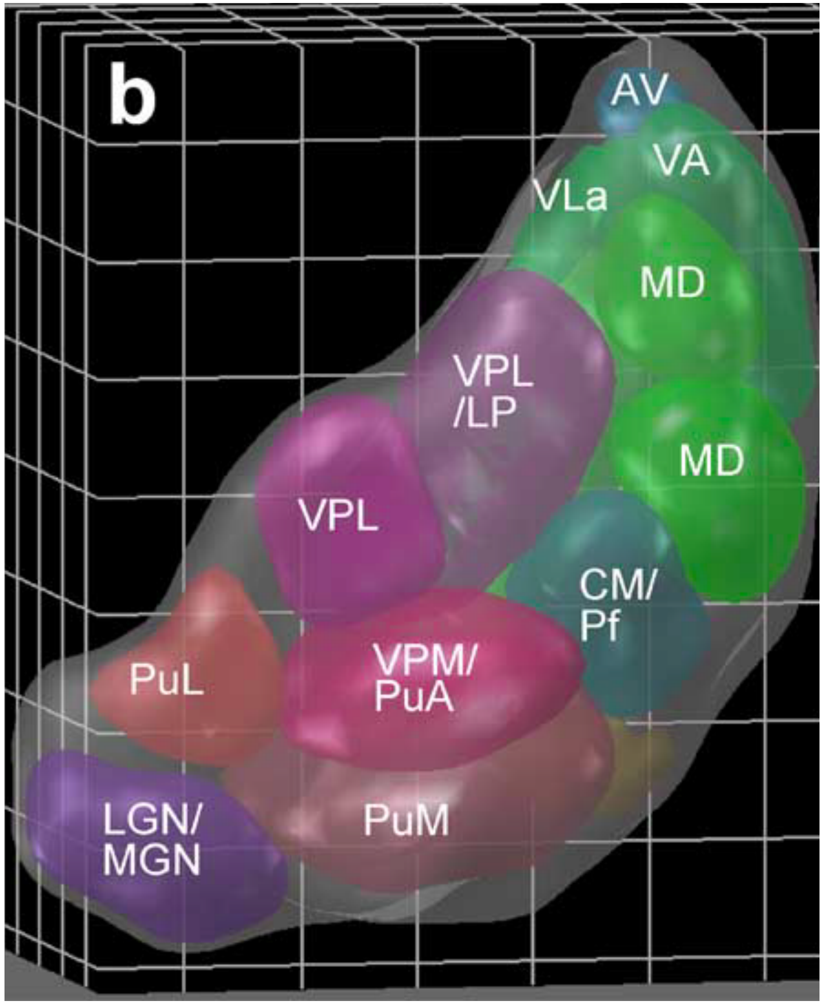
Extraction of different measures (tensors, T1)

Measures of the distance from each voxel to every voxel E'

Multidimensional scaling: E''

