Tract-Based Morphometry

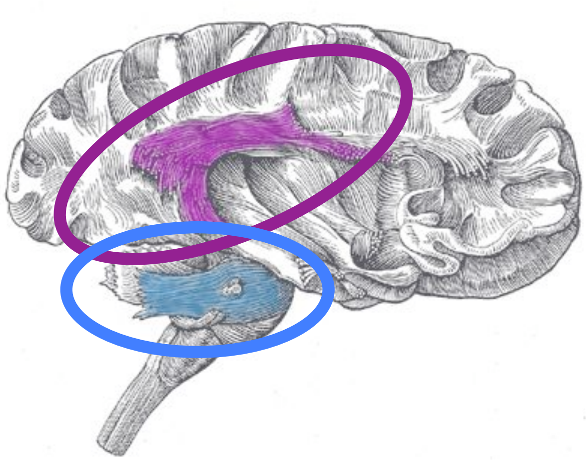
Lauren O'Donnell

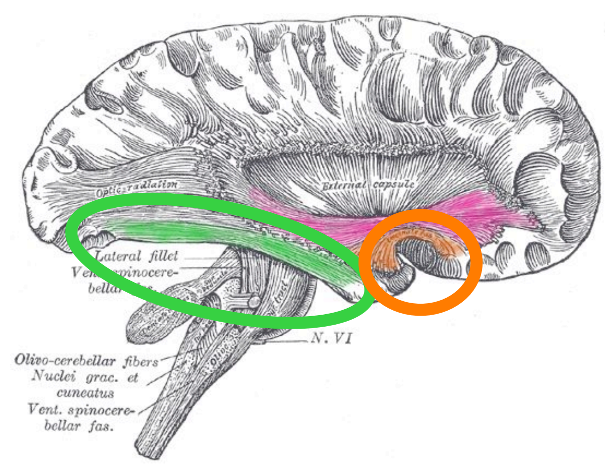
Golby Surgical Brain Mapping Laboratory

Harvard Medical School

Goal

- Analyze white matter within anatomically meaningful regions: fiber tracts

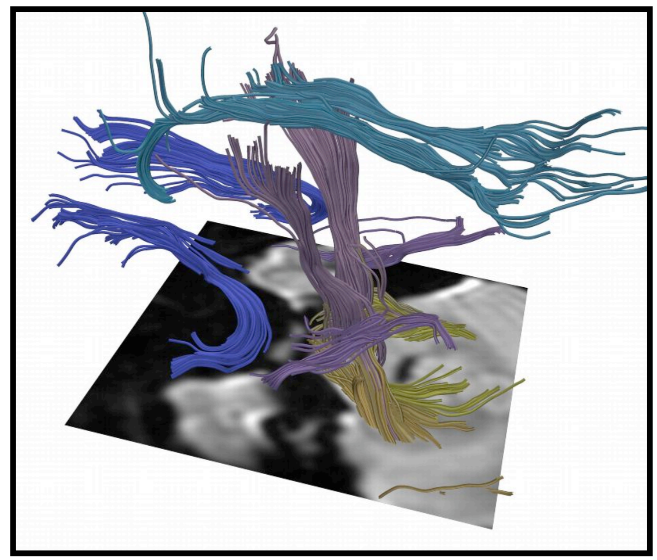




From Gray’s Anatomy

Approach

- Find white matter structures
  - Segmentation of tracts
- Quantitative analysis
  - Whole tracts
  - Along tracts



Outline

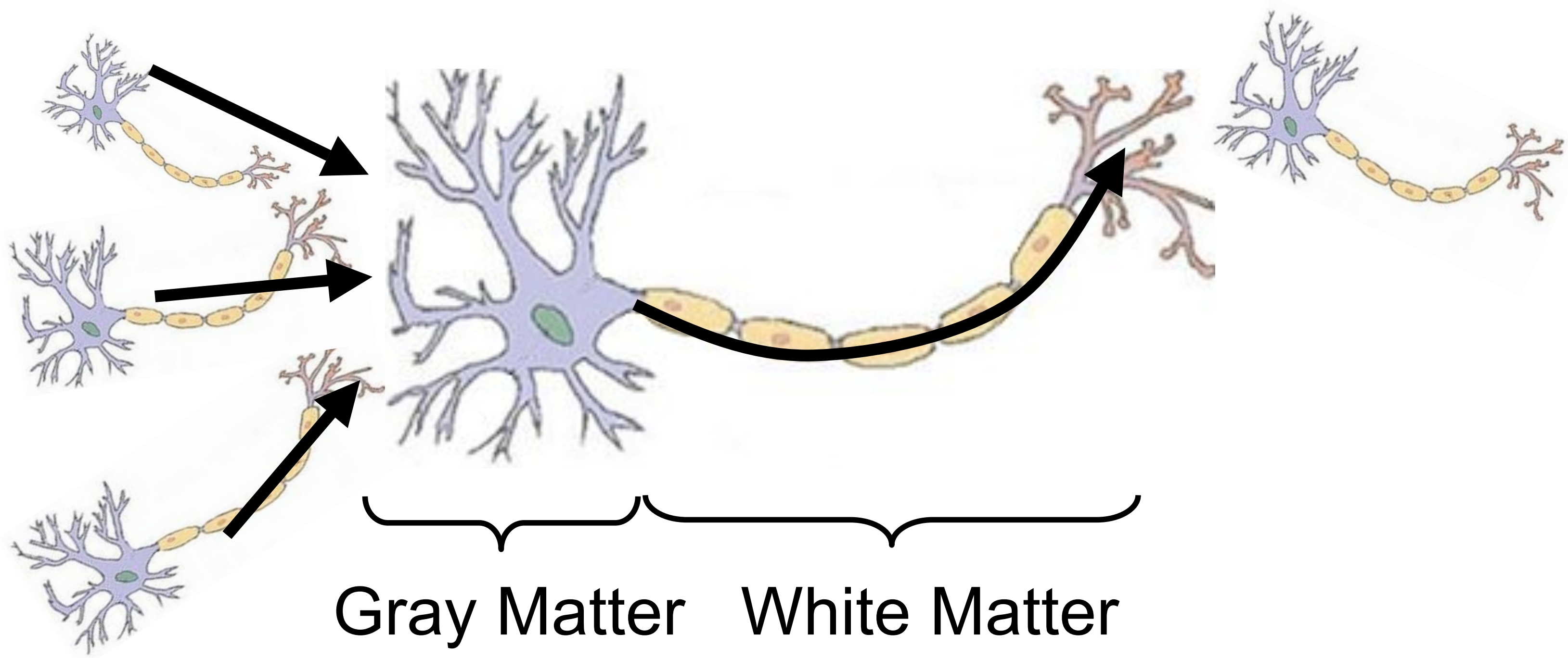
- White matter anatomy overview
- DTI overview
- White matter segmentation
  - Clustering and correspondence in groups
- Quantitative Analysis
  - Tract-based morphometry

Outline

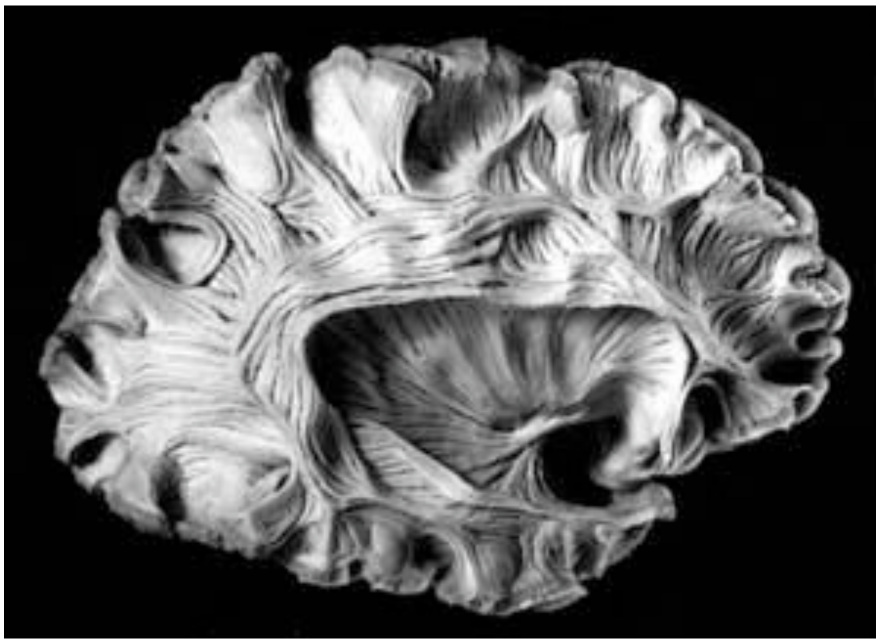
- **White matter anatomy overview**
- DTI overview
- White matter segmentation
  - Clustering and correspondence in groups
- Quantitative Analysis
  - Tract-based morphometry

