Introduction to DTI: Part I

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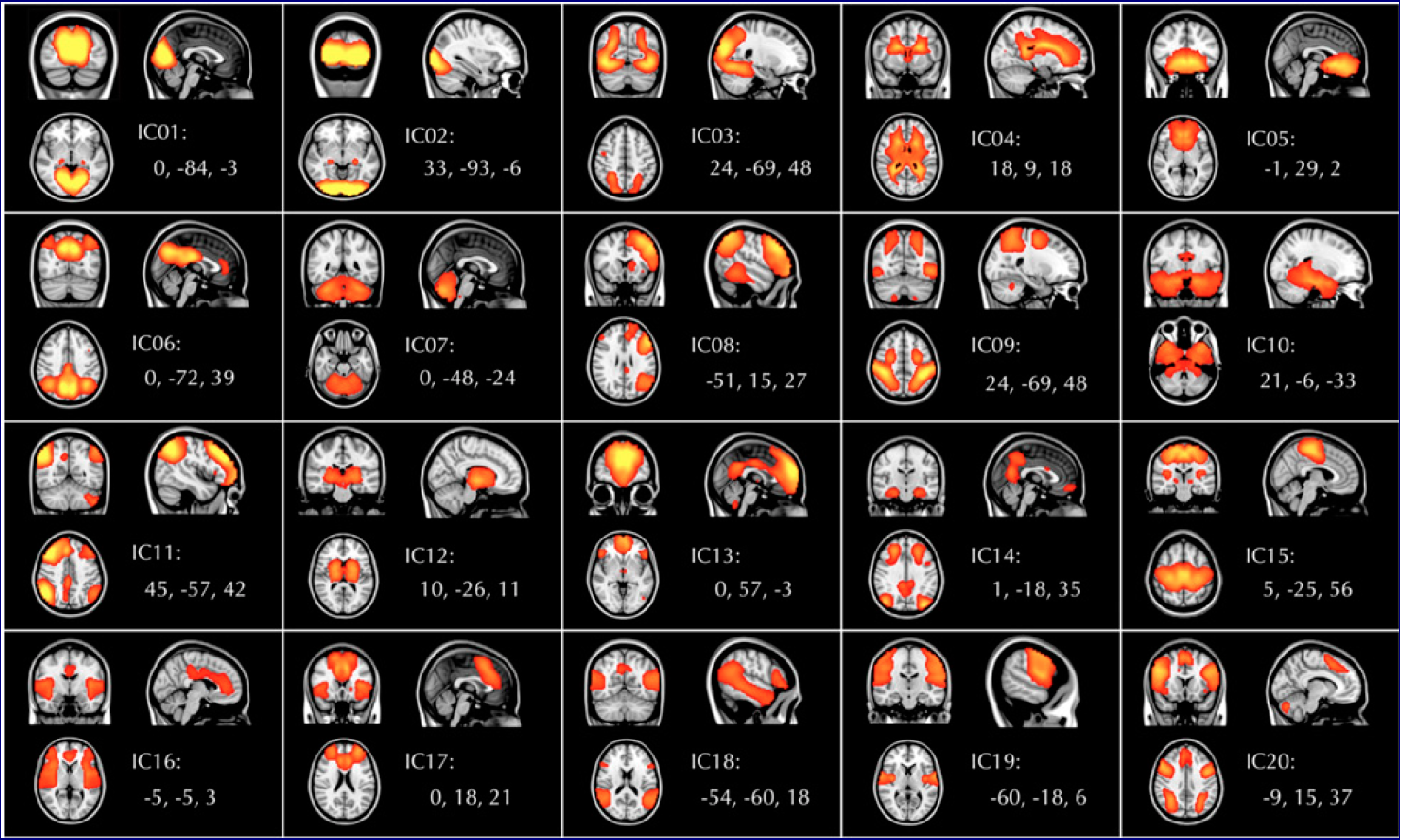
Outline

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

FMRI: GM Networks



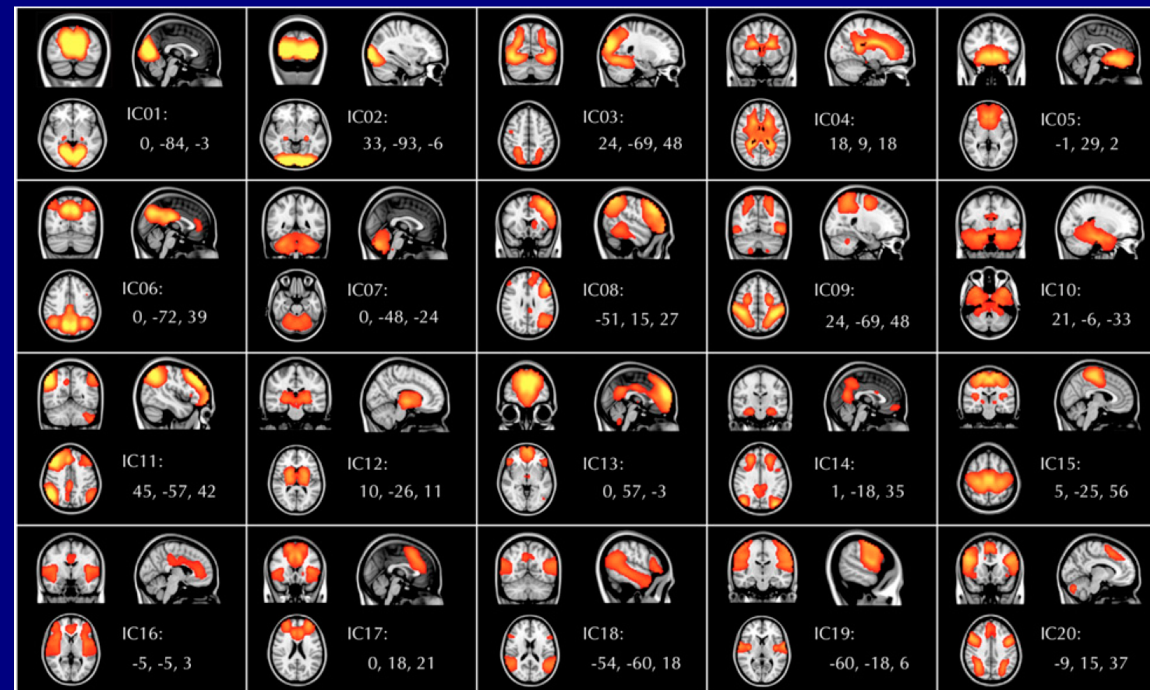
(Biswal et al., 2010 PNAS)

FMRI: GM Networks

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

+ Quantify GM properties: ALFF, fALFF, RSFA, σ, ReHo, GMV, etc.