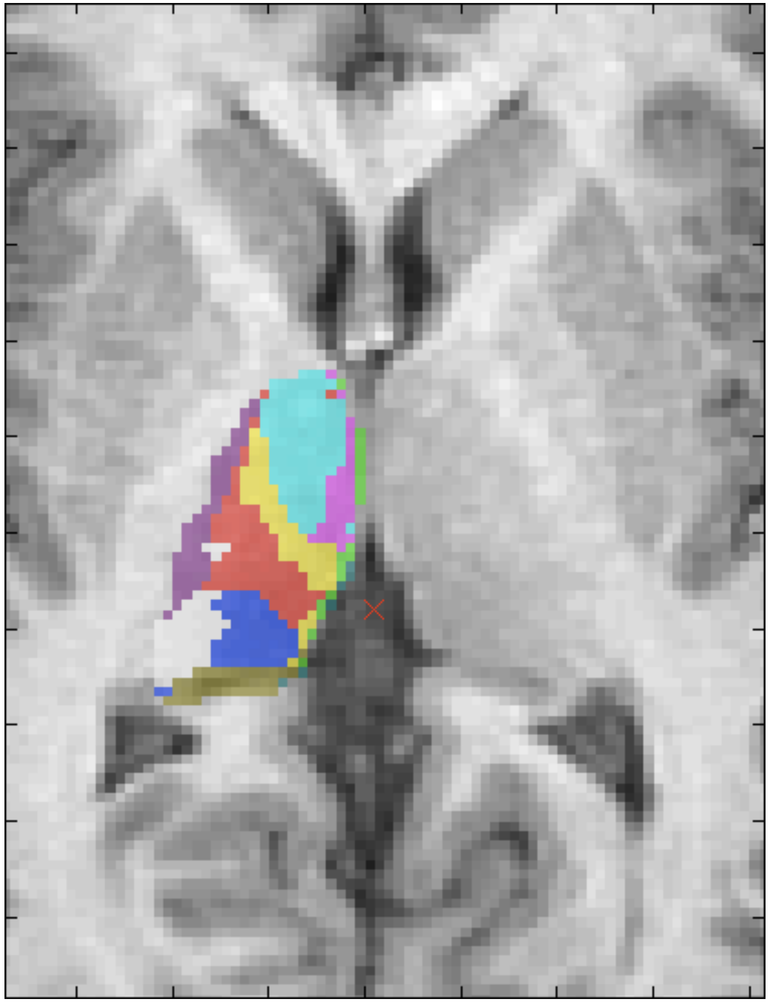
k-means clustering

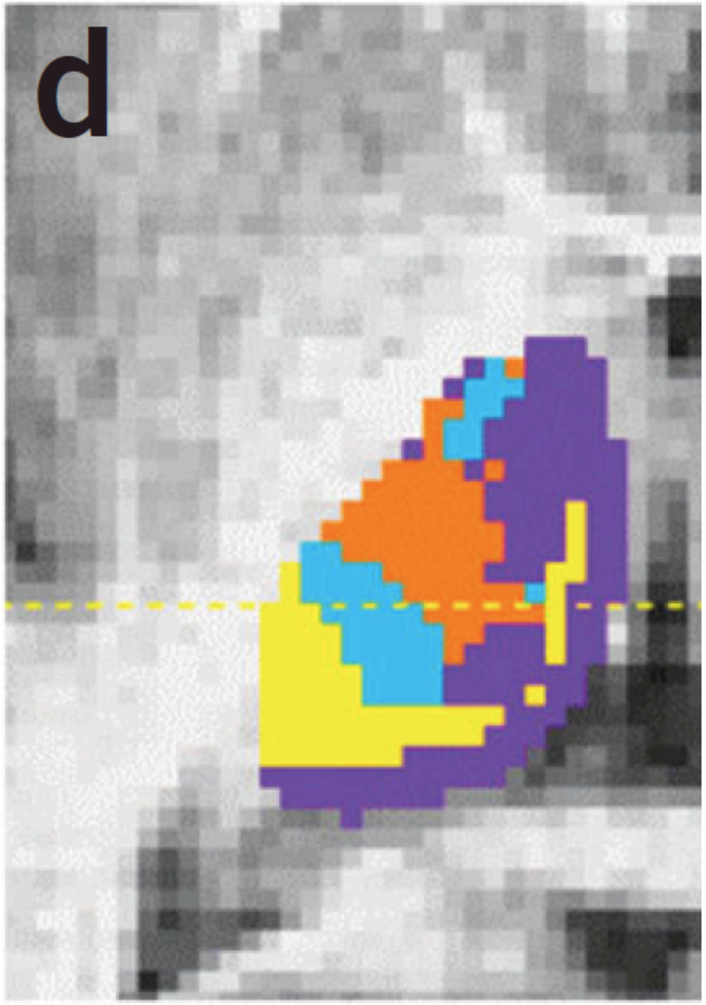
Thalamus: clustering results



Wiegell *et al.* 2003

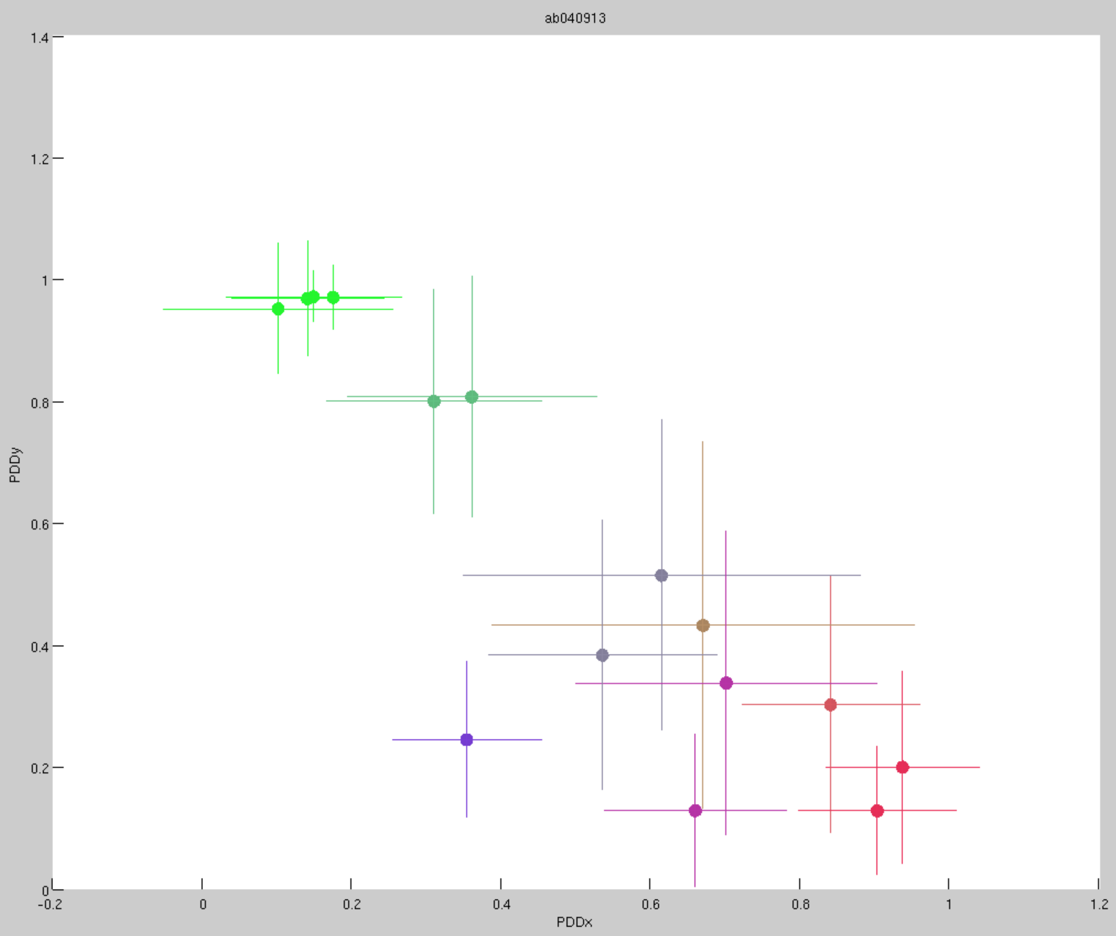
Thalamus: clustering results

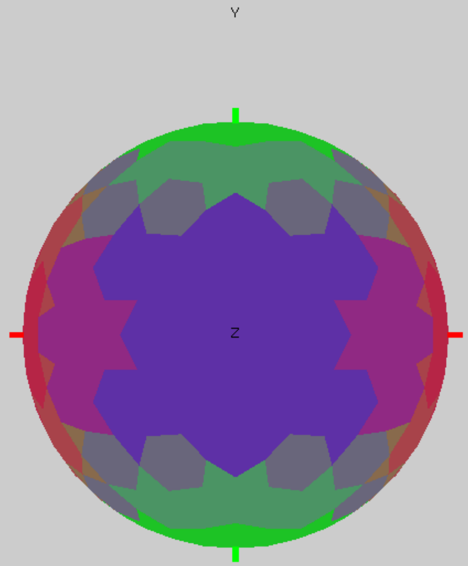




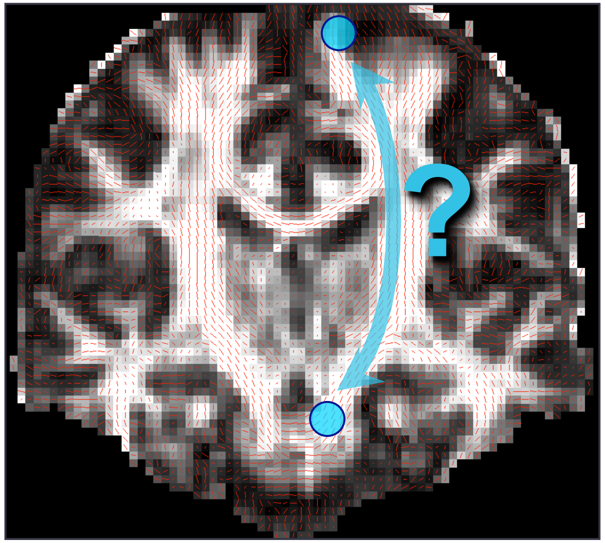
Behrens *et al.* 2003

Thalamus: clustering results





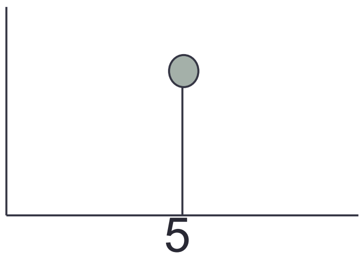
Tractography

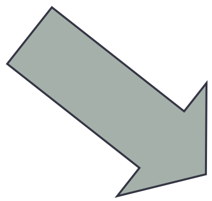


- Use local diffusion orientation at each voxel to determine pathway between distant brain regions
- Local orientation comes from diffusion model fit (tensor, ball-and-stick, etc.)
- Deterministic vs. probabilistic tractography:
  - Deterministic assumes a single orientation at each voxel
  - Probabilistic assumes a distribution of orientations
- Local vs. global tractography:
  - Local fits the pathway to the data one step at a time
  - Global fits the entire pathway at once