White Matter

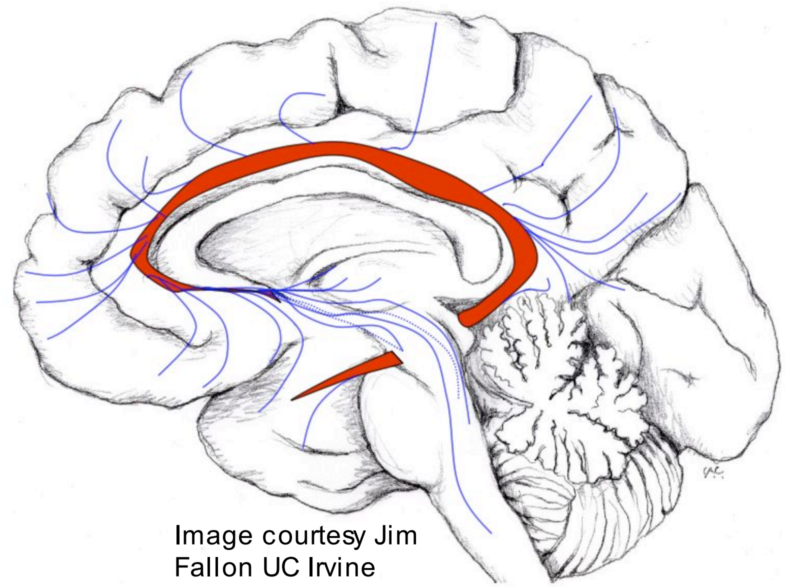
- Neurons send and receive information



White Matter Fiber Tracts

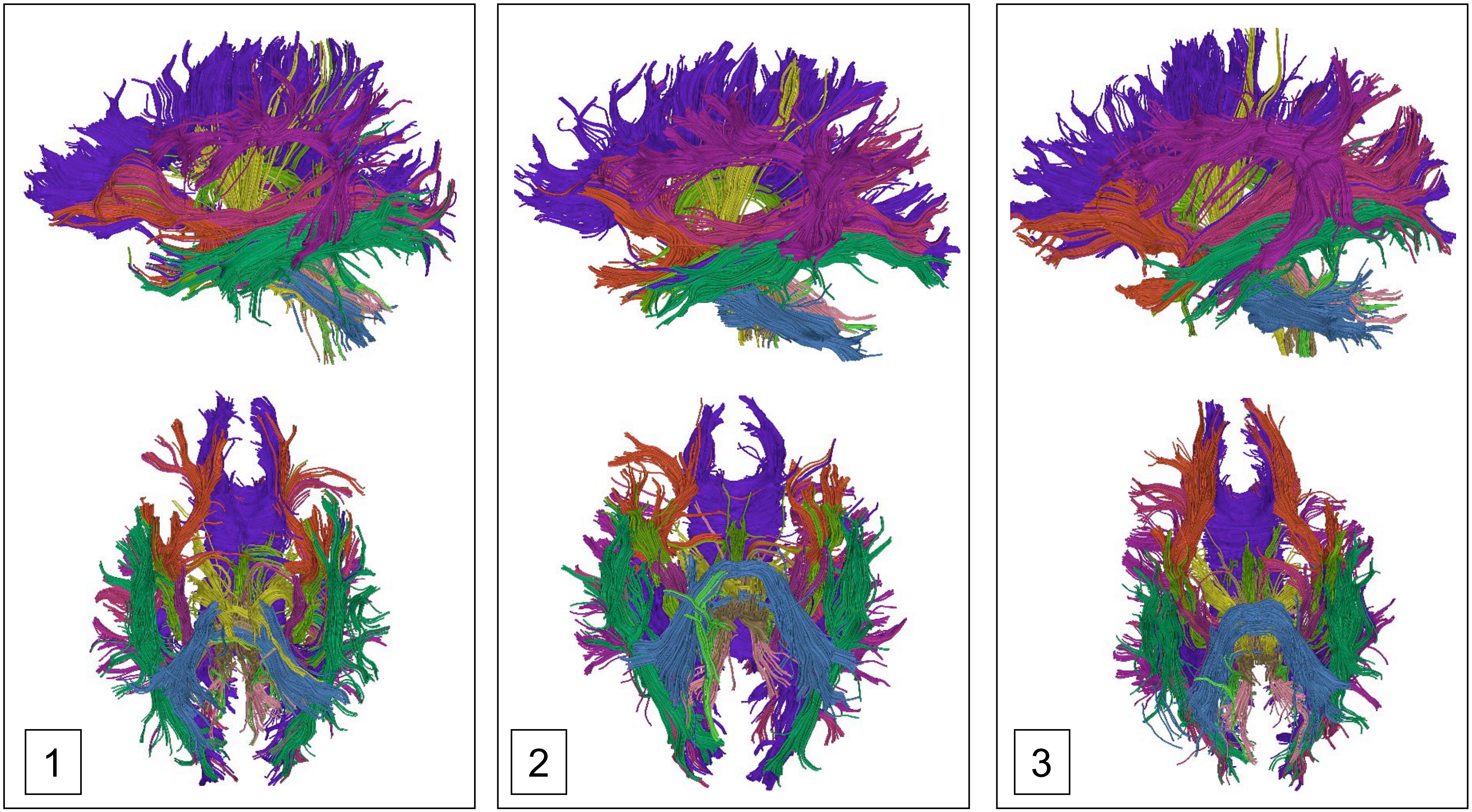


Elaborate white matter dissection



Example tract: cingulum bundle

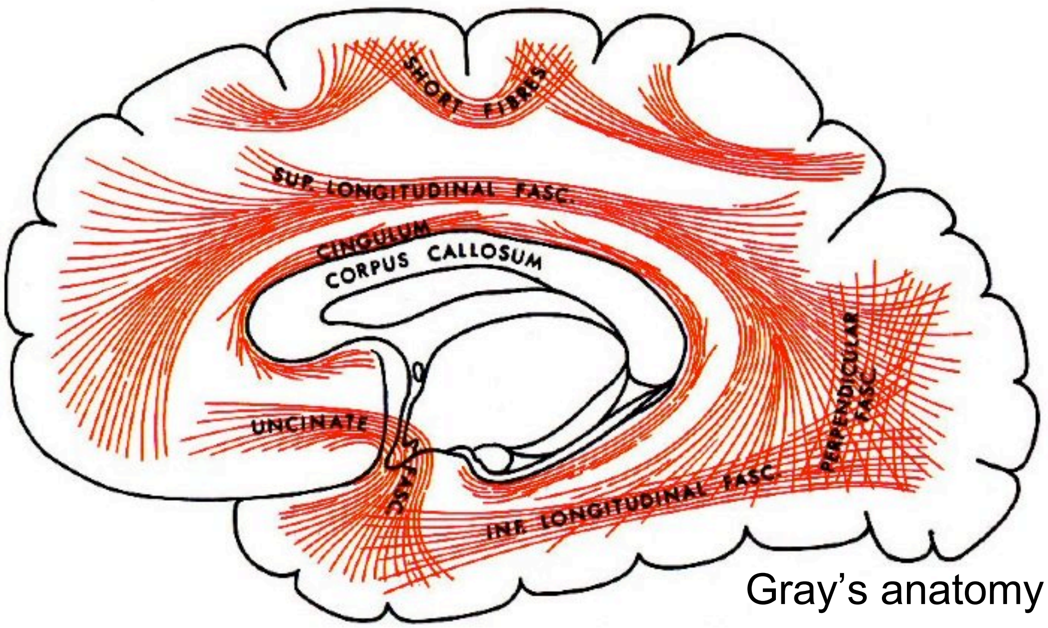
3D White Matter Segmentation



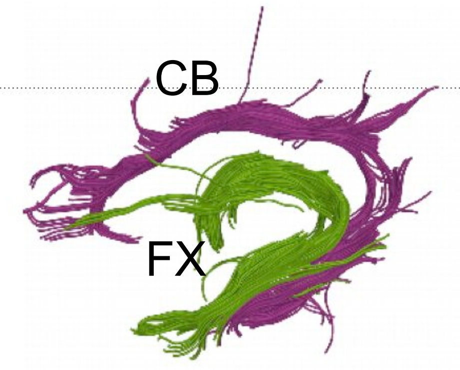
Fiber tract types

- Association
  - Cortical regions within one hemisphere
- Projection
  - Cortex to subcortical gray matter/spinal cord
- Commissural
  - Cortical regions in both hemispheres

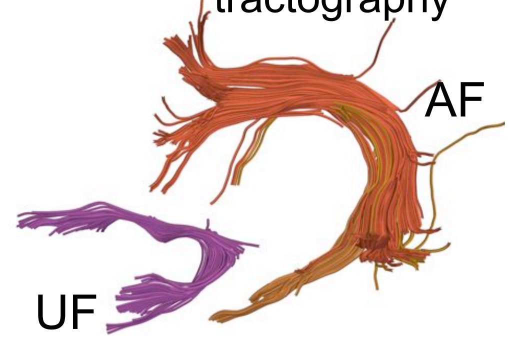
Association Tracts



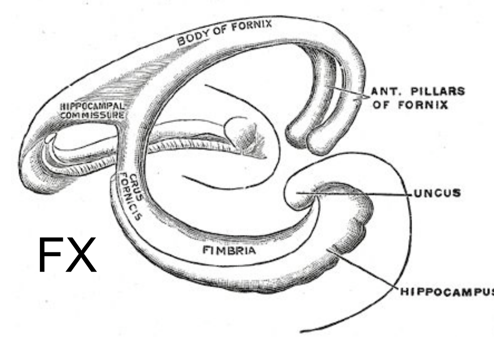
Gray's anatomy



tractography

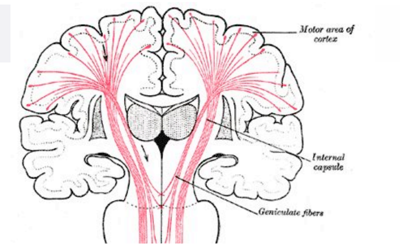


- uncinate fasciculus (UF)
- arcuate fasciculus (AF), SLF
- cingulum bundle (CB)
- fornix (FX)

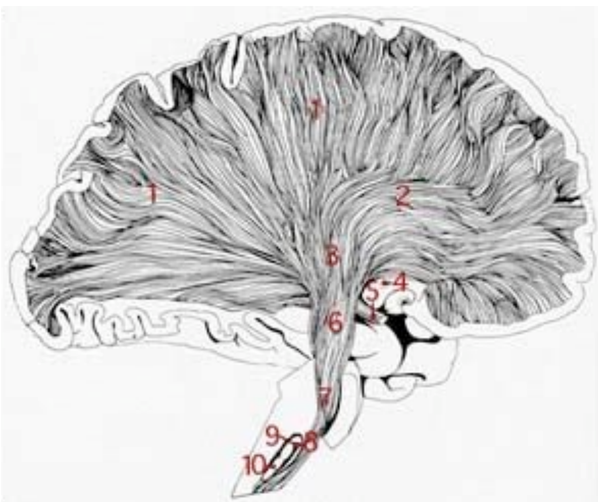


Gray's anatomy

Projection Tracts



Gray's anatomy
motor tract



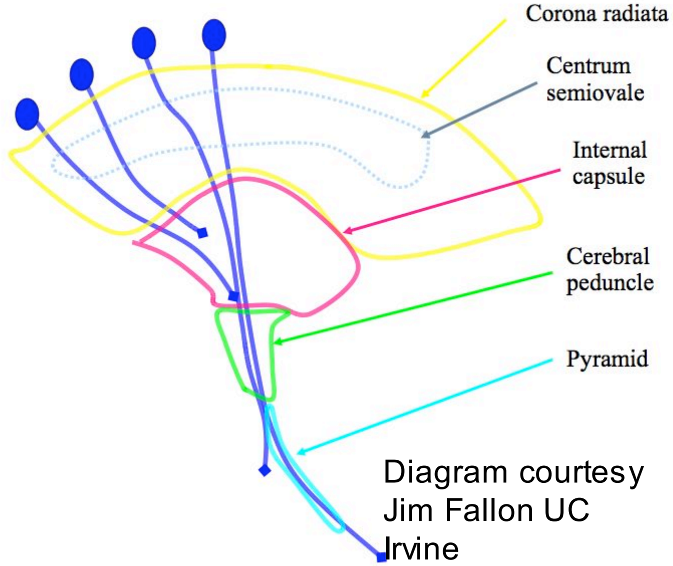
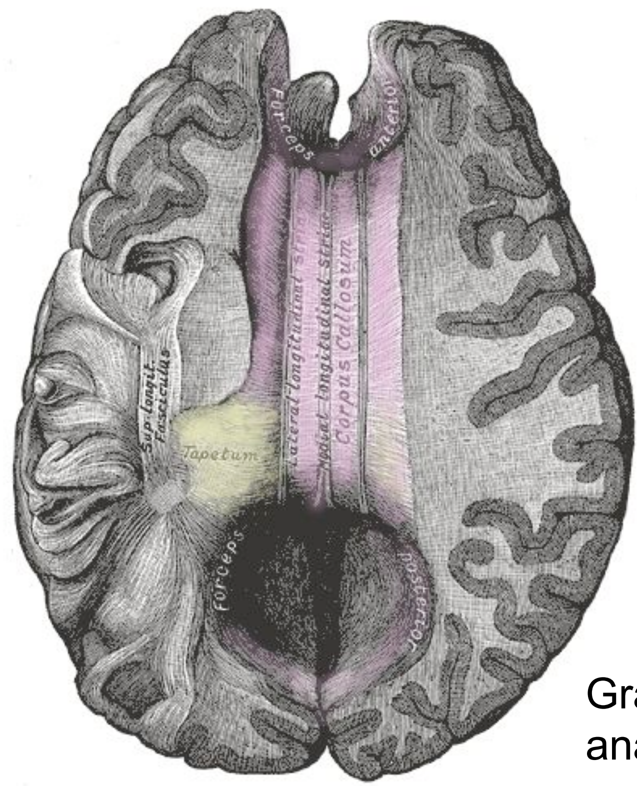


Diagram courtesy
Jim Fallon UC
Irvine

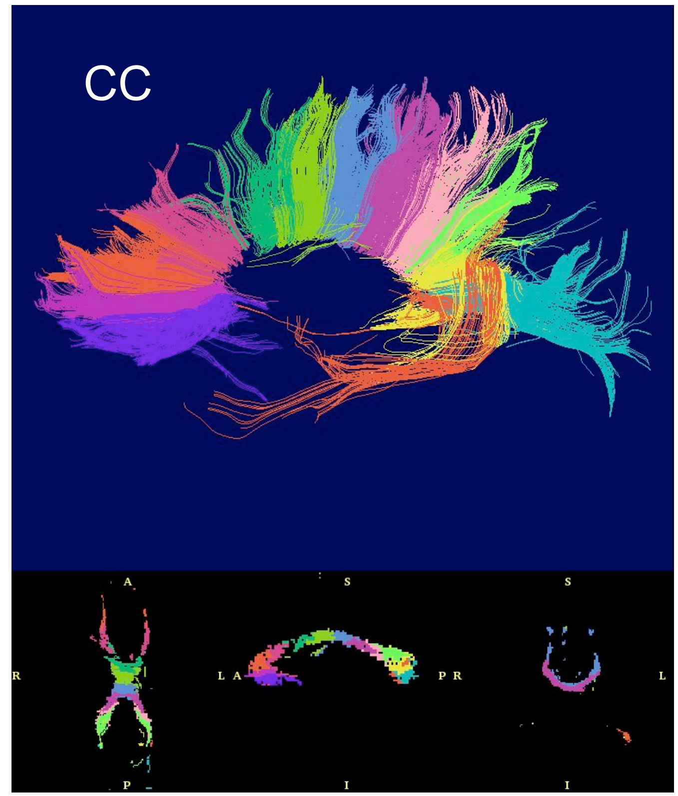
tractography

- motor tract
- thalamocortical connections

Commissural Tracts



Gray's anatomy



tractography

- corpus callosum (CC)
- anterior commissure

Outline

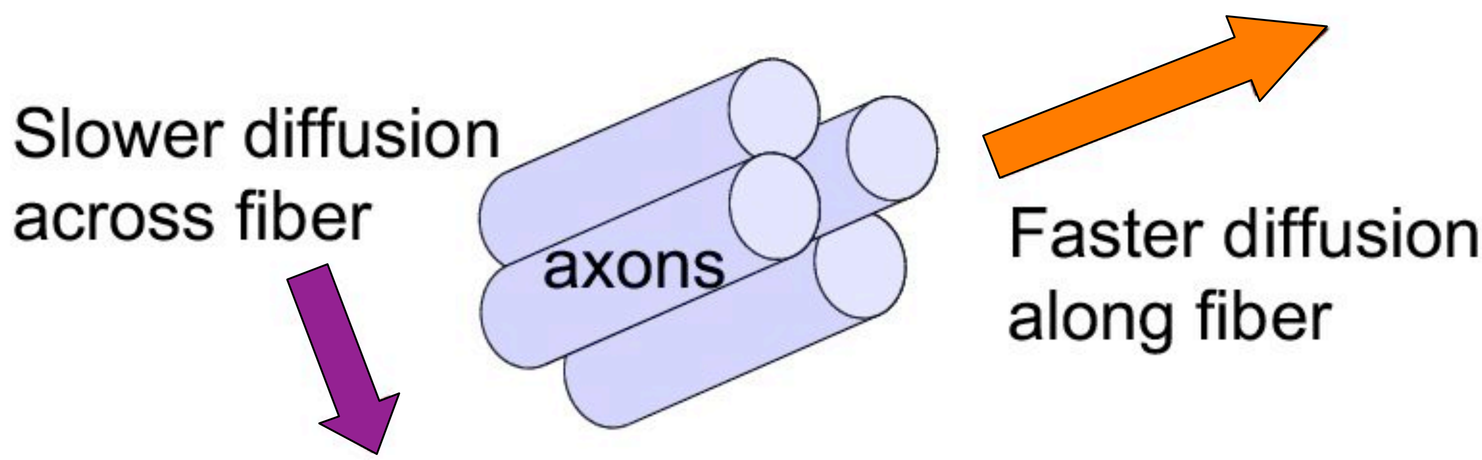
- White matter anatomy overview
- DTI overview
- White matter segmentation
  - Clustering and correspondence in groups
- Quantitative Analysis
  - Tract-based morphometry

Outline

- White matter anatomy overview
- **DTI overview**
- White matter segmentation
  - Clustering and correspondence in groups
- Quantitative Analysis
  - Tract-based morphometry