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



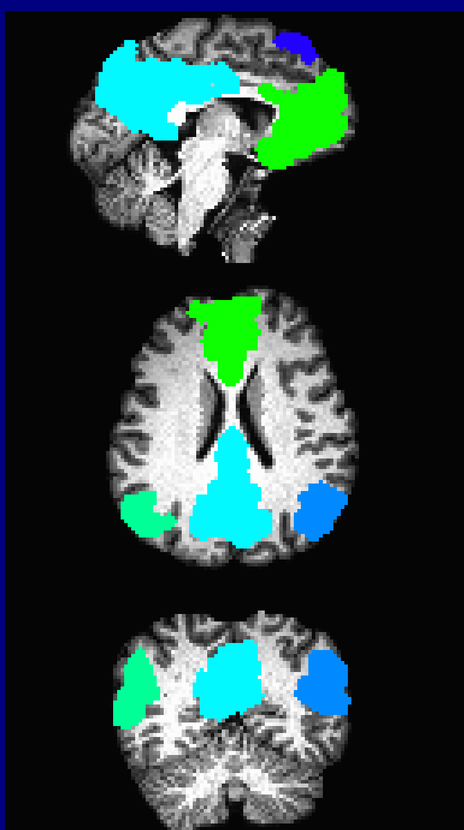
Sidenote:

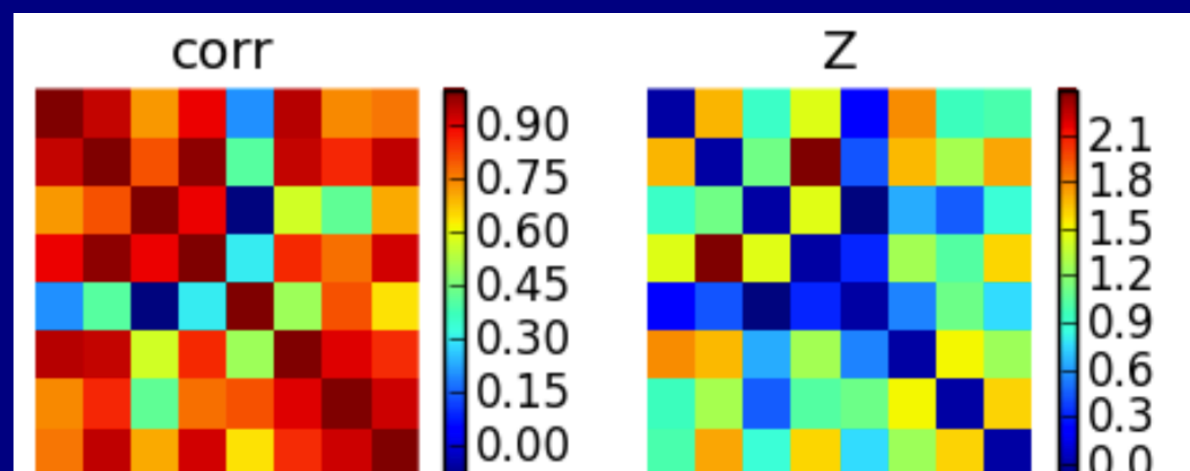
Mention of a few of the FMRI tools

Functional processing, 3

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

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

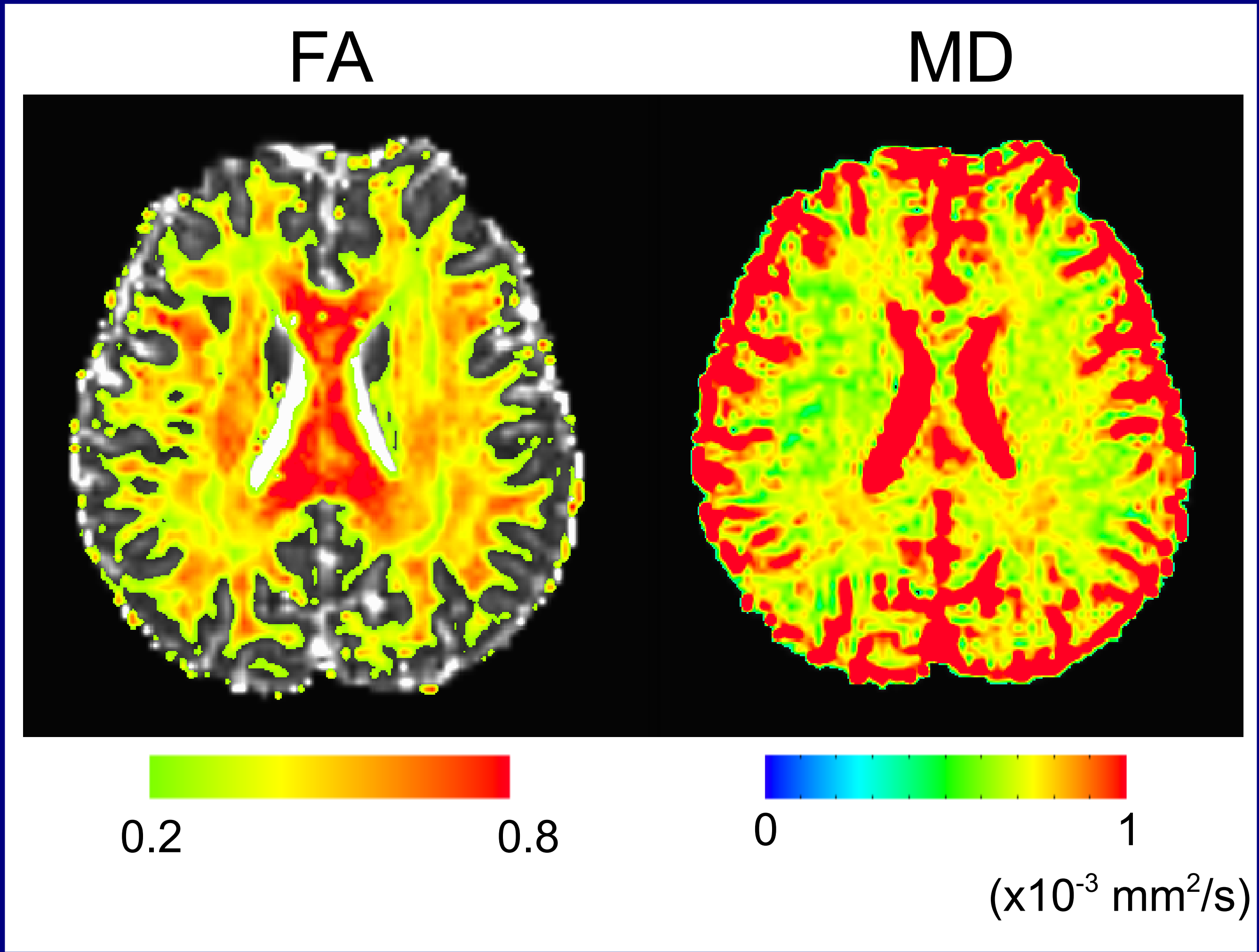




++ Can also calculate ReHo, ALFF, fALFF, etc. in FATCAT/AFNI.

DTI: WM structure

DTI-based parameters characterize some local structural properties and also show the presence of spatially-extended WM structures.

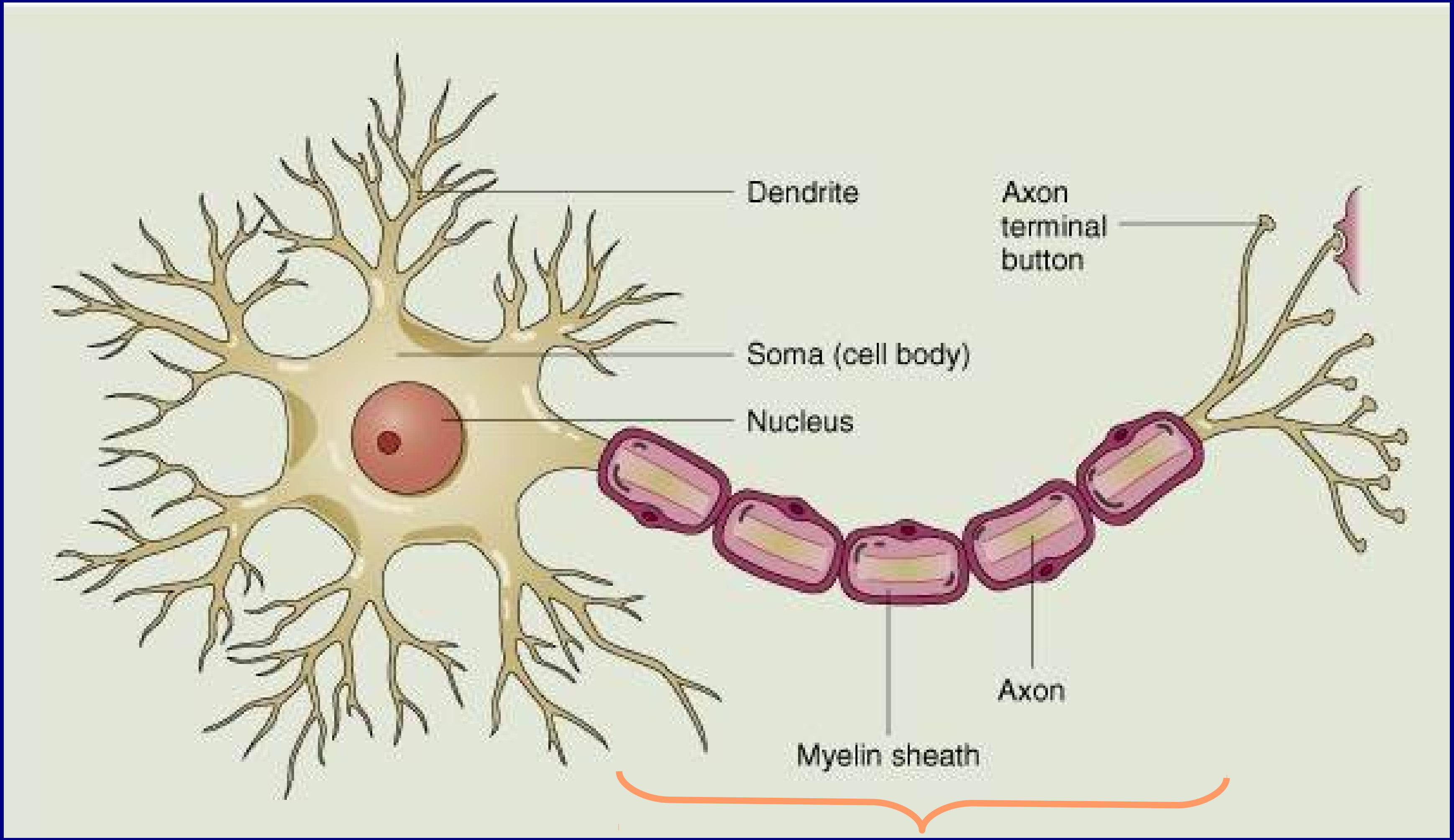


Can quantify structural (esp. WM) properties using:
FA, MD, RD, L1, etc.

Can investigate (and Quantify?) network relations with:
tractography

Structural connections in the brain

The (schematic) structure of neurons

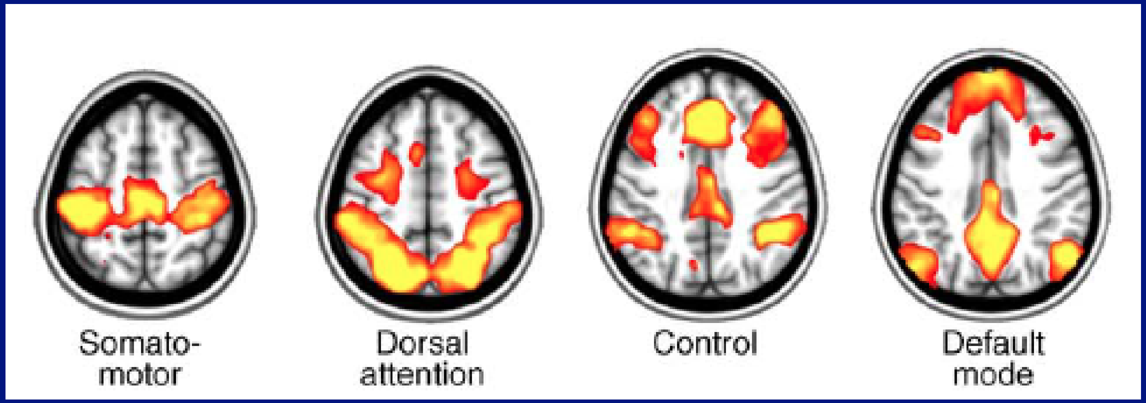


Extended white matter fibers,
often organized in bundles

Structure + Function

Simple example:

GM ROIs network:



Raichle (2010, TiCS)

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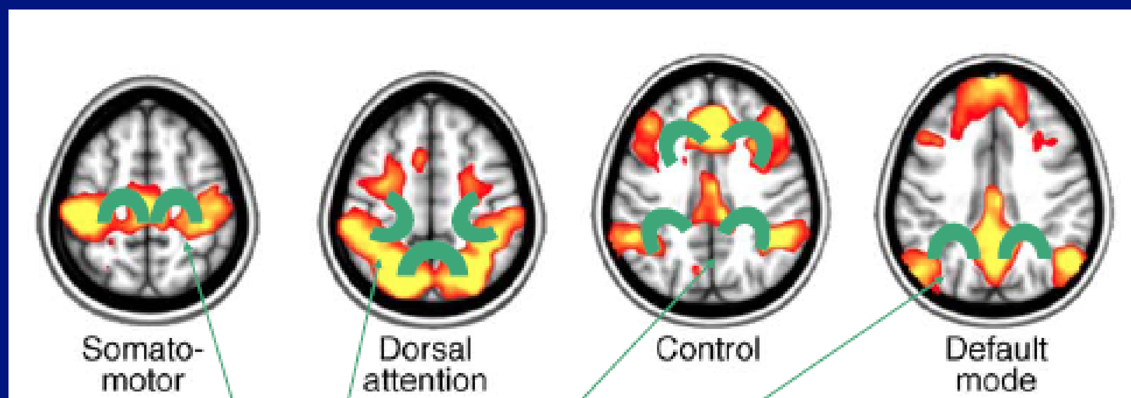

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Associated WM ROIs

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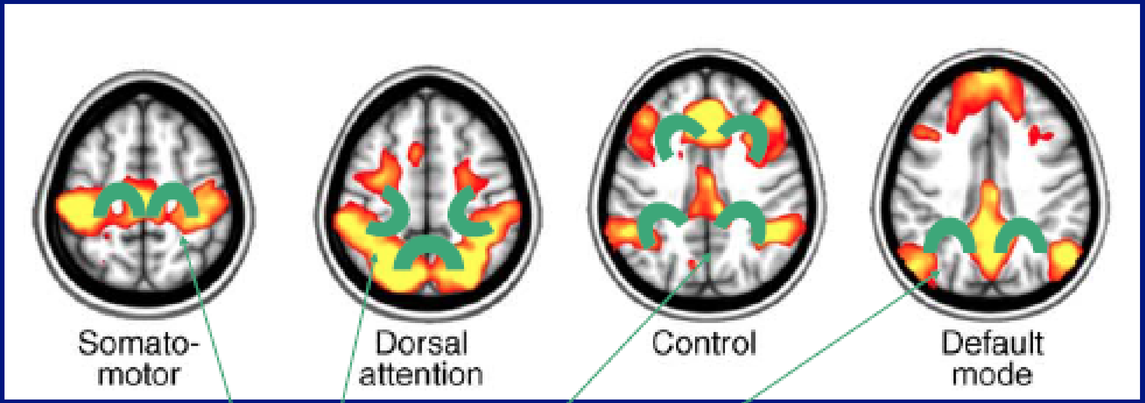

Raichle (2010, TiCS)

Associated WM ROIs

Our goal for tractography->
estimate likely/probable locations of WM associated with GM, and relate ROI quantities with functional/GM properties

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→ FC+SC provides sets of complementary quantities to describe a network, and can be further combined with behavioral/other measures (statistical modeling).

Tools for combining FC and SC:

Combining functional and tractographic connectivity will require:

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

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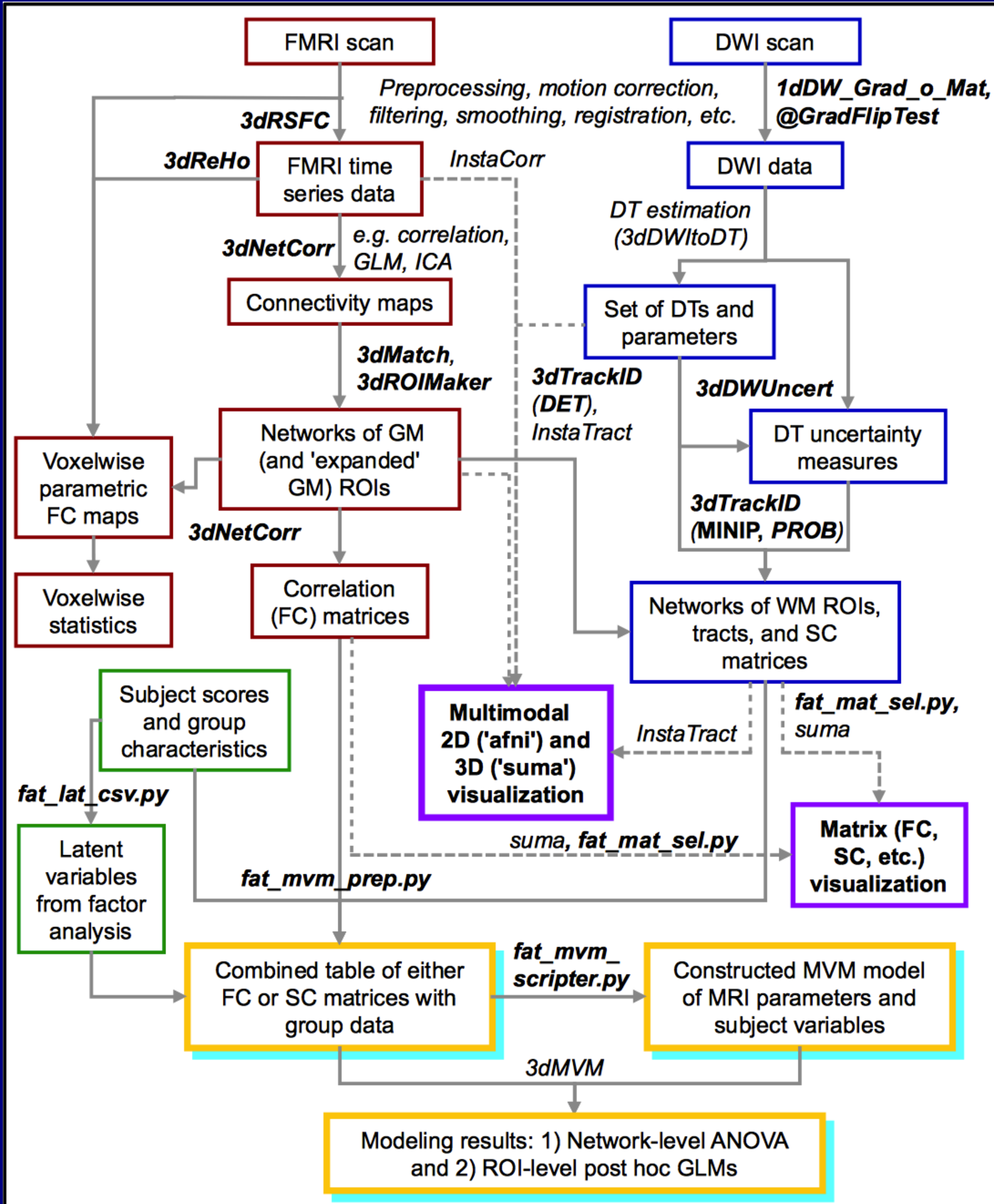
FATCAT: Functional And Tractographic Connectivity Analysis Toolbox (Taylor & Saad, 2013), available in AFNI with demo data+scripts.