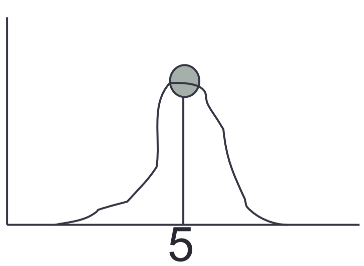
Deterministic vs. probabilistic

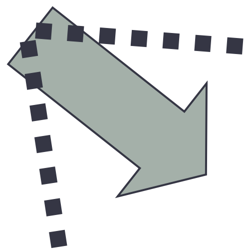
- Deterministic methods give you an estimate of model parameters



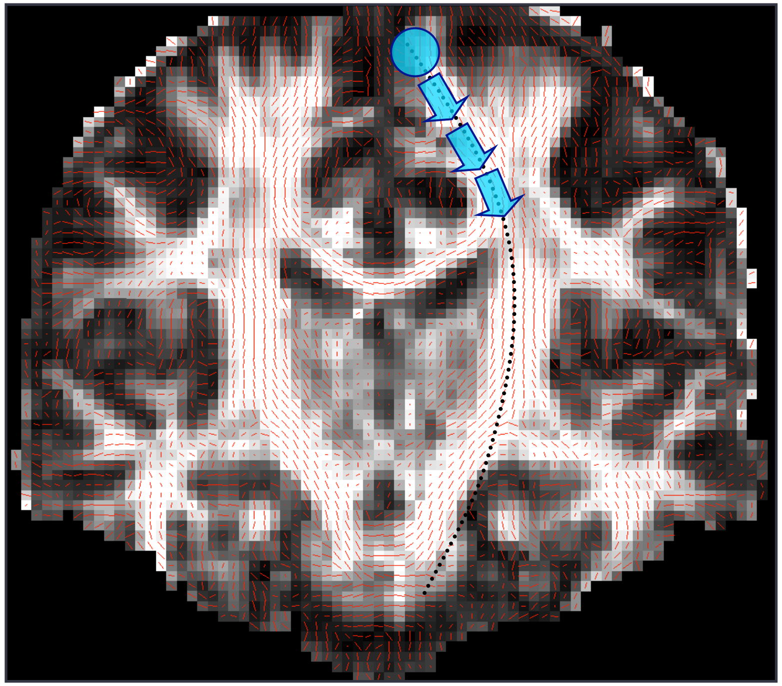


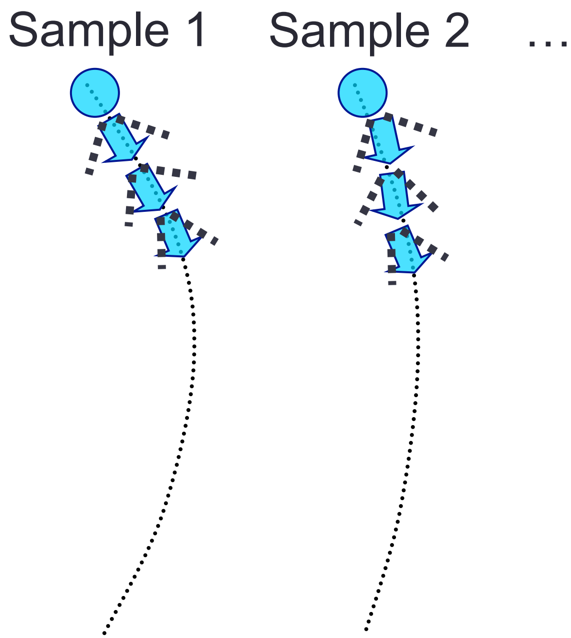
- Probabilistic methods give you the uncertainty (probability distribution) of the estimate