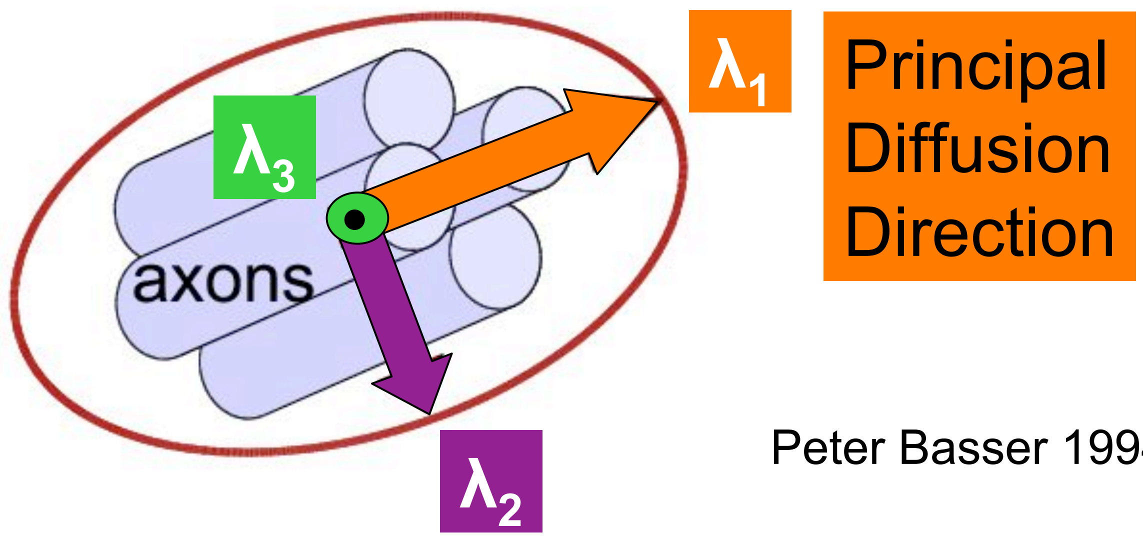
Diffusion MRI

- Measures water diffusion
  - Gives approximate fiber orientation



Diffusion Tensor MRI

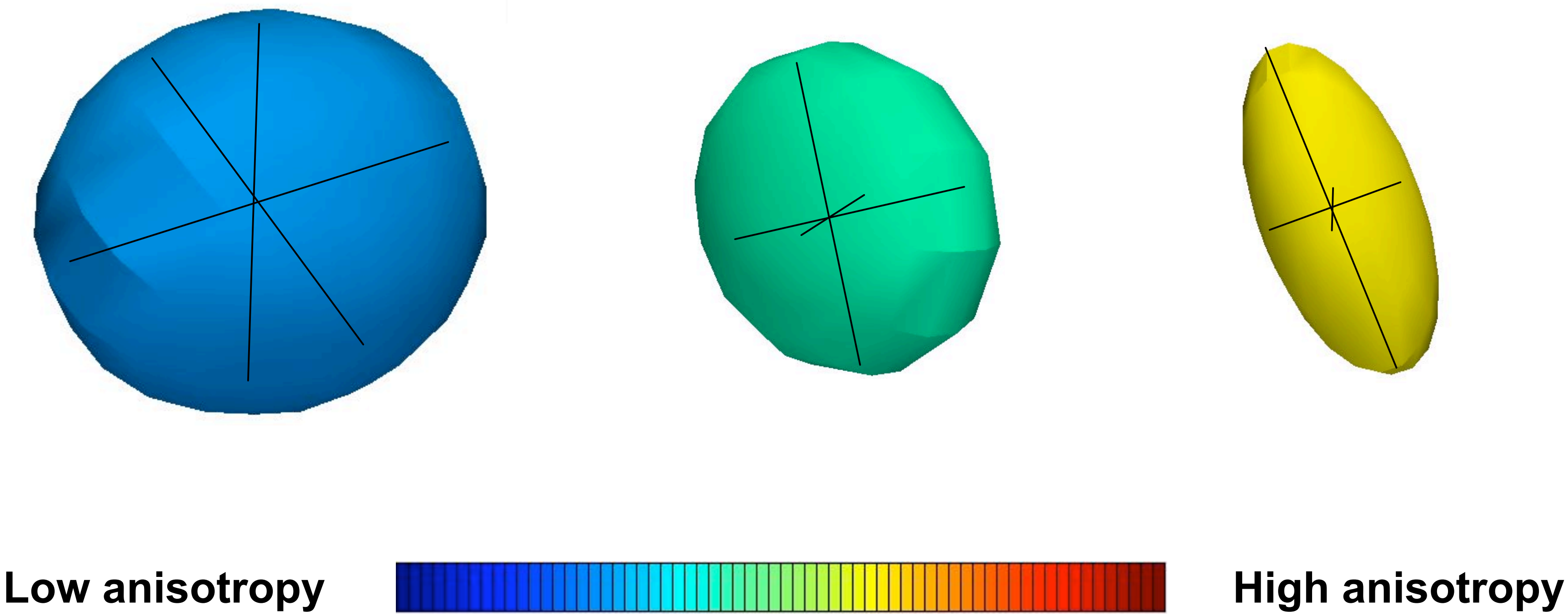
- Tensor model (Gaussian diffusion)
  - 3x3 symmetric, positive definite matrix



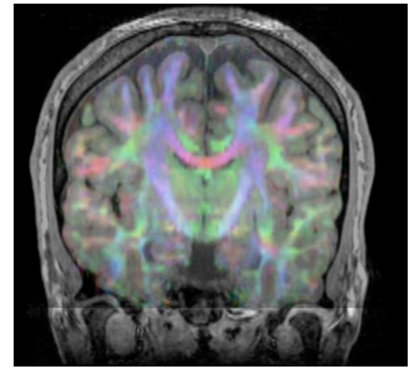
Peter Basser 1994

Diffusion Tensor MRI

- Diffusion shapes and magnitudes



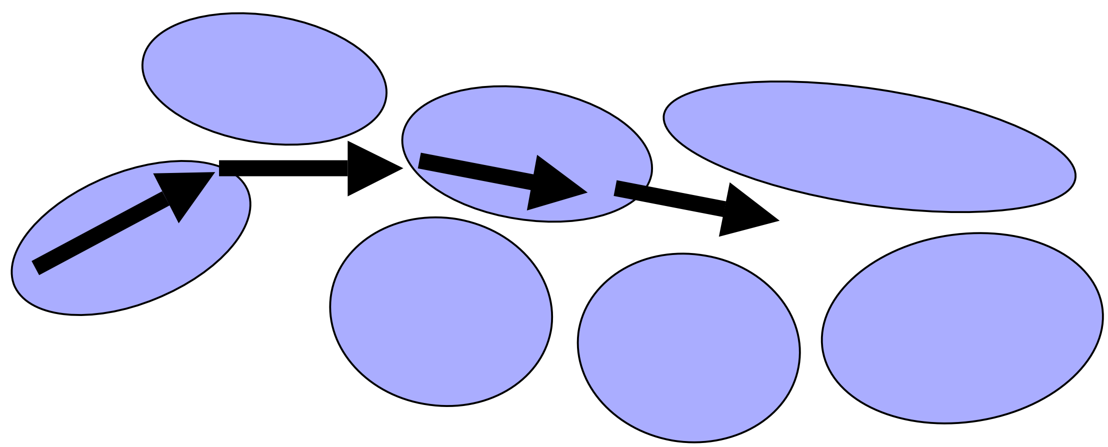
Diffusion Tensor MRI



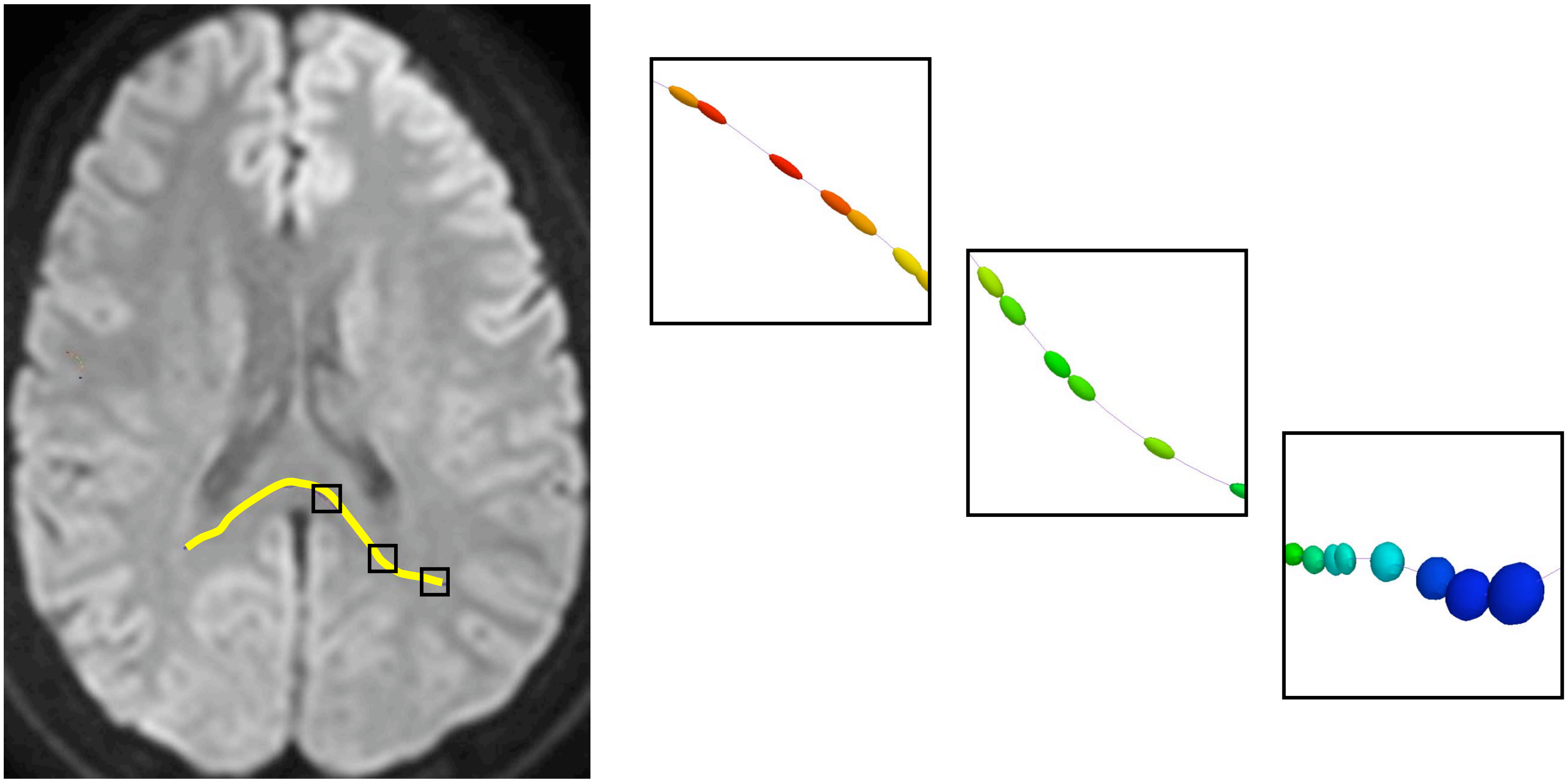
- Scalar invariants
  - Invariant to rotation/translation in MRI magnet
  - Quantify diffusion shapes and magnitudes
  - Used in clinical studies
  - Trace $$Tr = \lambda_1 + \lambda_2 + \lambda_3$$
  - Fractional anisotropy $$FA = \frac{1}{\sqrt{2}} \frac{\mathrm{var}(\lambda)}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$
    - How unlike a sphere?

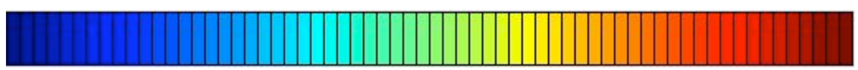
Tractography

- Estimate fiber trajectories in white matter
- Most common: Streamline method
  - Follow principal diffusion direction