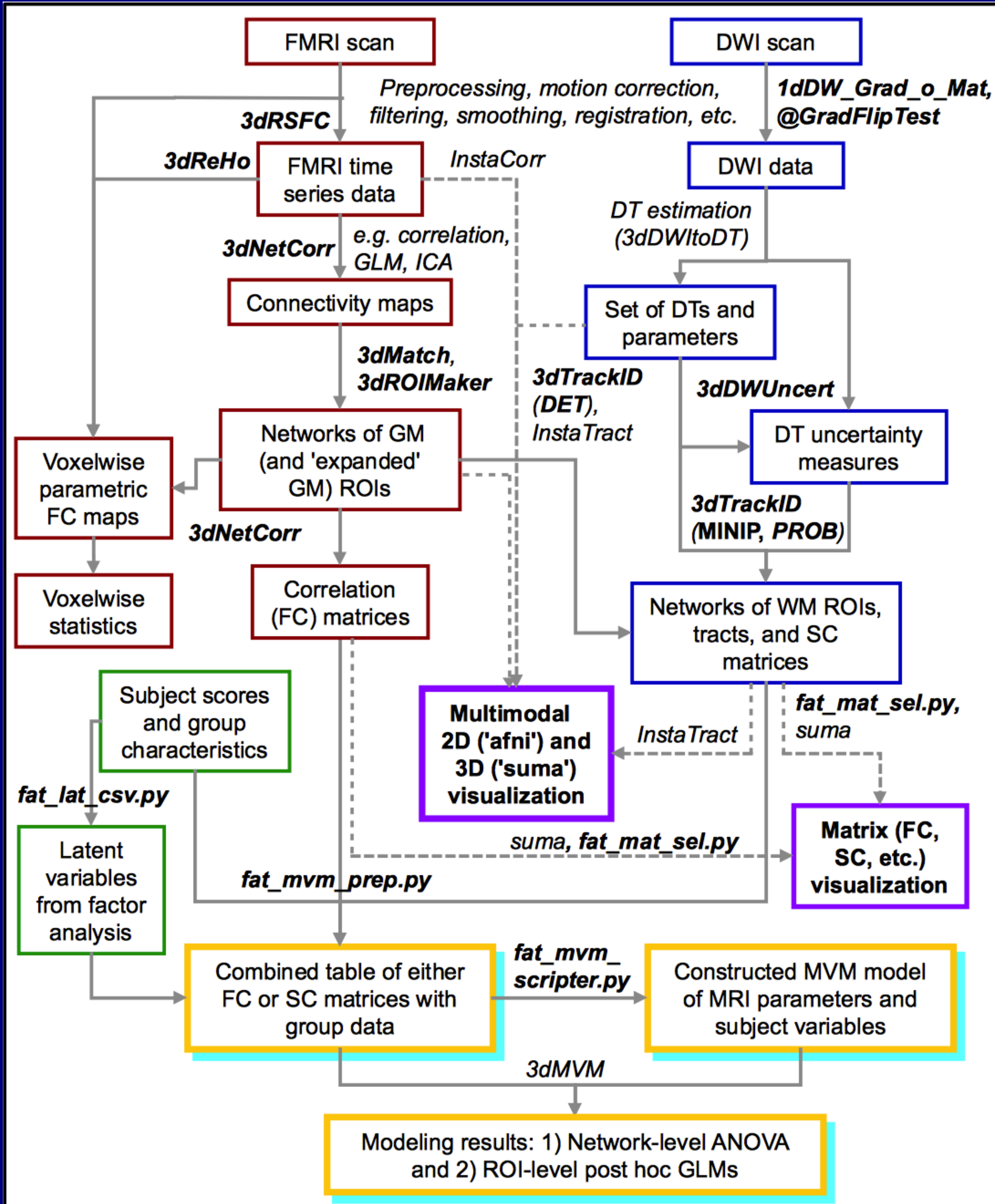
AFNI!

*picture from google search, not from/of either author

Schematic for combining FMRI and DTI-tractography via FATCAT



(Taylor, Chen, Cox & Saad, 2015?)