Deterministic vs. probabilistic

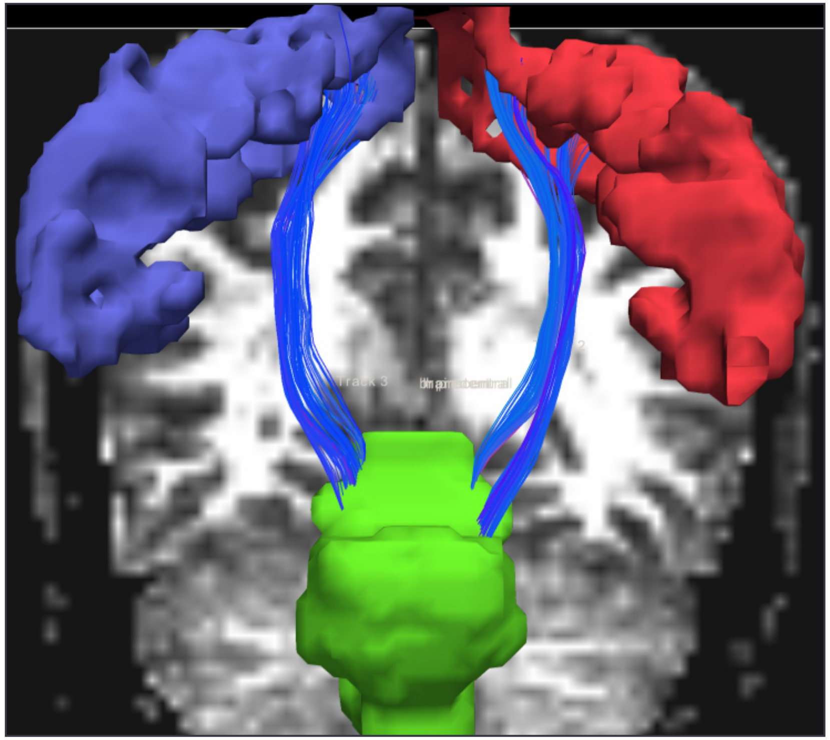




Deterministic tractography:
One streamline per seed voxel

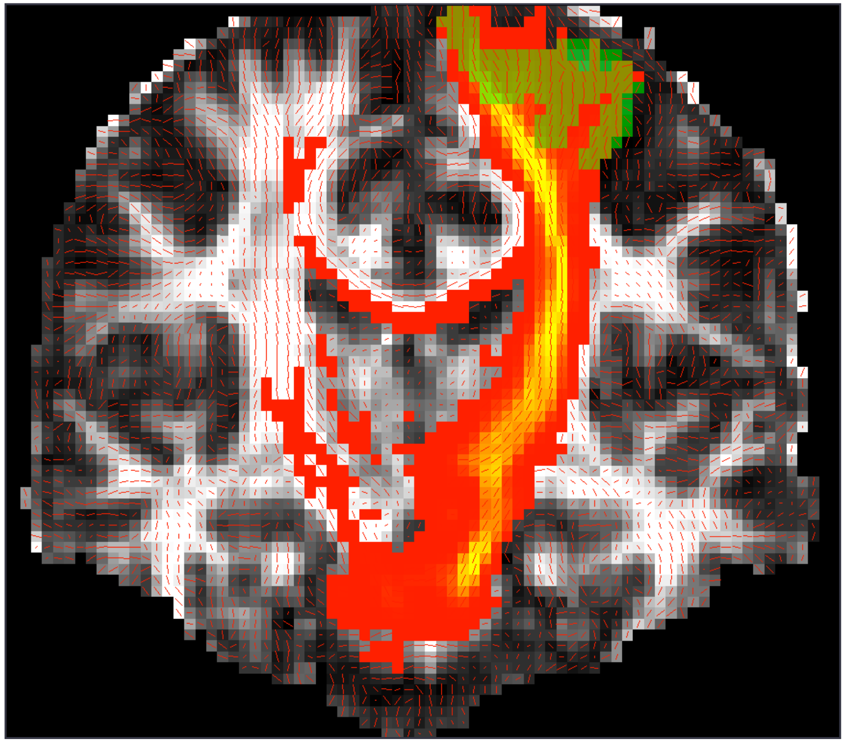
Probabilistic tractography:
Multiple streamline samples per seed voxel (drawn from probability distribution)

Deterministic vs. probabilistic



Deterministic tractography:

One streamline per seed voxel

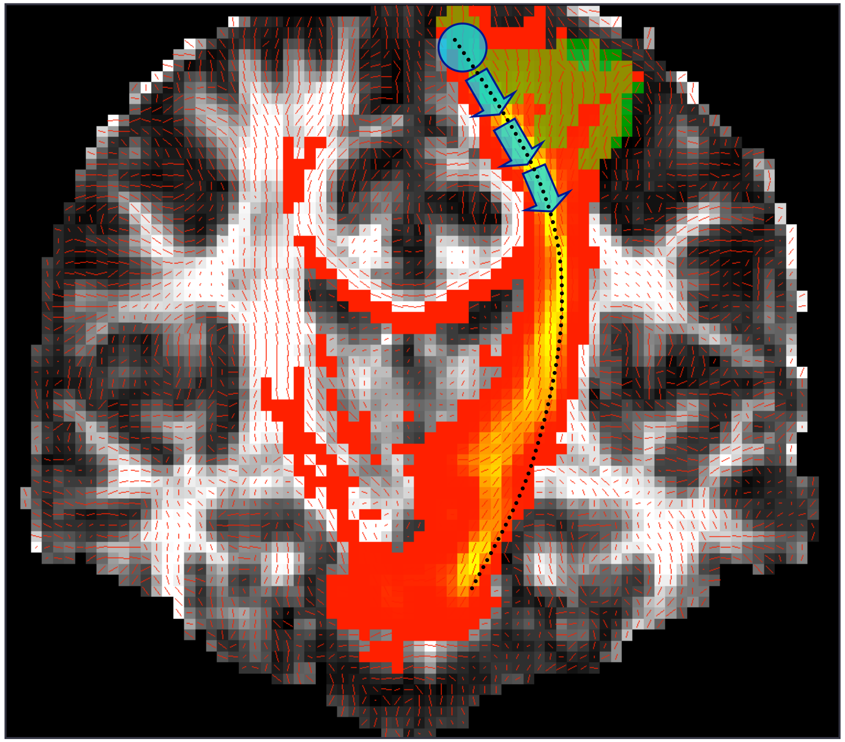


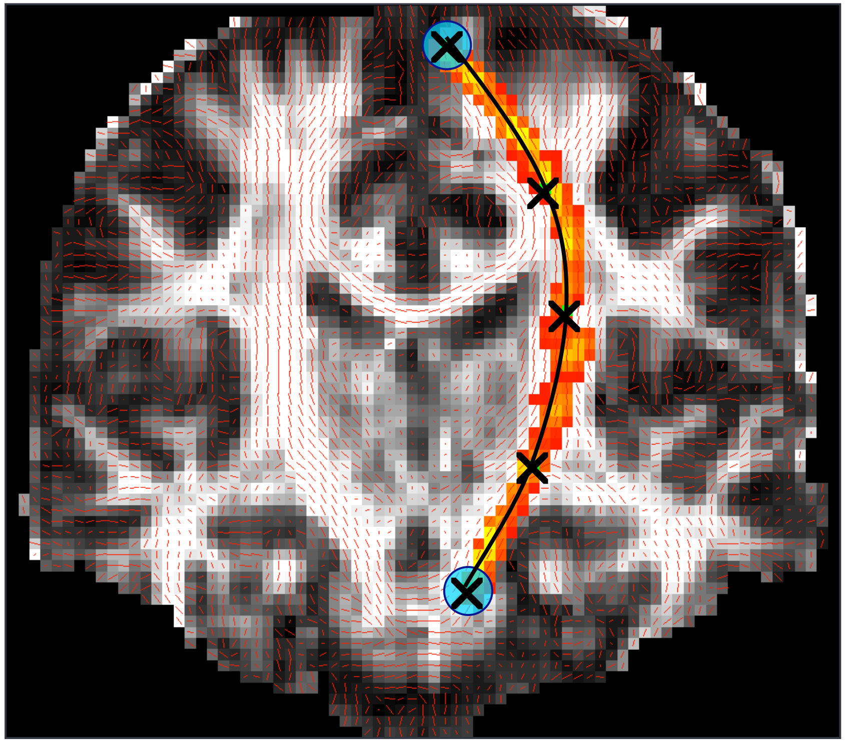
Probabilistic tractography:

A probability distribution

(sum of all streamline samples from all seed voxels)