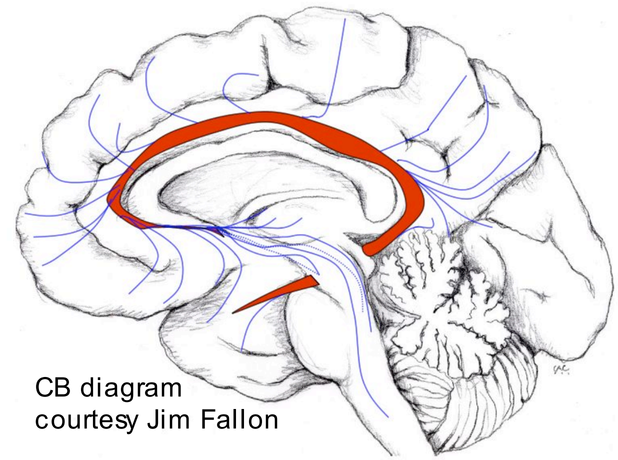
Tractography Example



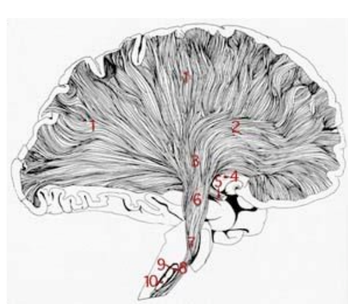
Low anisotropy  **High anisotropy**

Challenge/Caveat

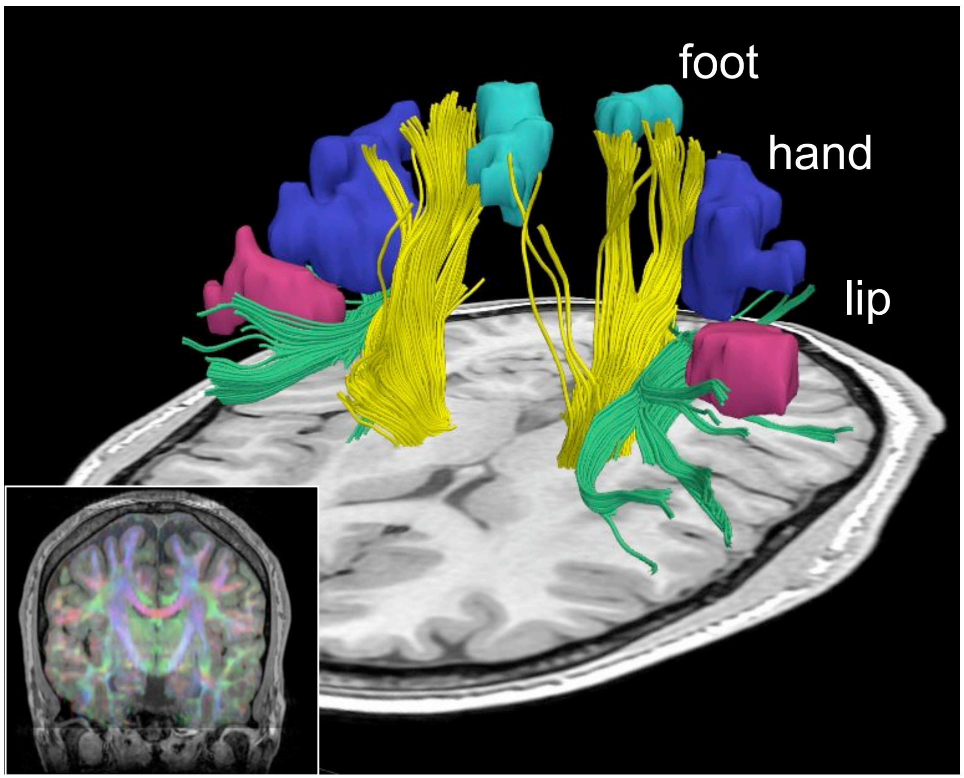
- Voxel size: mm
- Axon diameter: microns
- Single tensor model is insufficient
  - Crossing, fanning, bending
- Tractography methods are imperfect
  - Good for research…

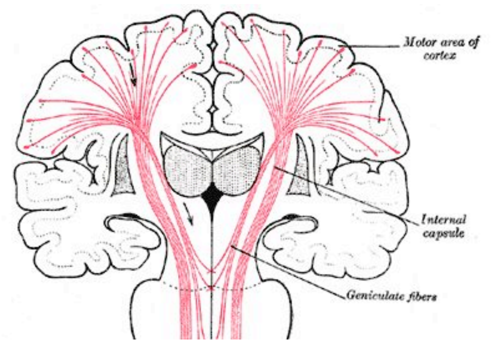


CB diagram
courtesy Jim Fallon

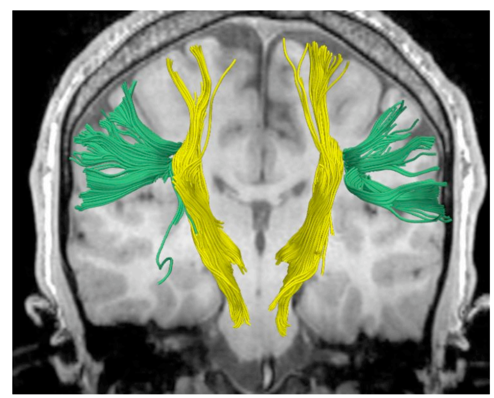


Challenge: Locate CST



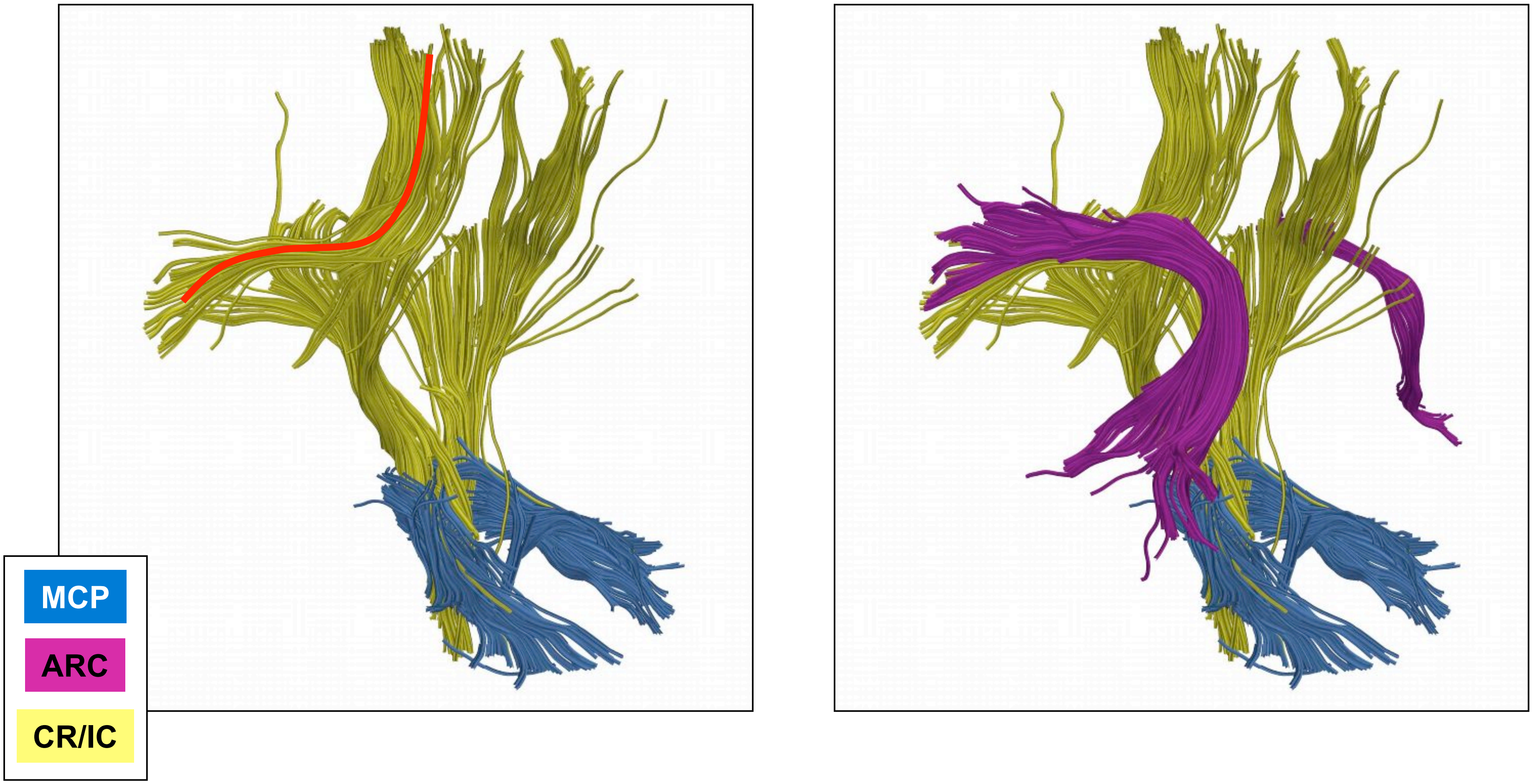


Corticospinal (Motor) Tract
Gray's Anatomy



Typical Streamline Tractography
One-Tensor Model Result

Challenge: Mixed Structures



Outline

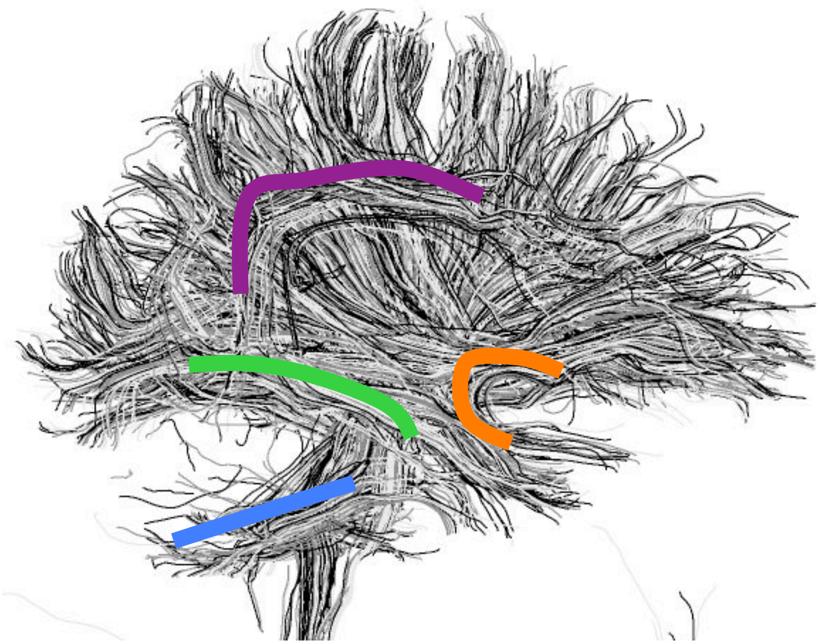
- White matter anatomy overview
- DTI overview
- White matter segmentation
  - Clustering and correspondence in groups
- Analysis along tracts
  - Tract-based morphometry

Outline

- White matter anatomy overview
- DTI overview
- **White matter segmentation**
  - Clustering and correspondence in groups
- Analysis along tracts
  - Tract-based morphometry

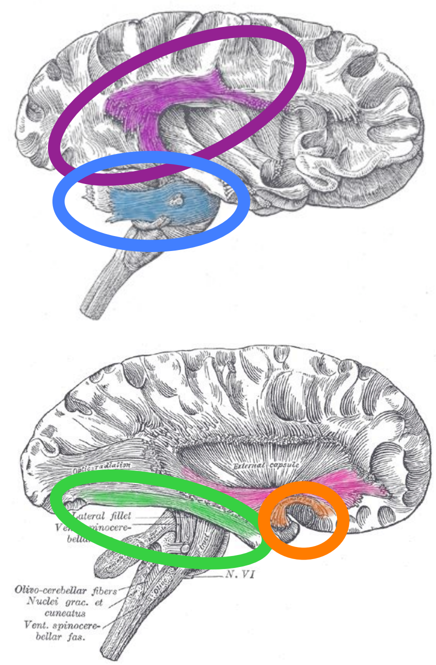
White Matter Segmentation

Processed diffusion MRI data



Whole-brain tractography input data

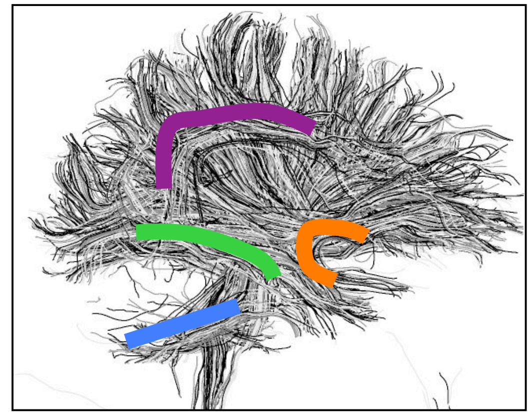
Meaningful brain regions



From Gray's Anatomy

White Matter Segmentation

- Tractography segmentation methods
- Interactive
  - "Virtual dissection" *(Catani Neuroimage 2002)*
  - Multiple region of interest *(Mori atlas 2005)*
- Automatic
  - Partial brain clustering
    - Hierarchical *(Corouge ISBI 2004, Gerig IEEE EMBS 2004)*
  - Whole brain clustering
    - Spectral *(Brun MICCAI 04)*
    - Matching across subjects *(Zhang ISMRM 2006)*
  - Anatomical labeling
    - White matter atlas *(Maddah MICCAI 05)*
    - Gray matter atlas *(Xia MICCAI 05)*

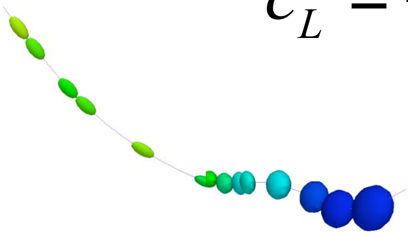


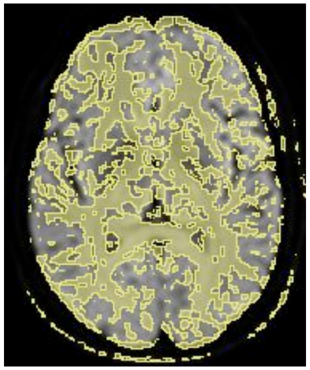
- **Learn tractography atlas from data…**

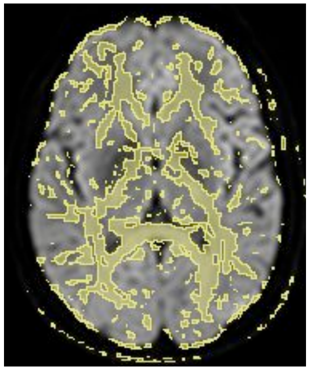
Whole-Brain Tractography

- Our input data
- 1,000's of trajectories
- Start and stop in white matter
  - use linear anisotropy

$$c_L = \frac{\lambda_1 - \lambda_2}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$