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FATCAT goals:

+ Do useful tasks
+ Integrate with existing pipelines/software
+ **Derive/use information from the data itself**
+ Be “simple” to implement
+ Be network-oriented, when possible
+ Be efficient
+ Be flexible and able to grow

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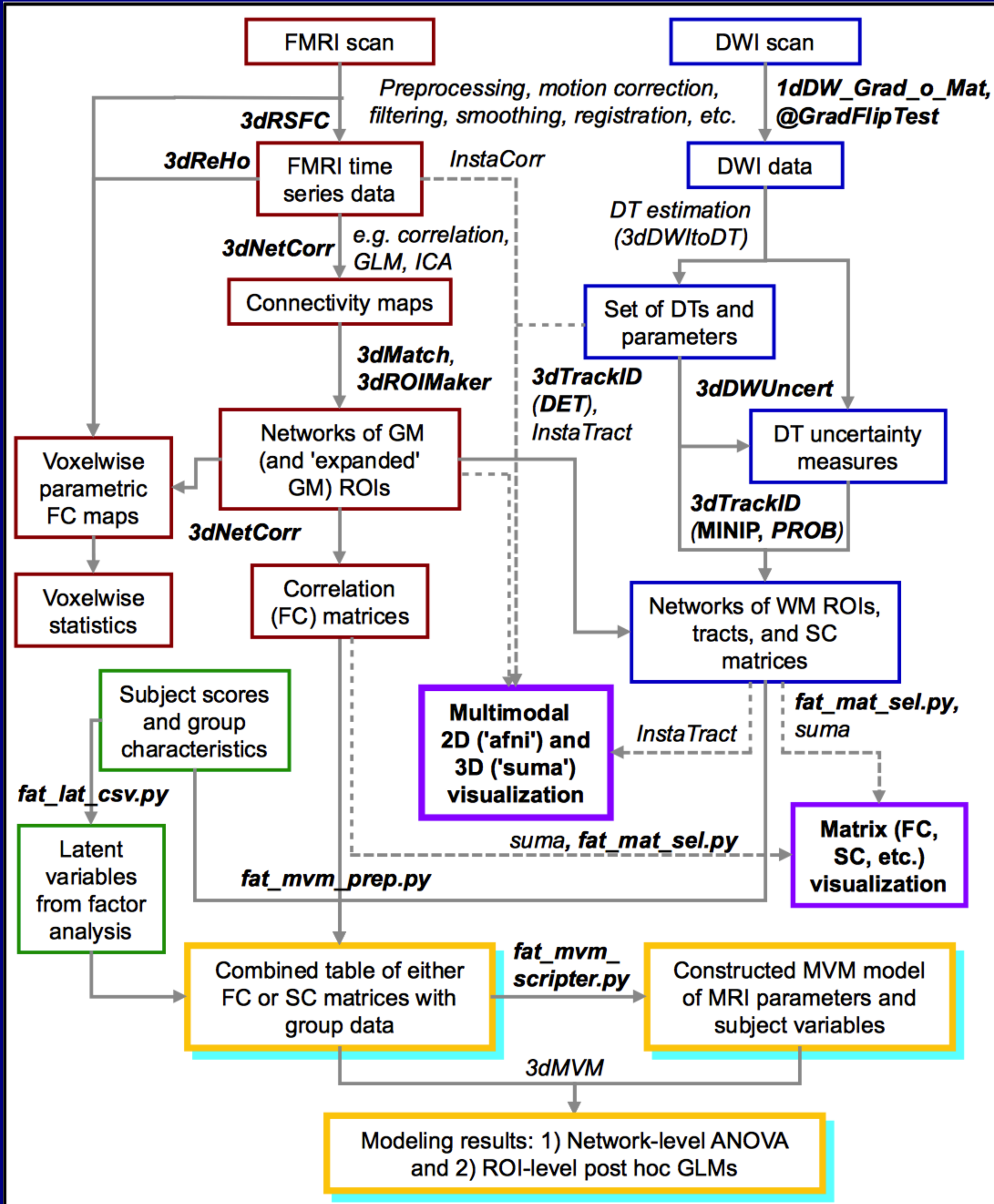

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Main focus today on DTI-tractography, including making ROIs from FMRI

(Taylor, Chen, Cox & Saad, 2015?)

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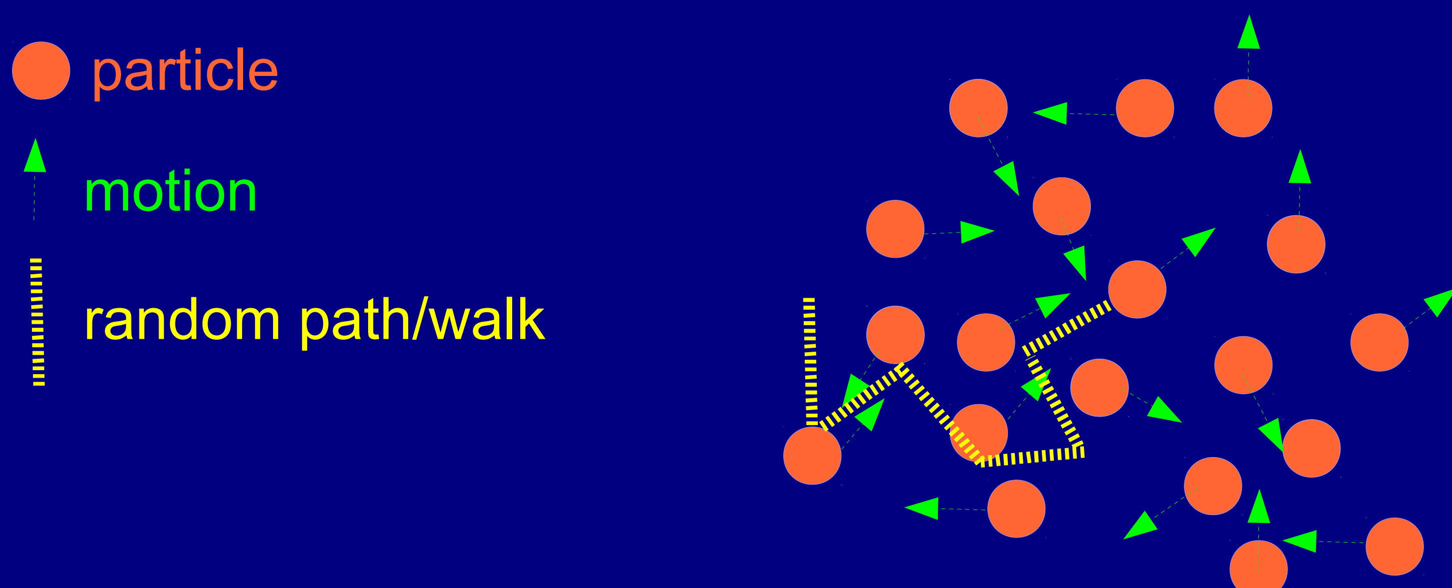
$\longrightarrow$ here, hydrogen atoms in aqueous brain tissue