Local vs. global





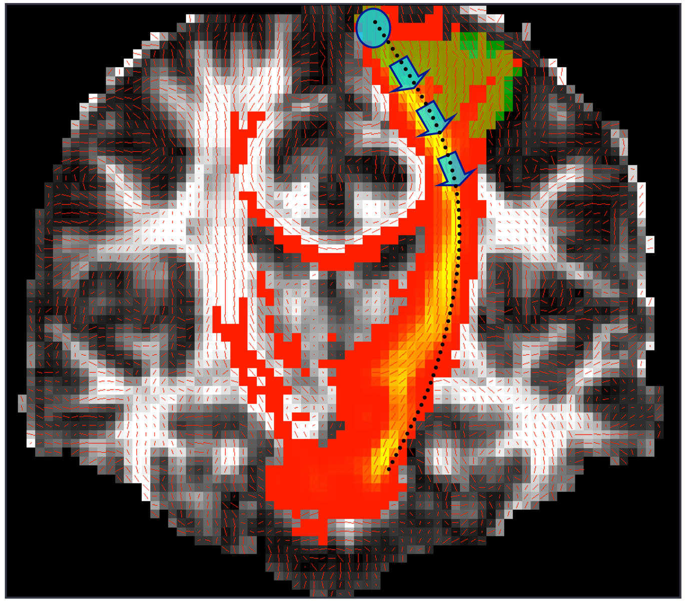
Local tractography:

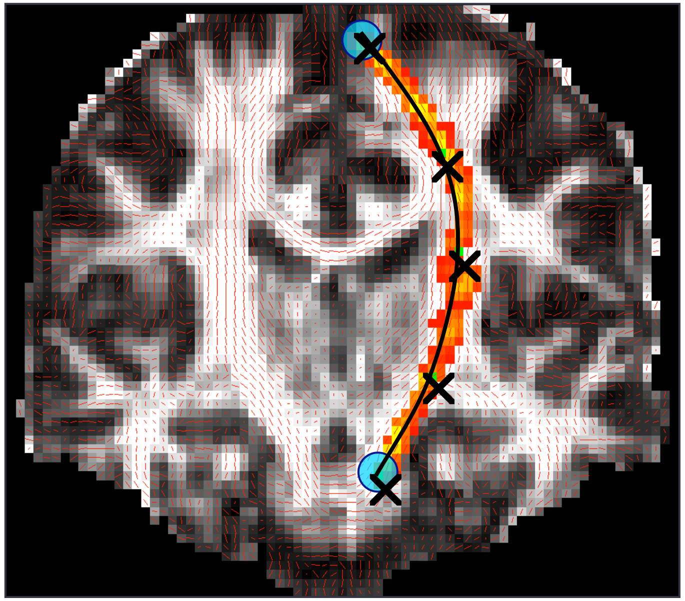
Fits pathway step-by-step, using local diffusion orientation at each step

Global tractography:

Fits the entire pathway, using diffusion orientation at all voxels along pathway length

Local vs. global





Local tractography:

– Deterministic: One direction at each step [DTIStudio, trackvis]

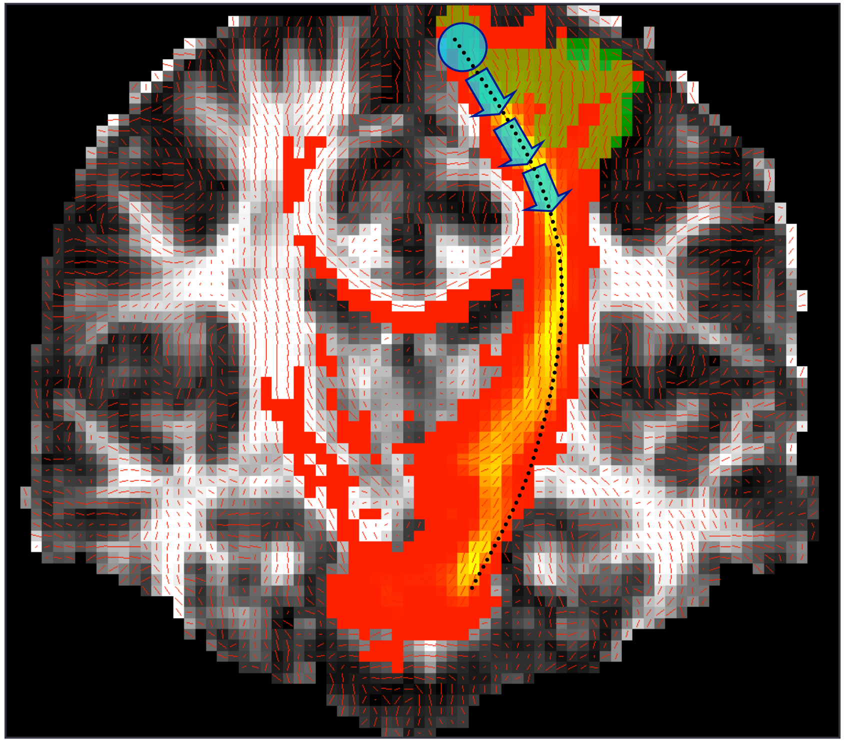
– Probabilistic: A distribution of directions at each step [FSL/ probtrack]

Global tractography:

– Deterministic: Fit path to diffusion orientations along its length

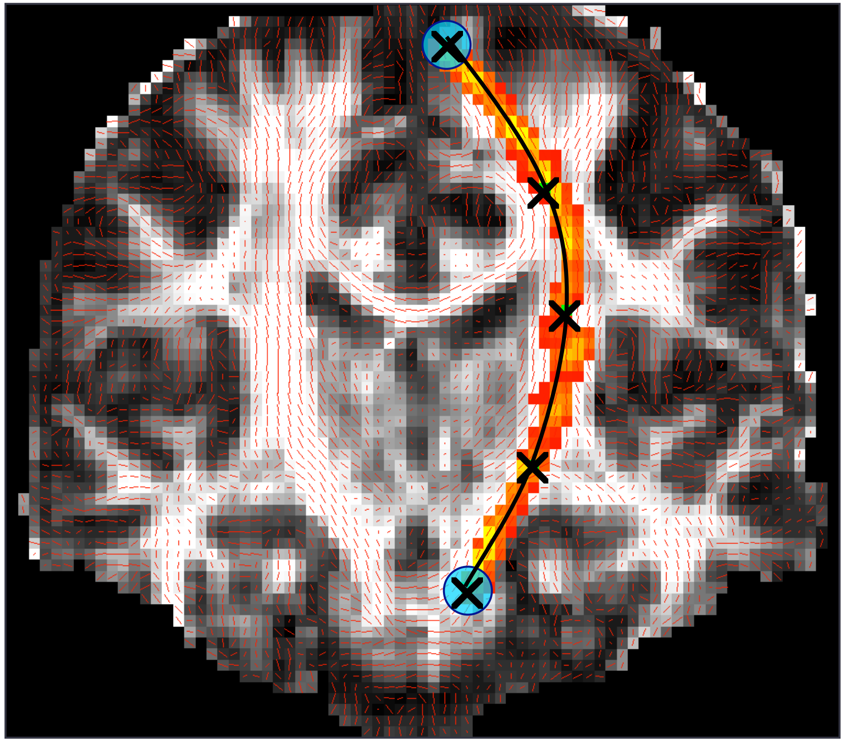
– Probabilistic: Fit path to diffusion orientation distributions along its length