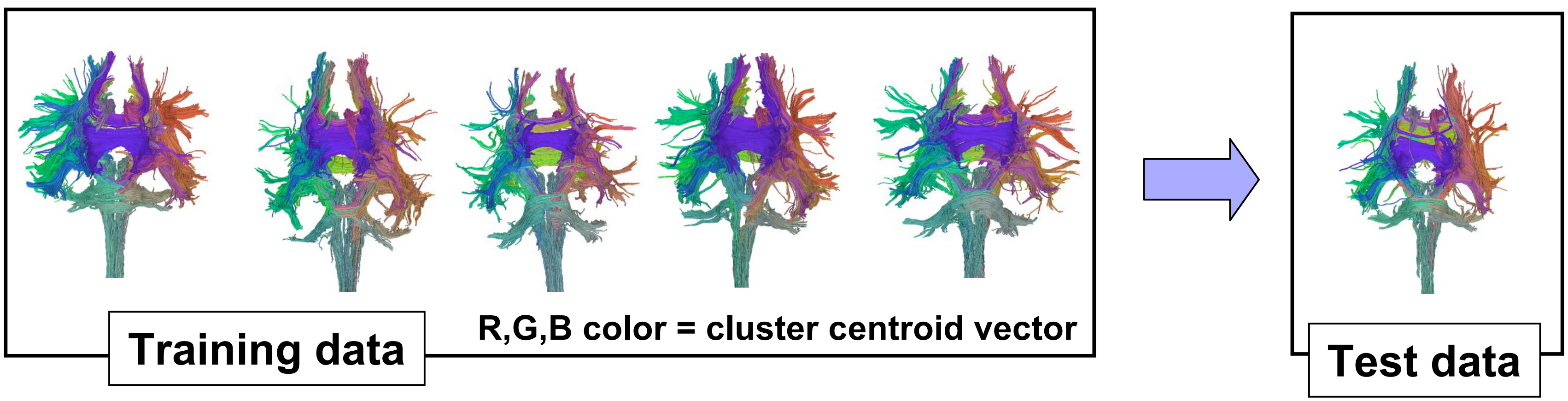




$c_L = 0.15$ 0.25

Atlas Generation

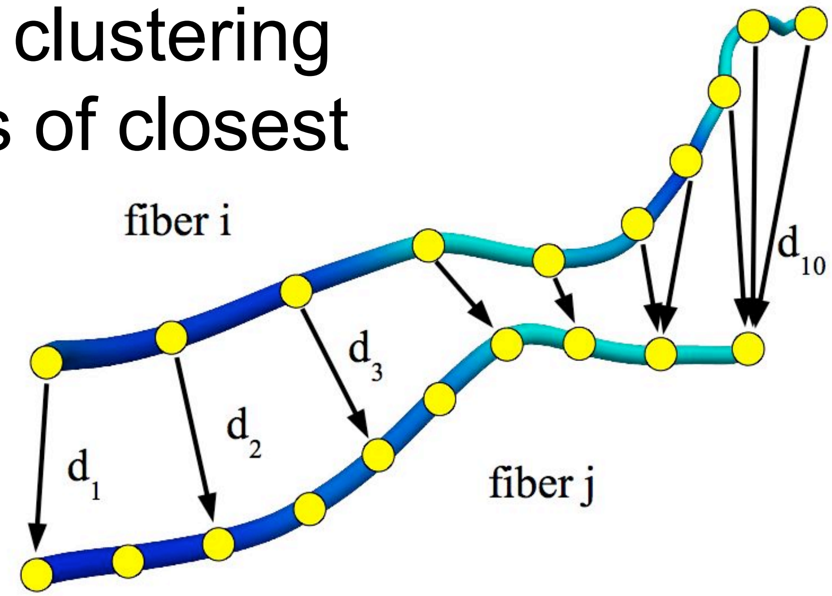
- Learn common structures
- Spectral clustering of all subjects (together)



Lauren O'Donnell and Carl-Fredrik Westin. Automatic Tractography Segmentation Using a High-Dimensional White Matter Atlas. IEEE Transactions in Medical Imaging 26(11):1562-1575, 2007

Fiber Affinity Measure

- Pairwise fiber affinity for clustering
- Distances between pairs of closest points



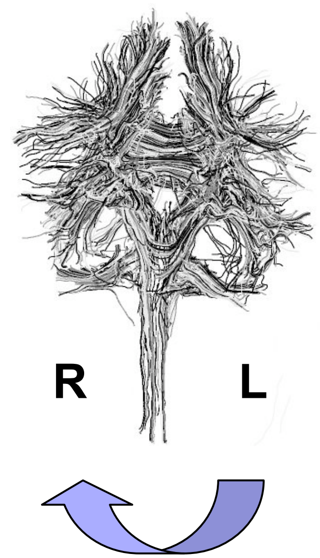
$$d_{ij} = \frac{1}{N}\sum_{n=1}^{N} d_n$$

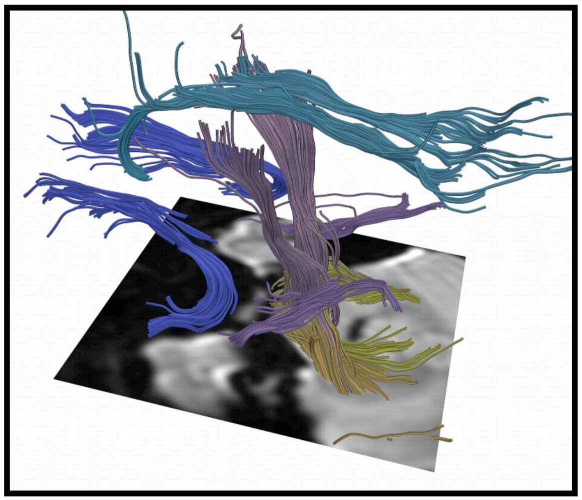
1. Directed distances (i->j and j->i)
2. Symmetrize: choose minimum
3. Convert to affinity with Gaussian kernel

$$\mathbf{A}_{ij} = e^{-d_{ij}^2/\sigma^2}$$

Bilateral Affinities

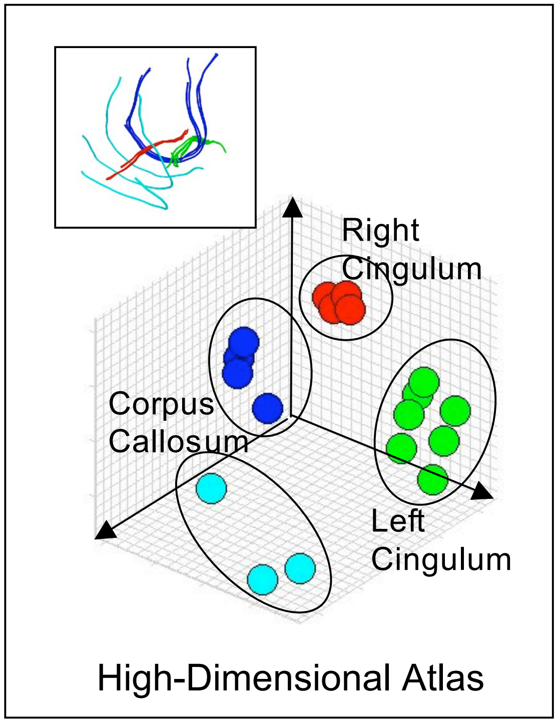
- Find structures in both hemispheres
- For each fiber, compute distance
  - To all fibers
  - To all fibers after reflection of brain across midsagittal plane
- For each pair of fibers, use minimum of 4 possible distances
- Convert to affinity with Gaussian kernel





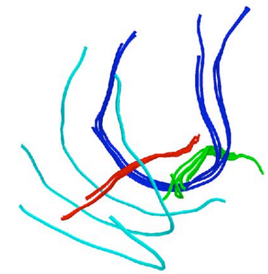
Atlas Generation Example

- Calculate affinities
- Spectral embedding
  - Eigenvectors of affinity matrix
  - Each fiber is a point
- Clustering
  - Atlas holds cluster centroids
- Add semantic labels



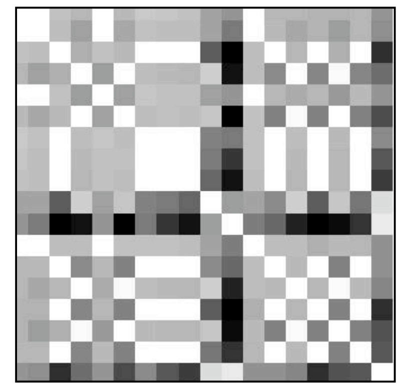
Lauren O'Donnell and Carl-Fredrik Westin. Automatic Tractography Segmentation Using a High-Dimensional White Matter Atlas. IEEE Transactions in Medical Imaging 26(11):1562-1575, 2007

Atlas Generation



1. Tractography
2. Trajectory distance
3. **Trajectory affinity**
4. Eigenvectors
5. Embedding
6. K-Means
7. Cluster labels

$$\mathbf{A}_{ij} = e^{-d_{ij}^2 / \sigma^2}$$

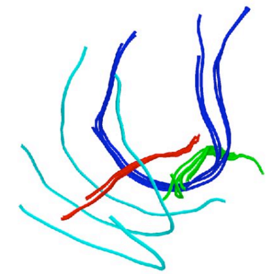


Pairwise affinity matrix A (from small example)

Each trajectory is represented by its affinities to all other trajectories.

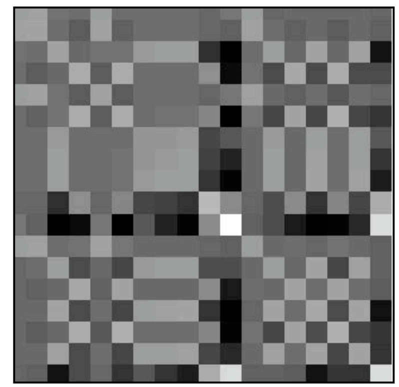
Steps 3-6 are known collectively as spectral clustering.

Atlas Generation



1. Tractography
2. Trajectory distance
3. **Trajectory affinity**
4. Eigenvectors
5. Embedding
6. K-Means
7. Cluster labels

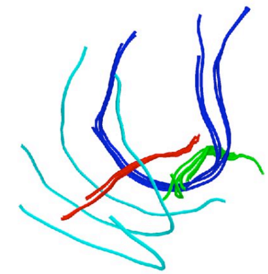
$$\mathcal{A} = \mathbf{D}^{-\frac{1}{2}}\mathbf{A}\mathbf{D}^{-\frac{1}{2}}$$



Normalized pairwise affinity matrix $\mathcal{A}$

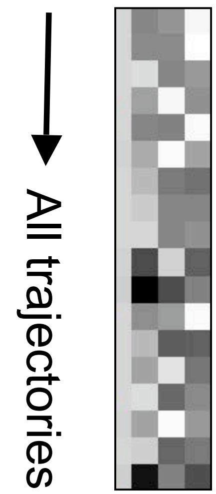
Matrix normalization.
Each entry is divided by square root of row and column sums.
Effect: avoid singleton clusters.

Atlas Generation



1. Tractography
2. Trajectory distance
3. Trajectory affinity
4. **Eigenvectors**
5. Embedding
6. K-Means
7. Cluster labels

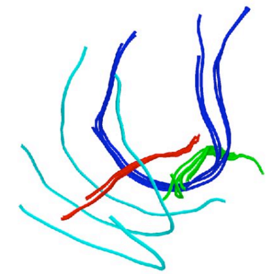
$$\mathcal{A} = \mathbf{U}\boldsymbol{\Lambda}\mathbf{U}^T$$



Top 4 eigenvectors of $\mathcal{A}$

Fowlkes, Belongie, Chung and Malik.
Spectral grouping using the Nystrom method. PAMI 2004

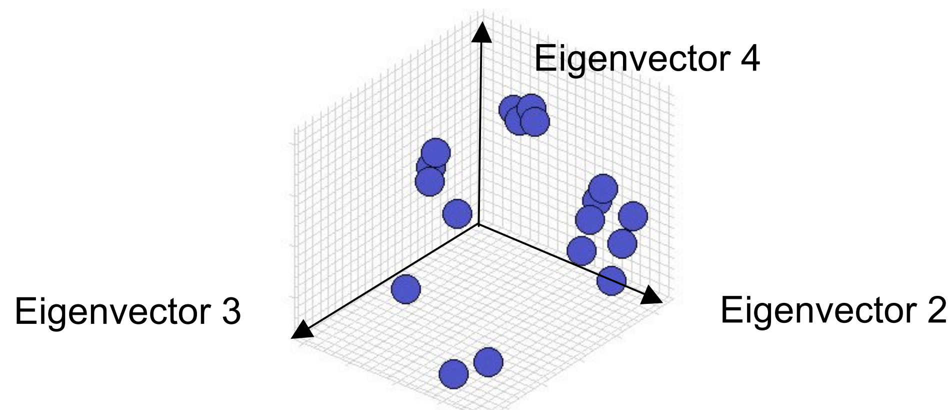
Atlas Generation



1. Tractography
2. Fiber distance
3. Trajectory affinity
4. Eigenvectors
5. **Embedding**
6. K-Means
7. Cluster labels

Use rows of eigenvector matrix to embed.

$$E_j = \frac{1}{\sqrt{D_{jj}}}(\bar{U}_{j,2}, \bar{U}_{j,3}, \ldots, \bar{U}_{j,n})$$

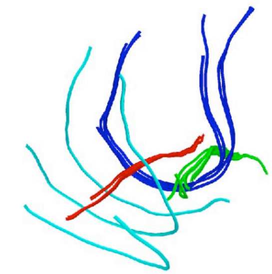


Embedding Space

Each trajectory is a point.

Row of eigenvector matrix U is projection of one fiber's normalized affinities (row of $\mathcal{A}$) onto basis $U\Lambda^{-1}$.