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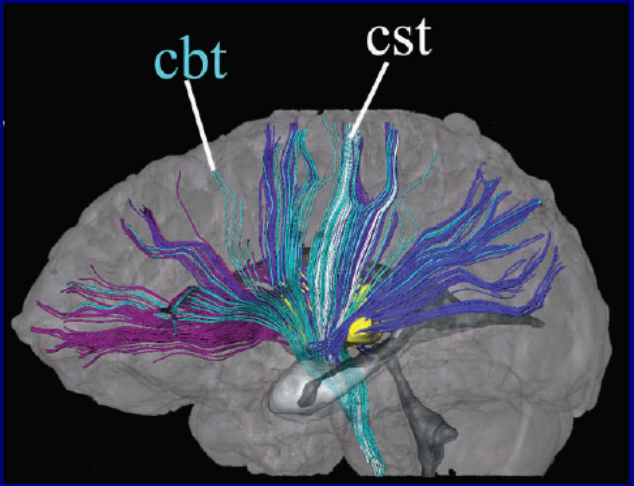
*I*maging: quantifying brain properties

$\rightarrow$ here, esp. for white matter



The DTI model:

Assumptions and relation to WM properties

Diffusion as environmental marker

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

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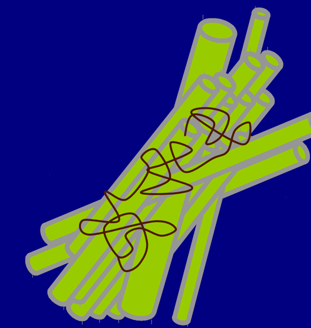
$\rightarrow$ *Diffusion shape tells of structure presence and spatial orientation*

Local Structure via Diffusion MRI

(In brief)



1) Random motion of molecules affected by local structures

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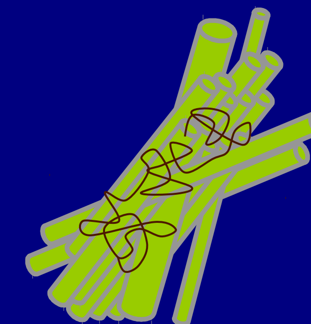

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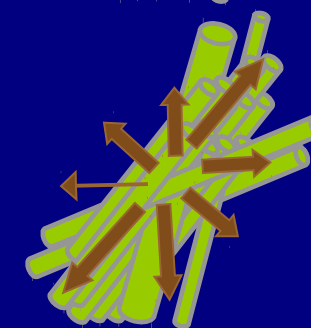

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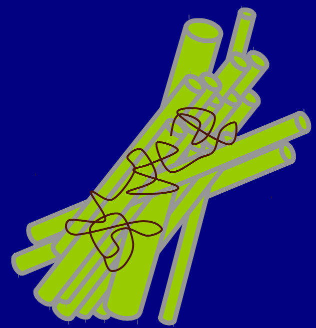

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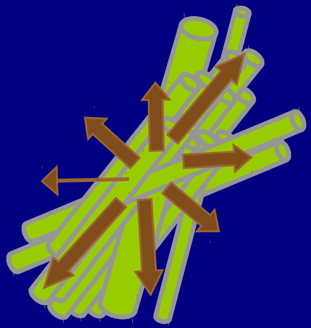

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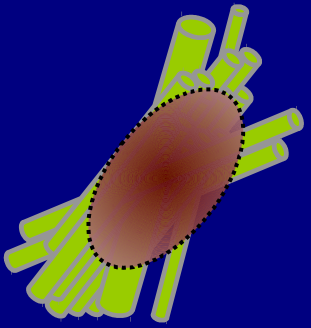
3) Bulk features of local structure approximated with various reconstruction models, mainly grouped by number of major structure directions/voxel:



+ one direction:
  DTI (Diffusion Tensor Imaging)

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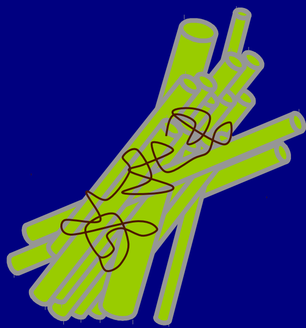

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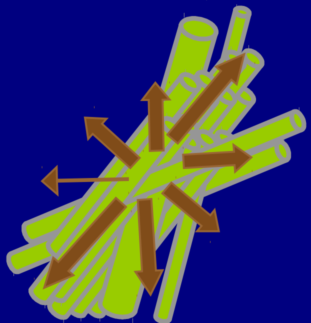

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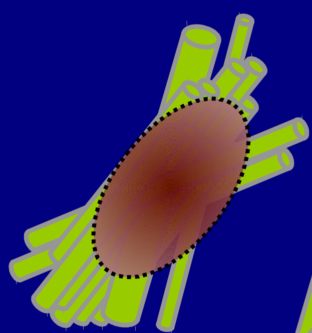
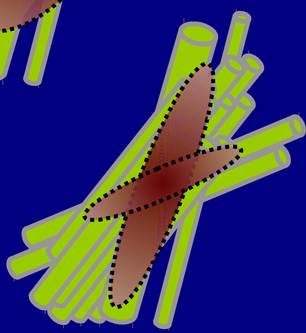


+ >=1 direction:
  HARDI (High Angular Resolution Diffusion Imaging)
  Qball, DSI, ODFs, ball-and-stick, multi-tensor, CSD, ...