Local tractography



- Best suited for exploratory study of connections
- All connections from a seed region, not constrained to a specific target region
- How do we isolate a specific white-matter pathway?
  - Thresholding?
  - Intermediate masks?
- Non-dominant connections are hard to reconstruct
- Results are not symmetric between "seed" and "target" regions
- Sensitive to areas of high local uncertainty in orientation (*e.g.*, pathaway crossings), errors propagate from those areas

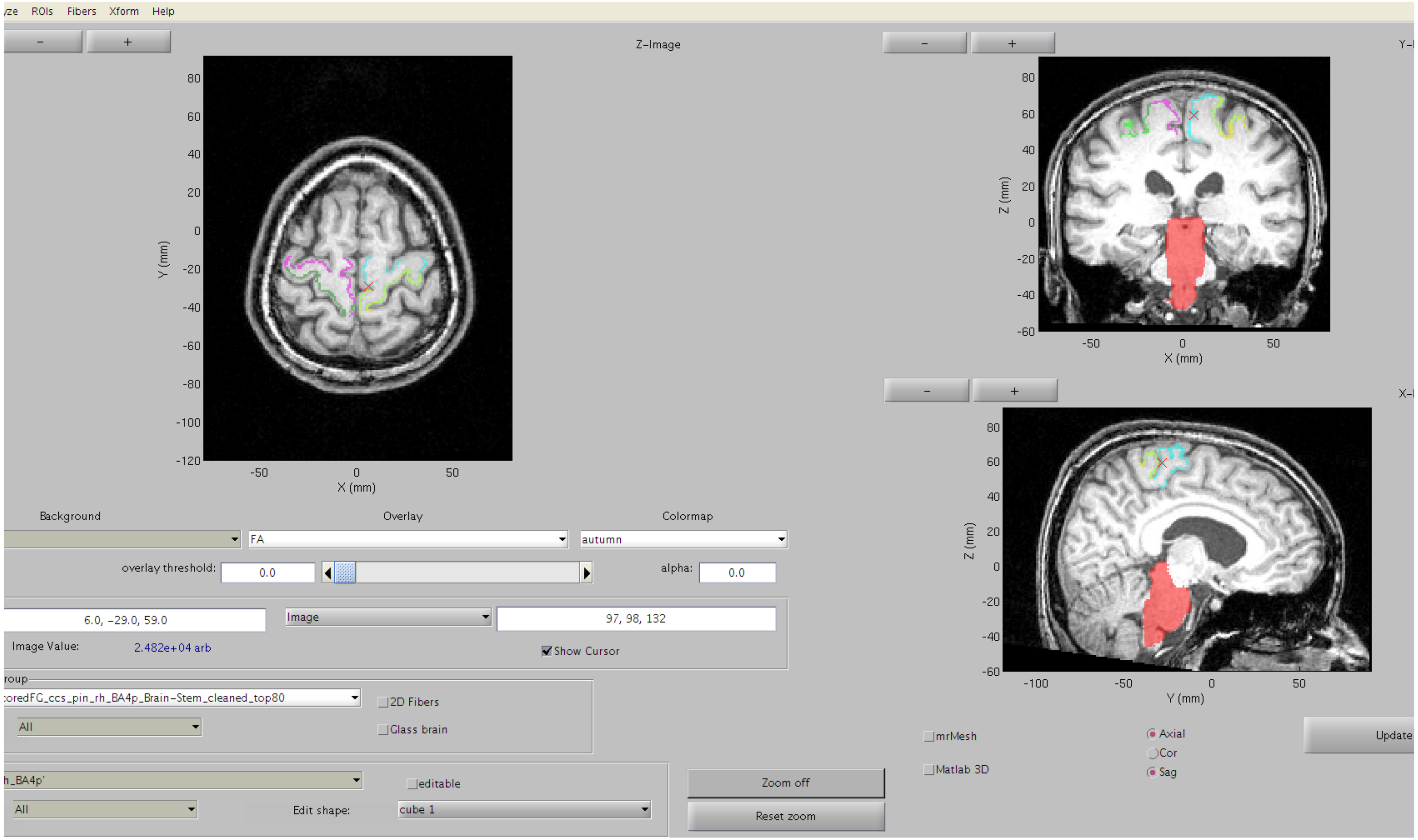
Global tractography



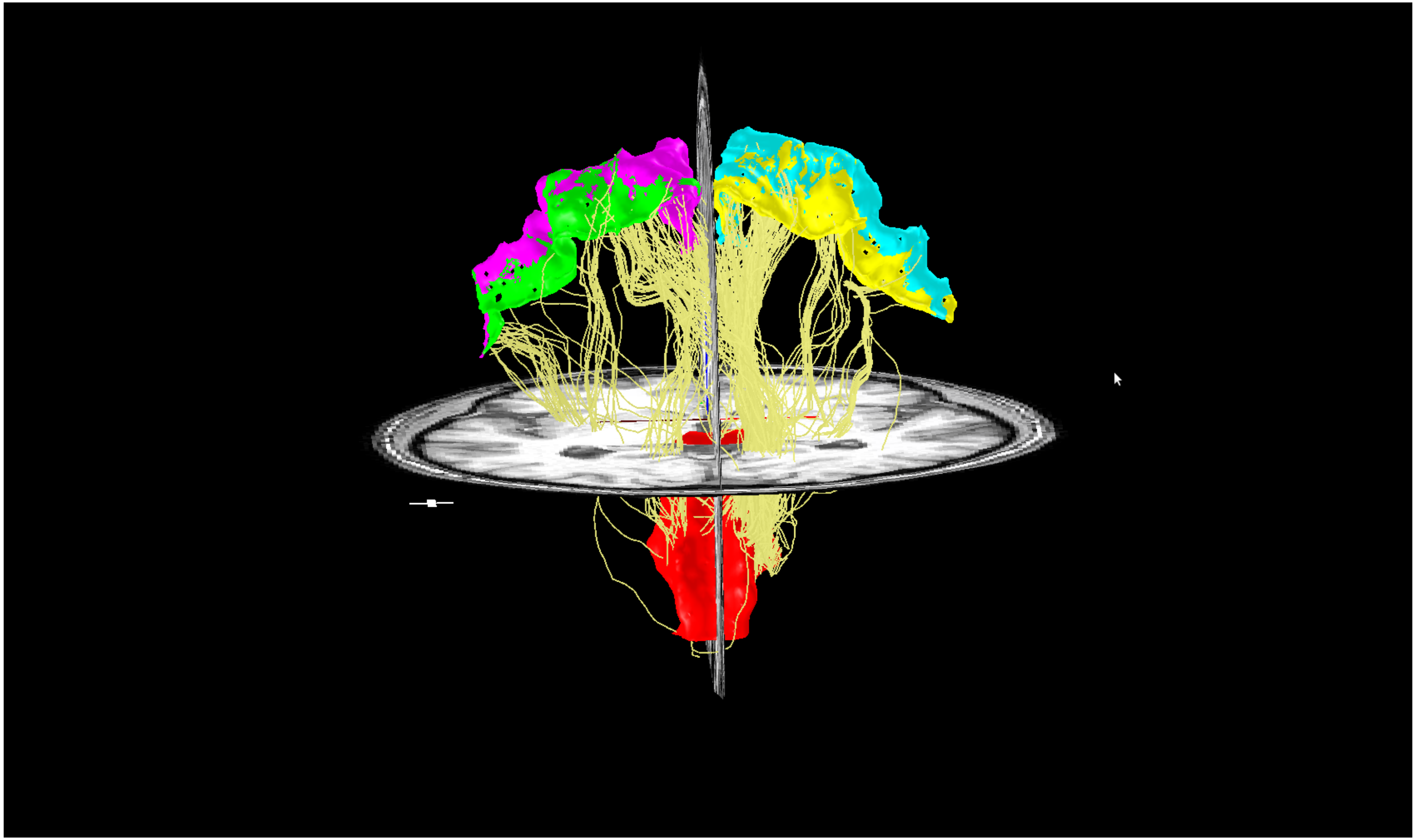
- Best suited for reconstruction of known white-matter pathways
- Constrained to connection of two specific end regions
- Not sensitive to areas of high local uncertainty in orientation, integrates over entire pathway
- Symmetric between "seed" and "target" regions