Atlas Generation

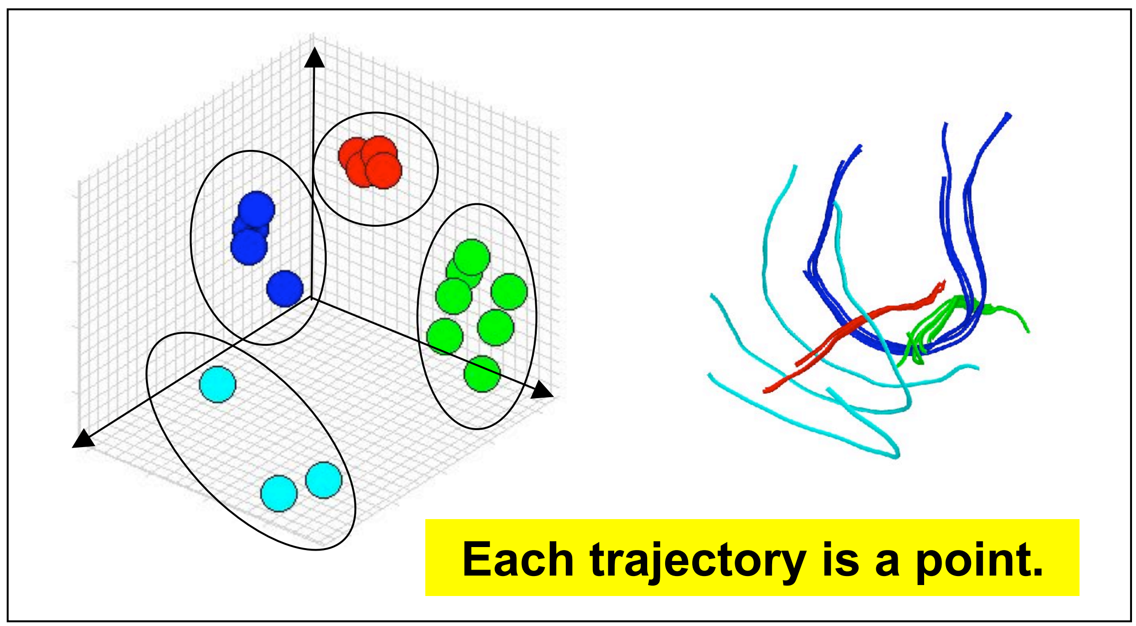


1. Tractography
2. Fiber distance
3. Trajectory affinity
4. Eigenvectors
5. Embedding
6. **K-Means**
7. Cluster labels

Find clusters in embedding space.

$$\Phi(\text{clusters,data}) = \sum_{i\in \text{clusters}} \left[\sum_{j\in i\text{th cluster}} (\mathbf{x}_j - \mathbf{c}_i)^T (\mathbf{x}_j - \mathbf{c}_i) \right]$$

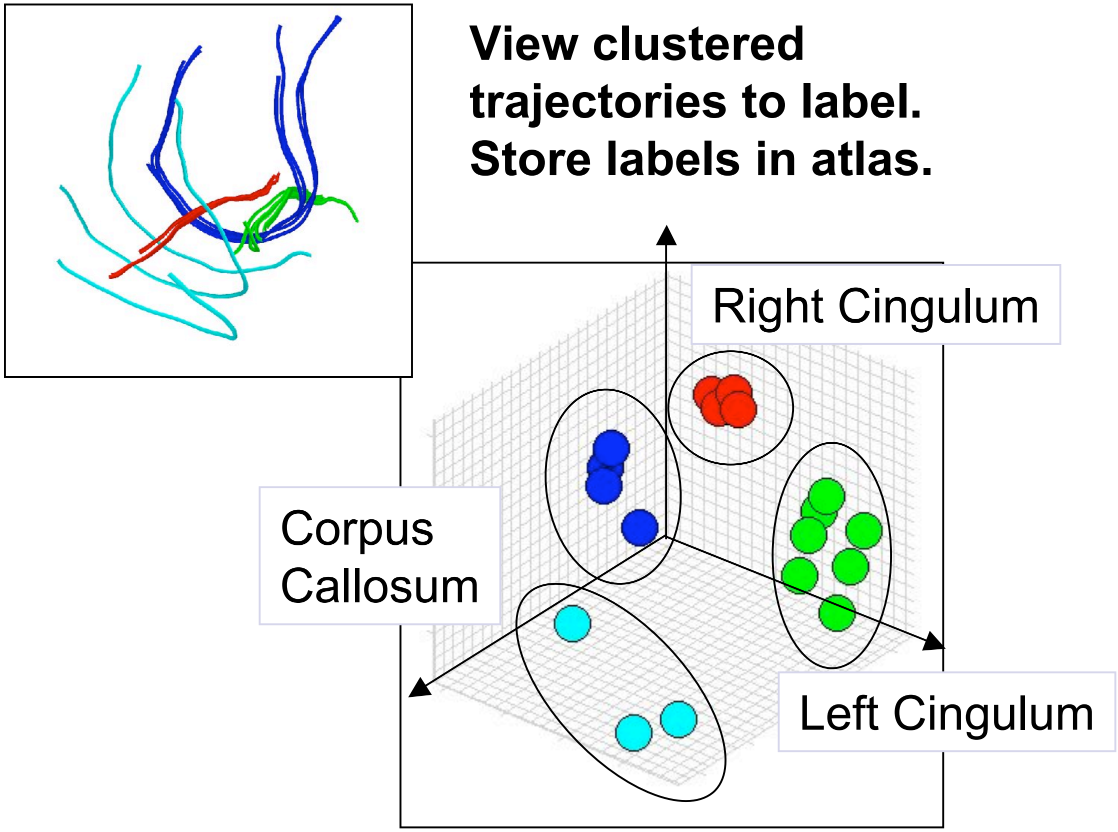
Minimize sum of point-to-cluster-centroid distances.



Atlas Generation

1. Tractography
2. Fiber distance
3. Trajectory affinity
4. Eigenvectors
5. Embedding
6. K-Means
7. **Cluster labels**

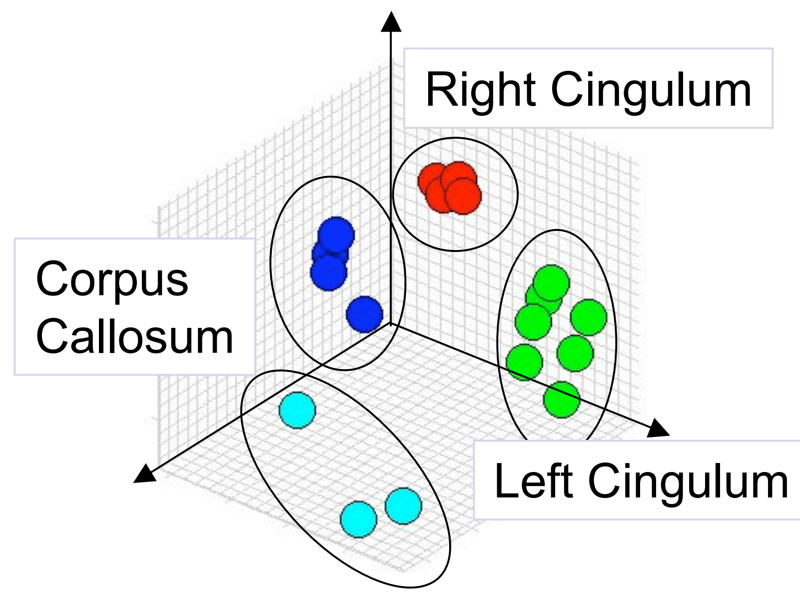
View clustered trajectories to label. Store labels in atlas.



Each trajectory is a point.

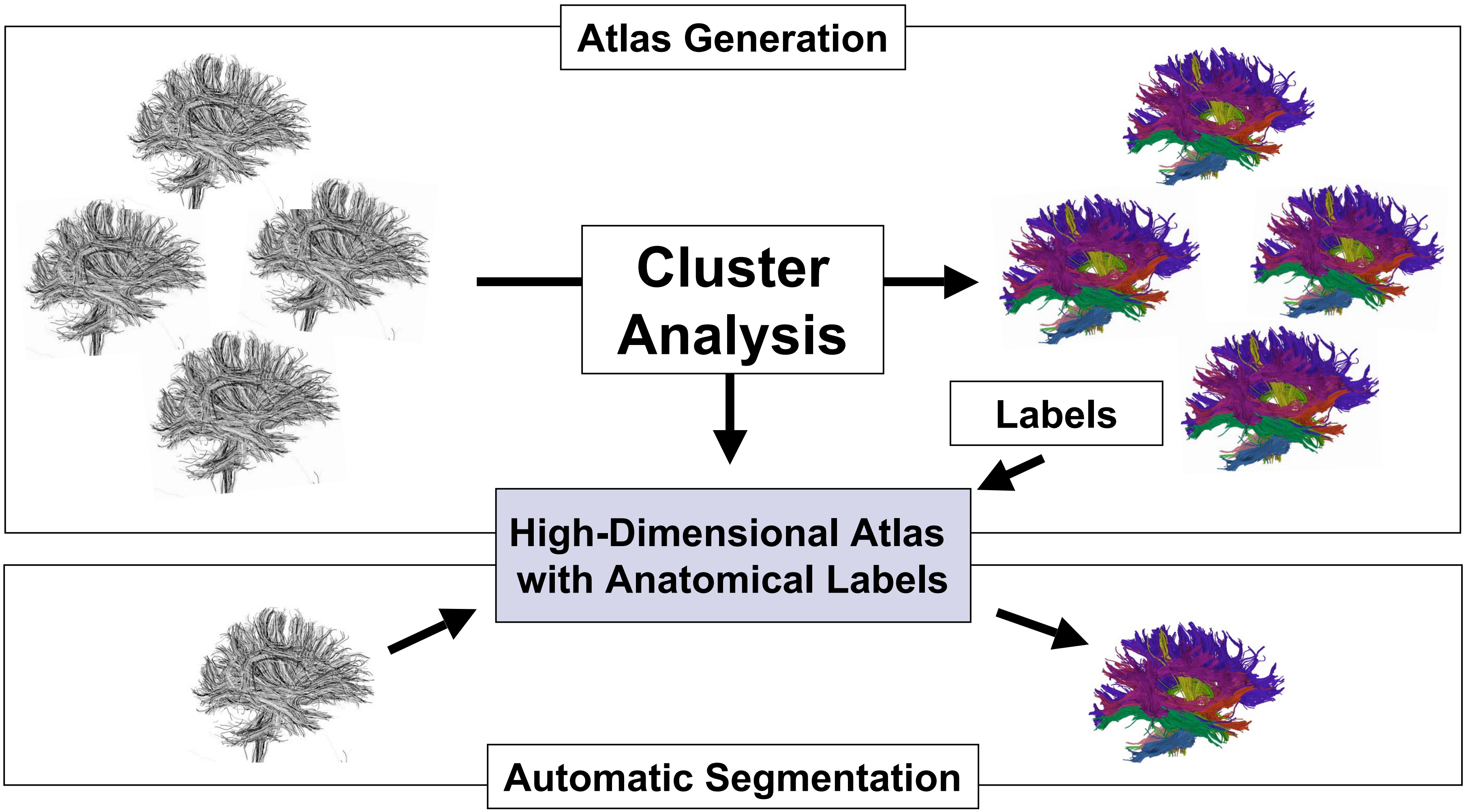
High-Dimensional Atlas

- In embedding space
  - Contains cluster centroids
  - Contains anatomical names
- High-dimensional
  - 10-20 dimensions
    - 2^{nd} to 21^{st} Eigenvectors
  - Not a voxel atlas
- Created using many subjects
  - Need Nystrom method
- Allows automatic segmentation…
  - Affinity computation to subset
  - Embed new trajectories
  - Gives clusters and labels



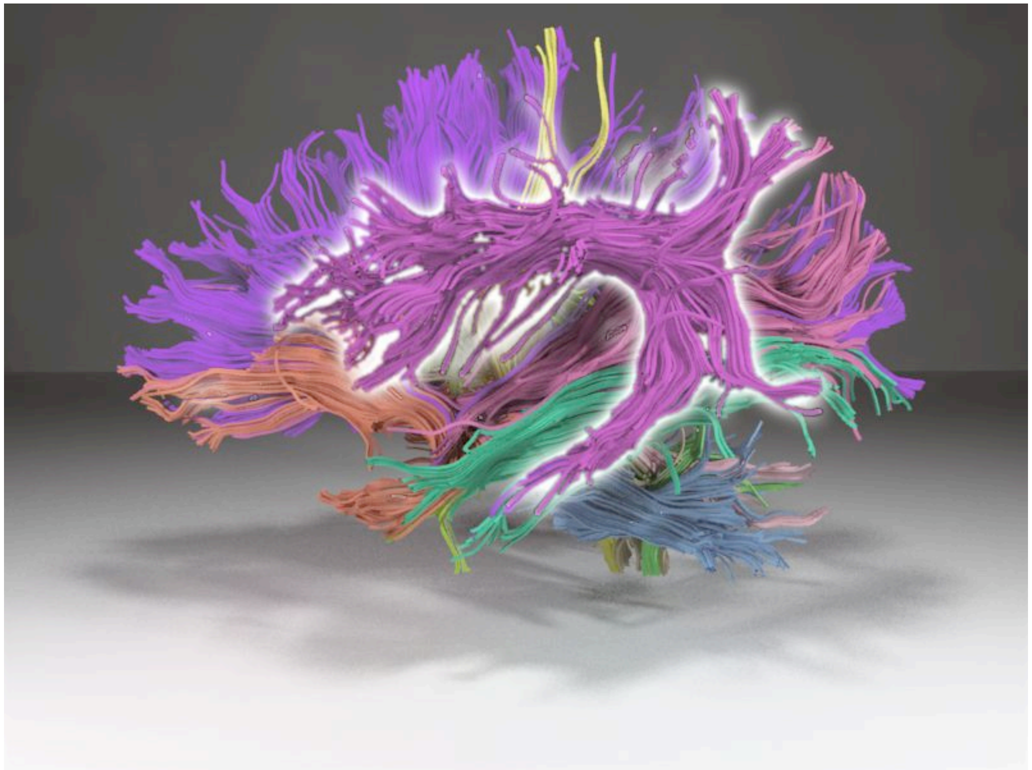
"Toy" example atlas
(Using only 3 dimensions)