- Need to search through a large solution space of all possible connections between two regions:
  - Computationally expensive
  - Sensitive to initialization

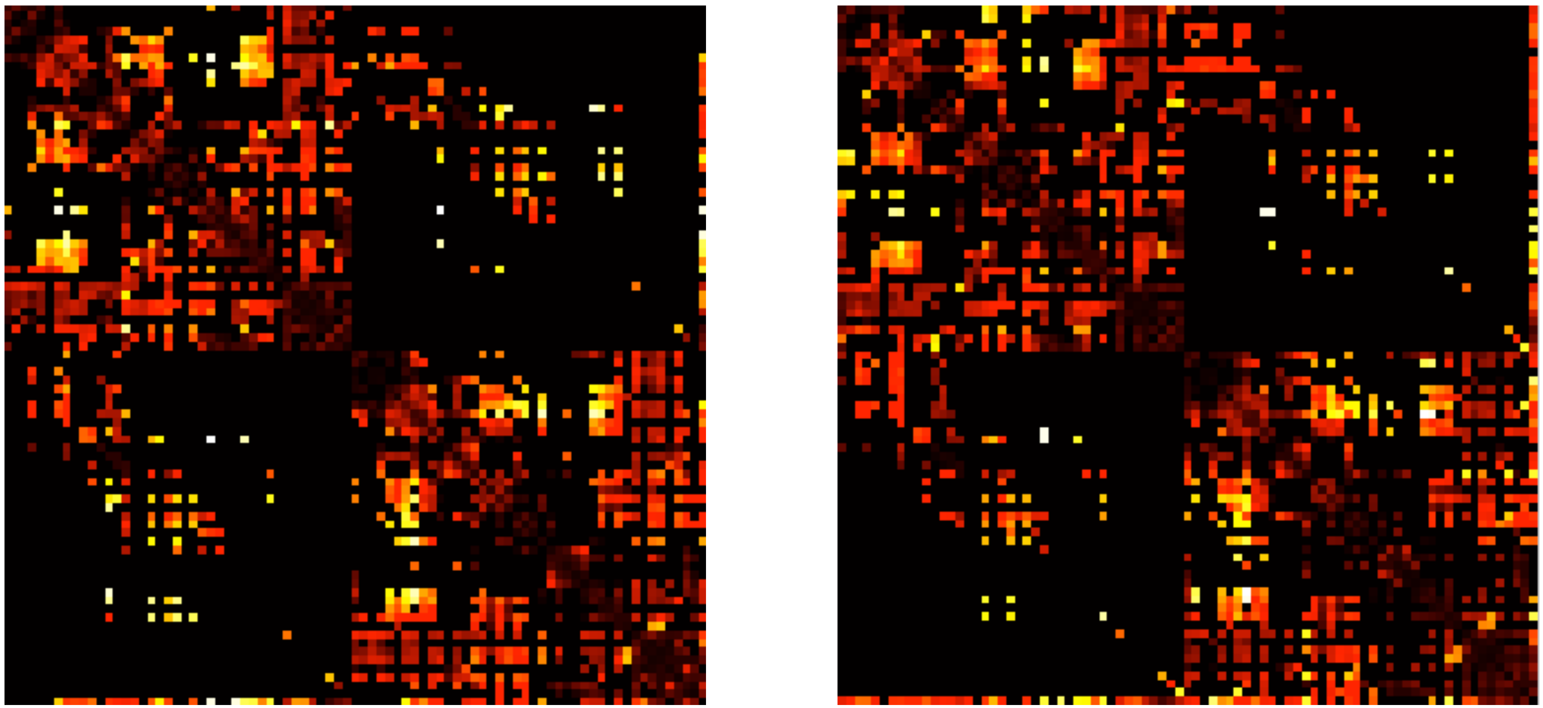
Tractography



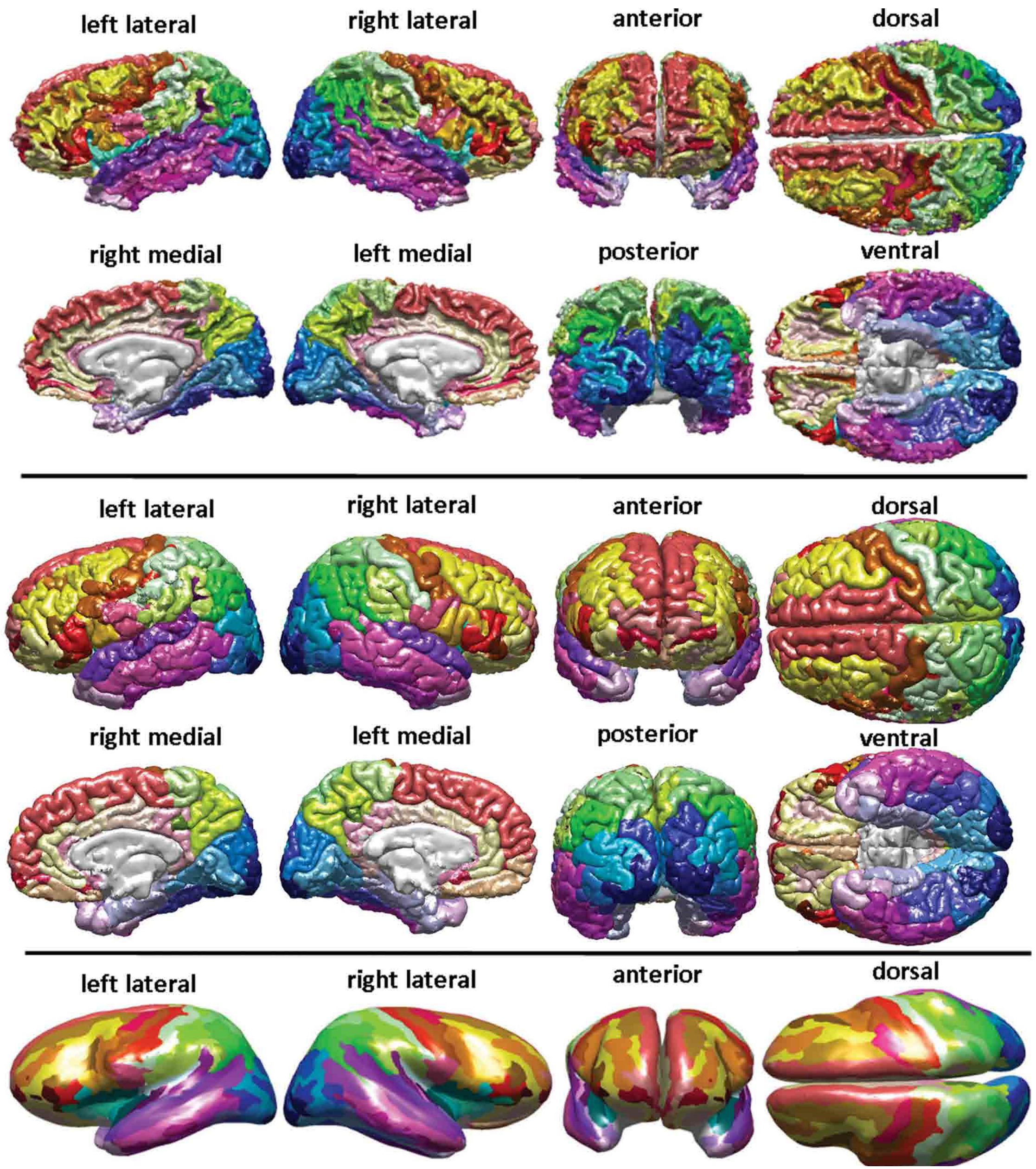
Tractography: ipsilateral fibers



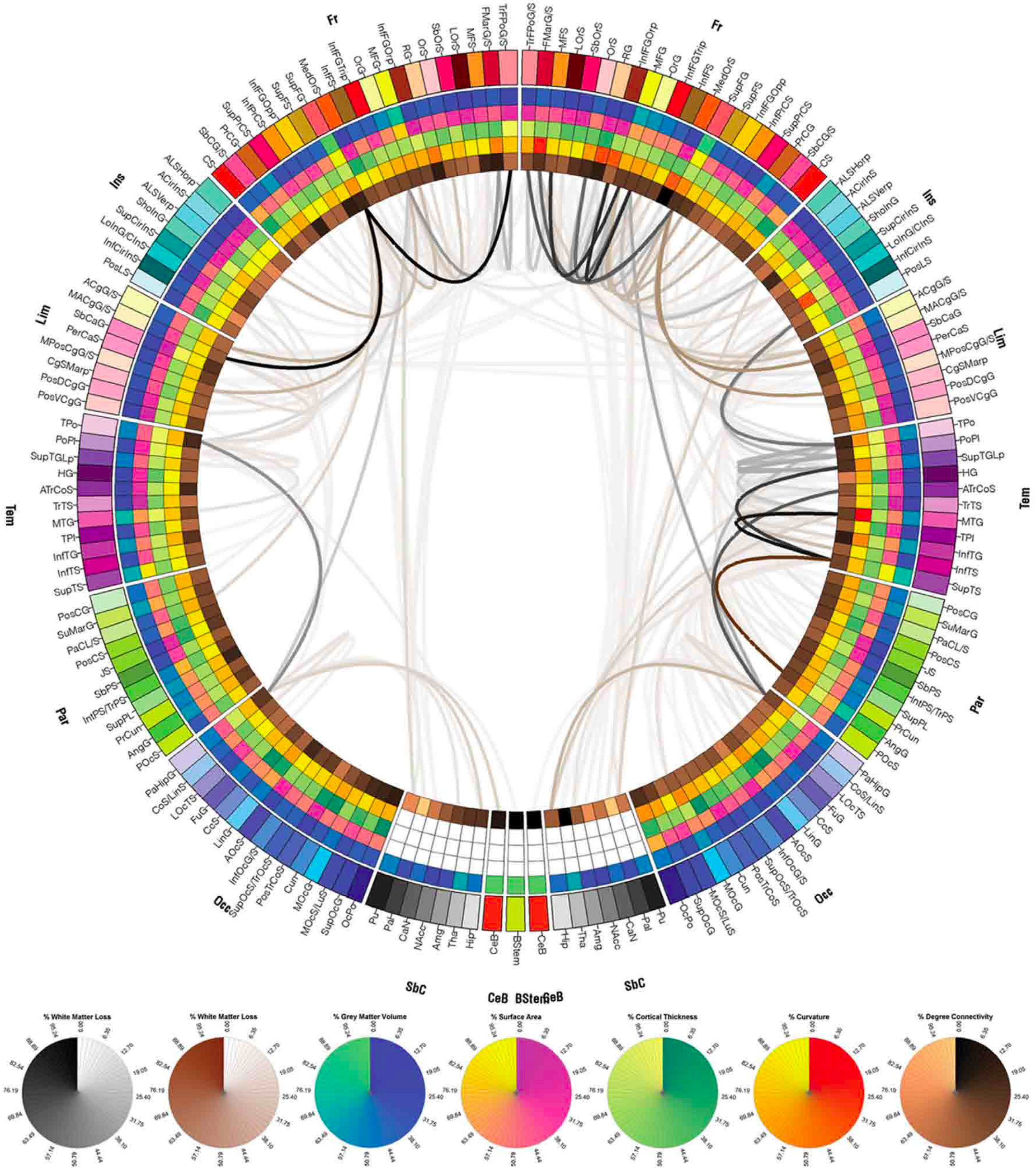
Connectivity



Connectivity



Connectivity



THANK YOU!