High-Dimensional Atlas Pipeline



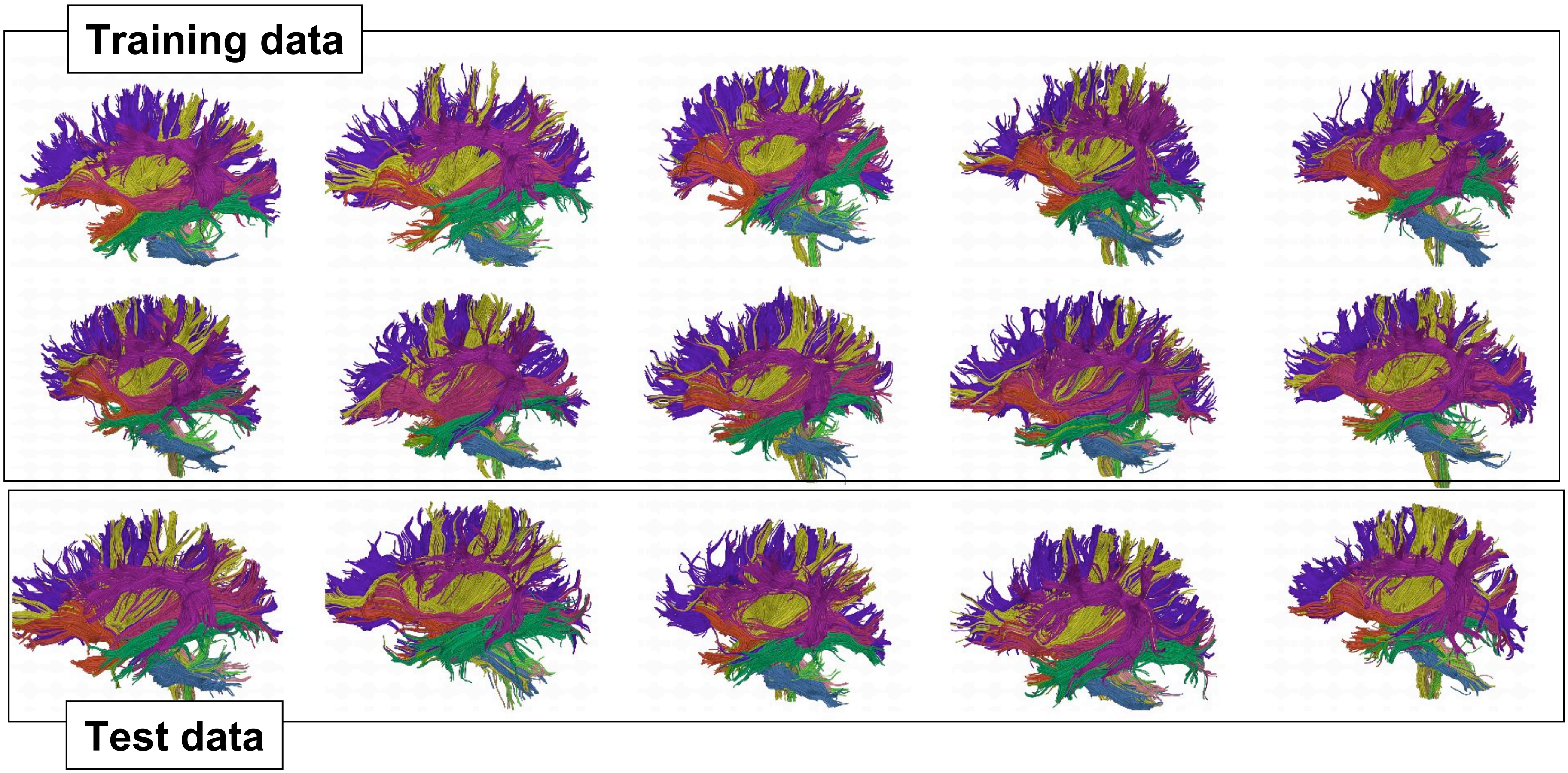
Anatomical Structures in Atlas

CC
IOFF
OTF
MCP
UNC
ARC
SCP
CR/IC

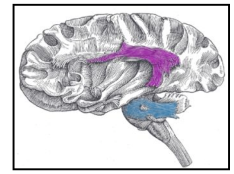


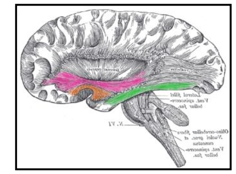
Rendered by Dr. David Banks, FSU

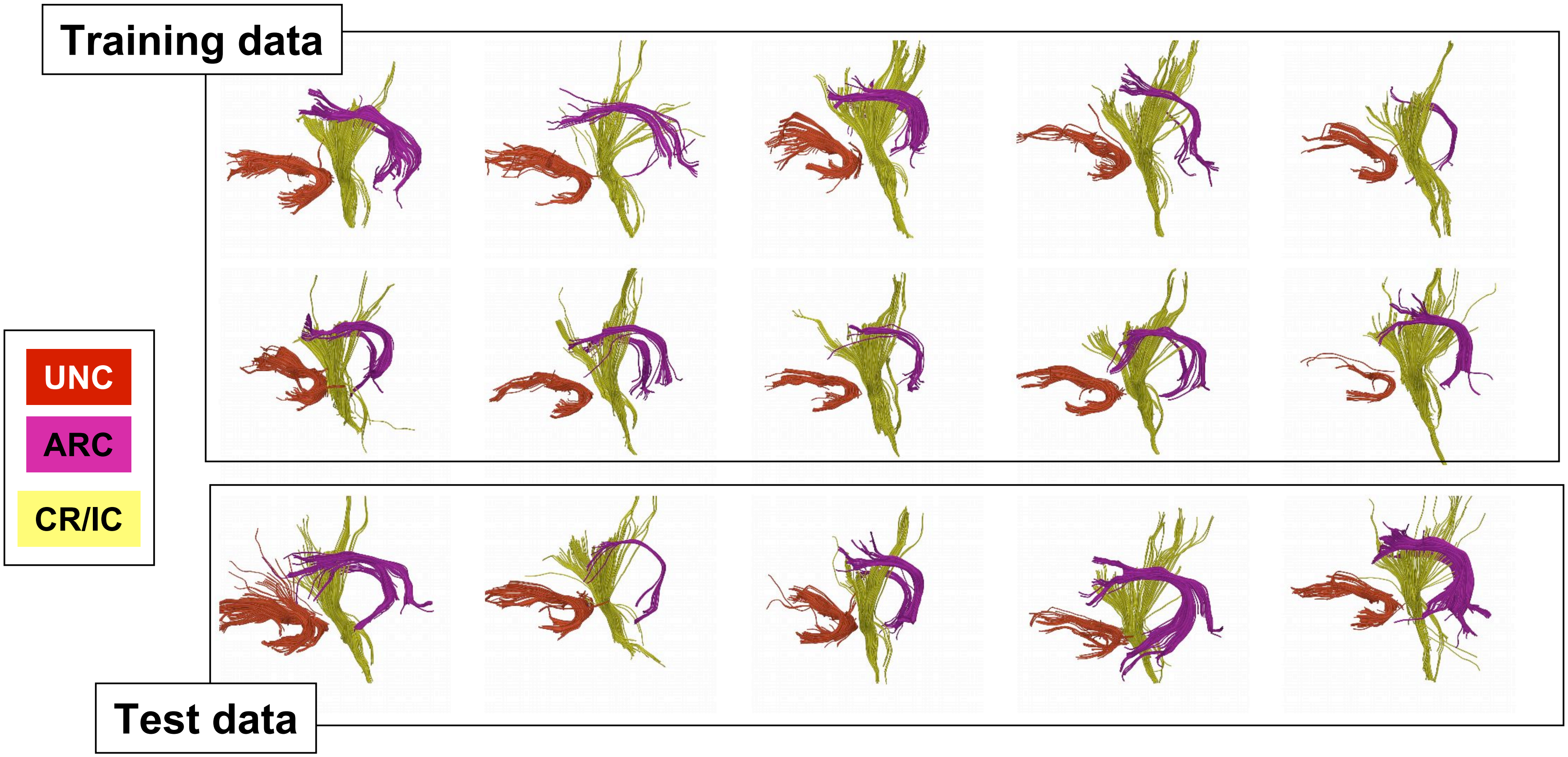
Automatic Segmentation



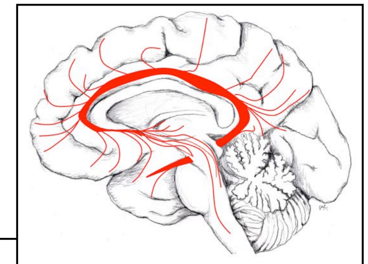
Arcuate and Uncinate

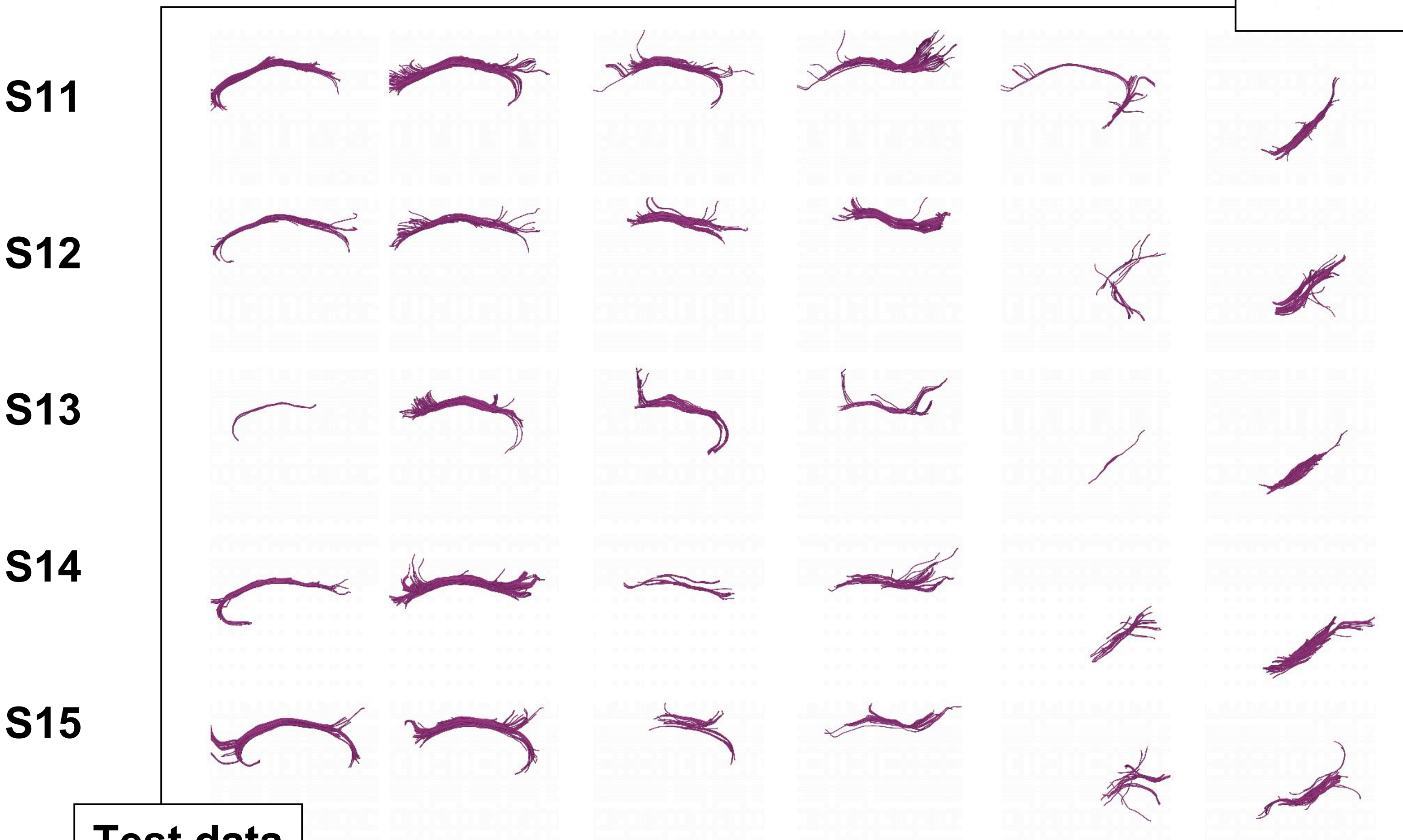






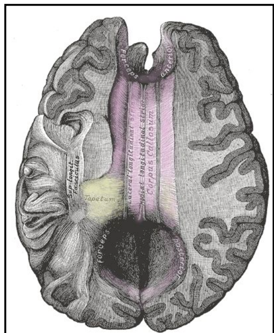
Cingulum Clusters



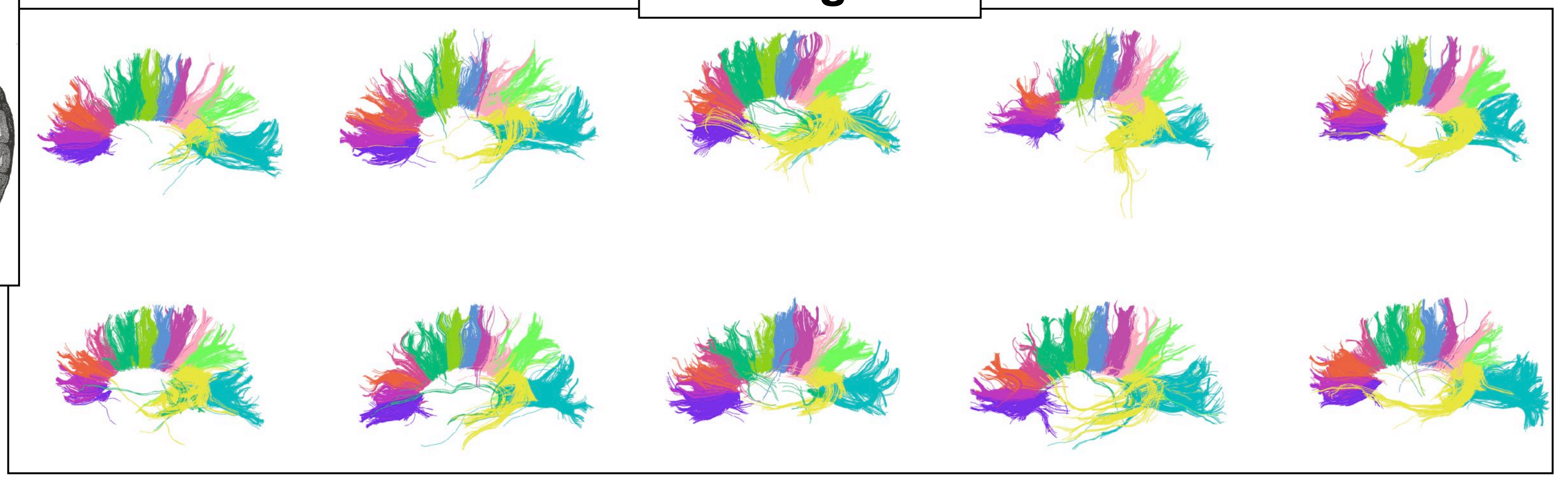


Test data

Corpus Callosum Subdivision



Training data



Test data

Unsupervised method for learning CC divisions.

Outline

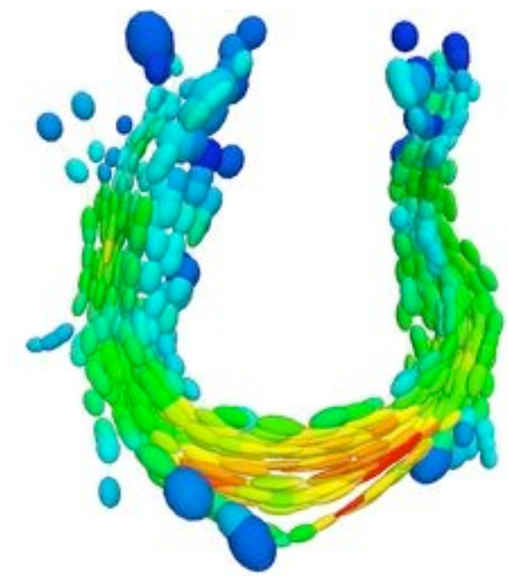
- White matter anatomy overview
- DTI overview
- White matter segmentation
  - Clustering and correspondence in groups
- Quantitative analysis
  - Tract-based morphometry

Outline

- White matter anatomy overview
- DTI overview
- White matter segmentation
  - Clustering and correspondence in groups
- **Quantitative analysis**
  - Tract-based morphometry

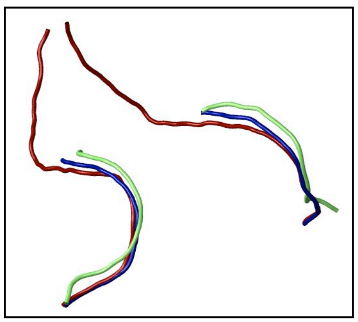
Tract-Based Morphometry

- Diffusion varies along tracts
  - Neuroanatomy
    - Crossing fibers, CSF
  - Pathology
    - Tumor infiltration
- Study diffusion along tracts
  - Gerig, Goodlet, Corouge
  - Maddah
  - O'Donnell MICCAI 2007

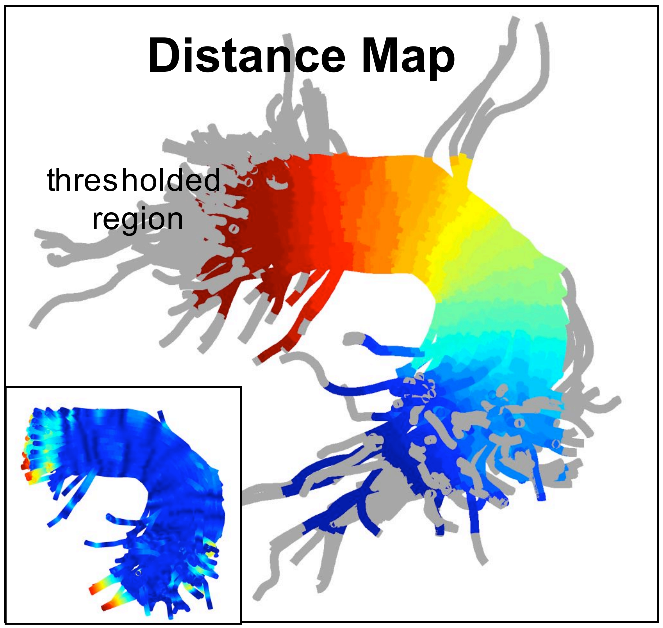


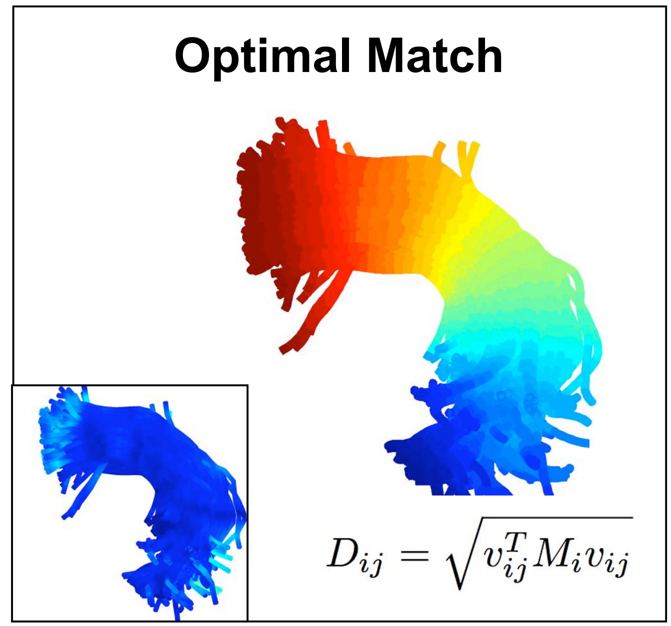
Coordinate System Generation

- Match all subjects' fiber points to prototype



Bilateral Prototypes:
Arc Length
Correspondence
In Rhem and LHem

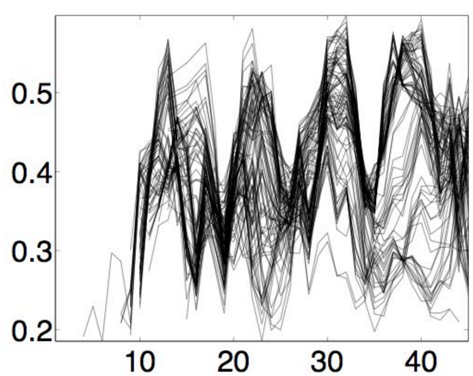




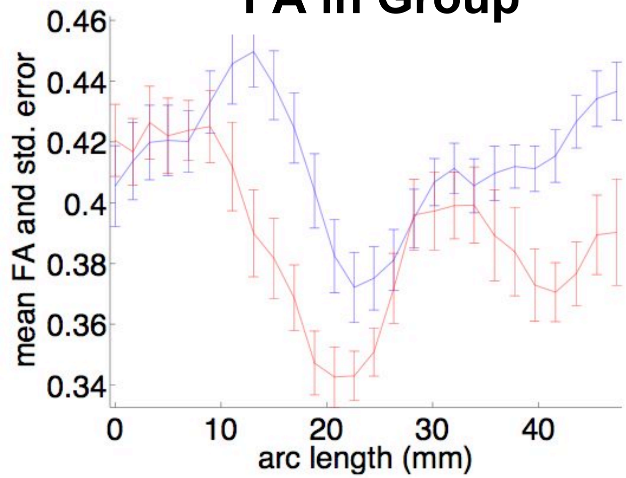
Hungarian Algorithm Cost Function

Measurement

- Don't average tensors
  - Why confound orientation and anisotropy?
- Directly measure FA, etc. vs arc length



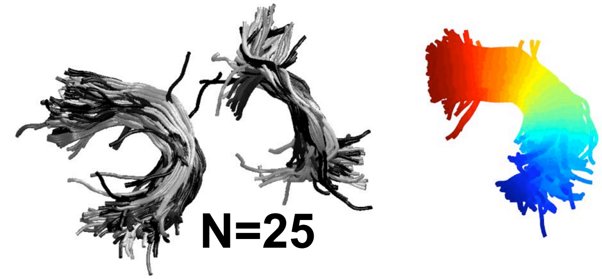
Single subject

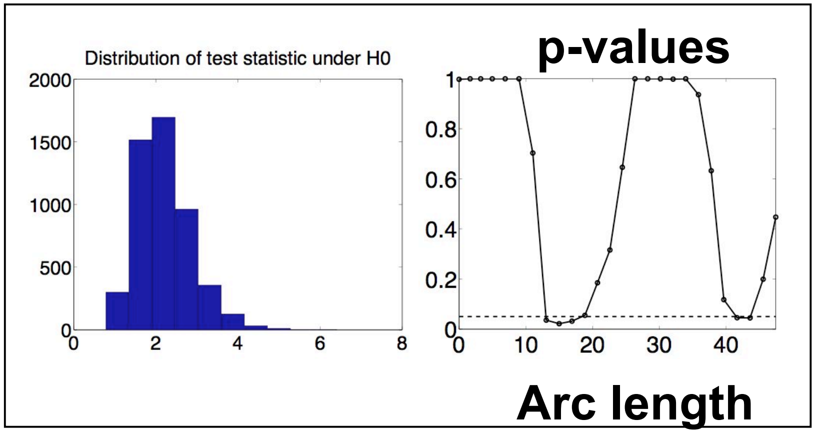


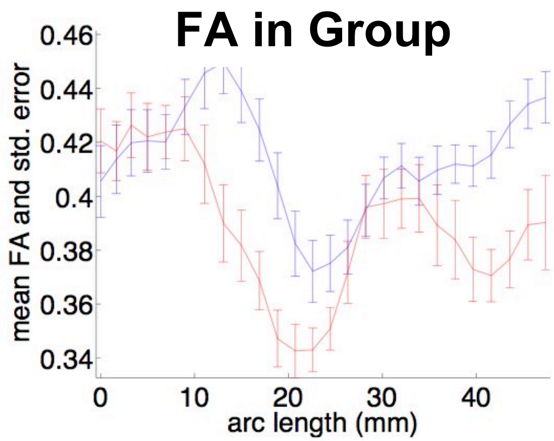
Simple Statistics

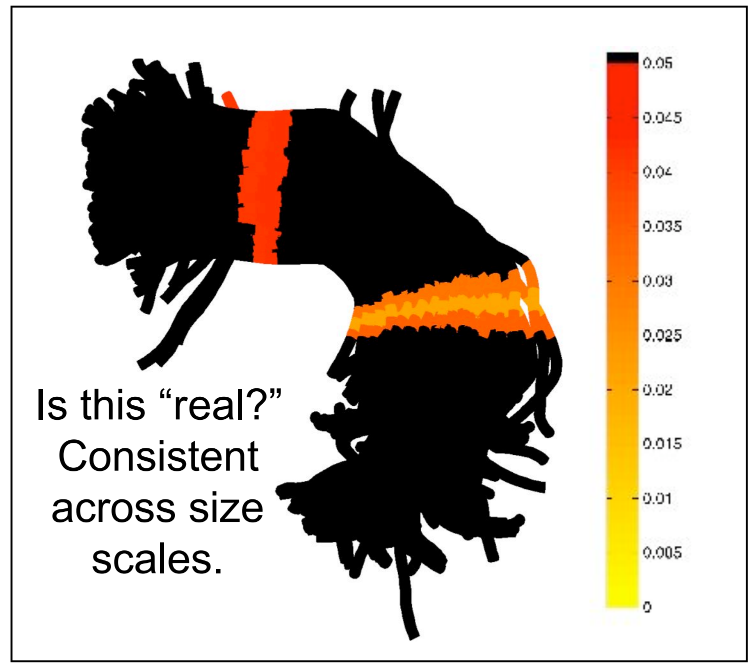
- Test statistic
  - Paired t-test (LHem vs Rhem) along fiber
- Null hypothesis:
  - No difference in FA in right/left hemisphere.
- Multiple comparison correction: permutation testing
  - Two-sided permutation test (don't assume L>R)
  - Estimate distribution of test statistic under null hypothesis
  - Permute labels for right/left within each subject
  - For each permutation:
    - Compute statistic (abs value of paired t-test) for each arc length
    - Record maximal statistic over all arc lengths
- Distribution of these maximal statistics gives corrected p-value

FA in Arcuate









LHem FA differs from RHem FA

Acknowledgements

- Susumu Mori, JHU (DTI dataset)
- Lilla Zollei (congealing registration)
- David Banks, FSU (photon renderings)
- Alexandra Golby and Golby Lab
- Carl-Fredrik Westin
- Ruth Propper (R/L handers project)
- Aristotle Voineskos (validation of clusters)
- NIH grants U54EB005149, R01MH074794, P41RR13218, and U41RR019703.

golbylab.bwh.harvard.edu

References

- Anatomy and DTI Intro:
  - Jellison et al. *Diffusion Tensor Imaging of Cerebral White Matter: A Pictorial Review of Physics, Fiber Tract Anatomy, and Tumor Imaging Patterns.* AJNR Am J Neuroradiol 2004 25: 356-369