Diffusion in MRI

Mathematical properties of the matrix/tensor:

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

Having: 3 eigenvectors: $\mathbf{e}_i$

3 eigenvalues: λ_i

- Real-valued
- Positive definite ($\mathbf{r}^T\mathbf{D}\mathbf{r} > 0$)

$$\mathbf{D}\mathbf{e}_i = \lambda_i \mathbf{e}_i, \qquad \lambda_i > 0$$

- Symmetric ($D_{12} = D_{21}$, etc), 6 independent values

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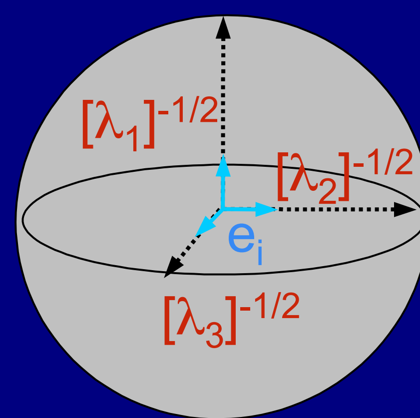
Geometrically, this describes an ellipsoid surface:

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

isotropic case

$\lambda_1 = \lambda_2 = \lambda_3$



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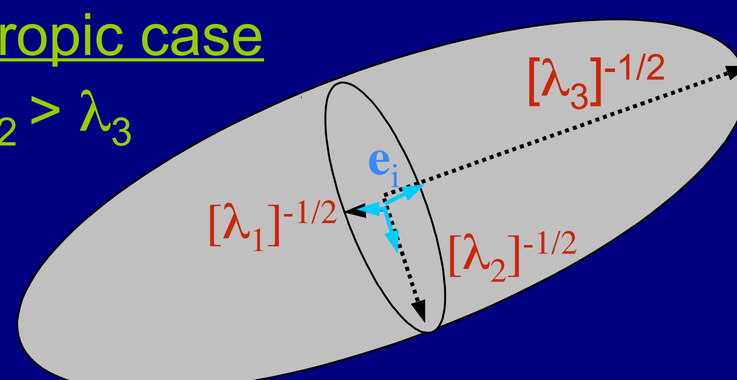
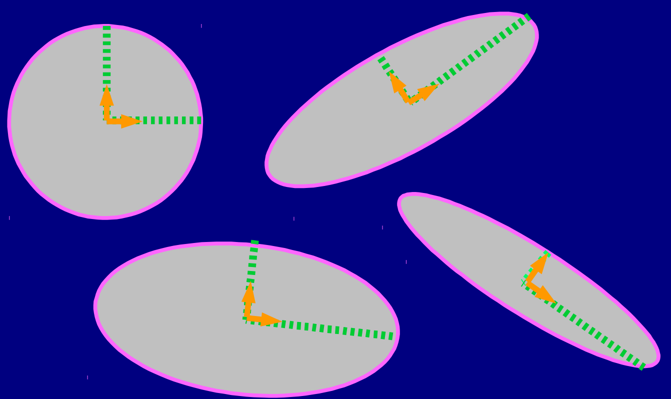


DTI: ellipsoids

Important mathematical properties of the diffusion tensor:



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    eigenvectors → orientation in space

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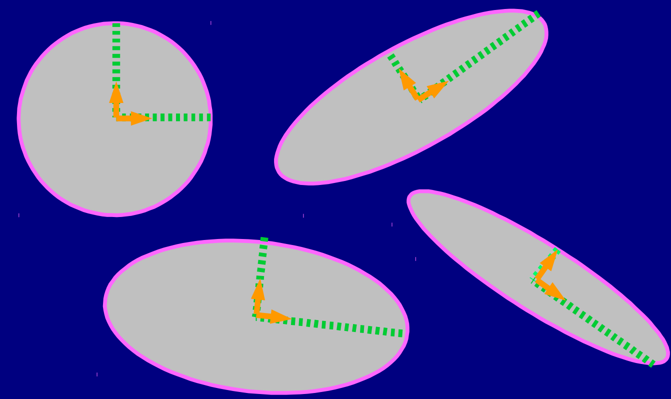

+ Determine the minimum number of
  DWIs measures needed (6 + baseline)

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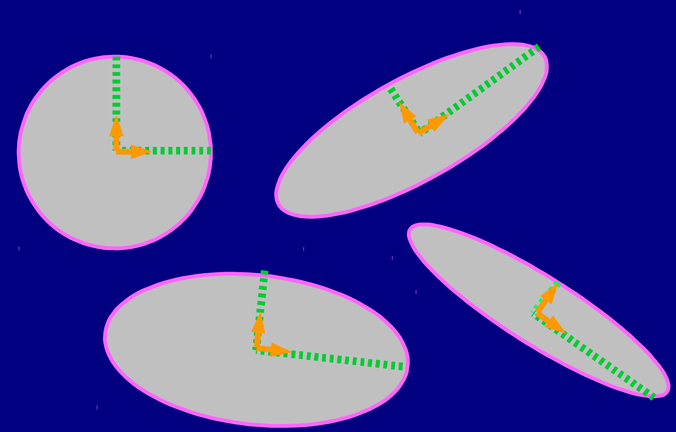

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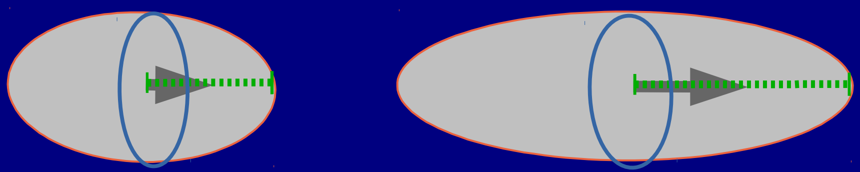
+ Determine much of the processing and noise minimization steps

"Big 5" DTI ellipsoid parameters

Main quantities of diffusion (motion) surface

first eigenvalue, L1
(= λ_1, parallel/axial diffusivity, AD)



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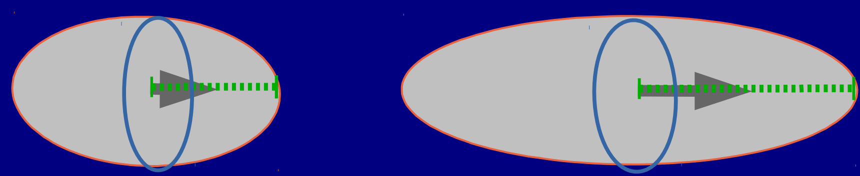

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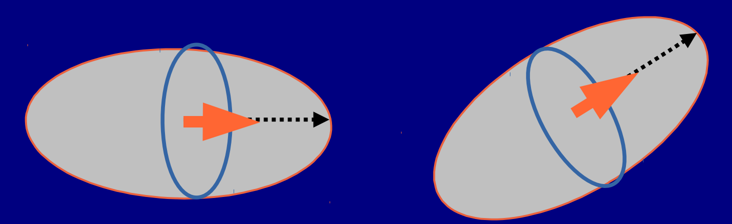
first eigenvector, e_1
(DT orientation in space)



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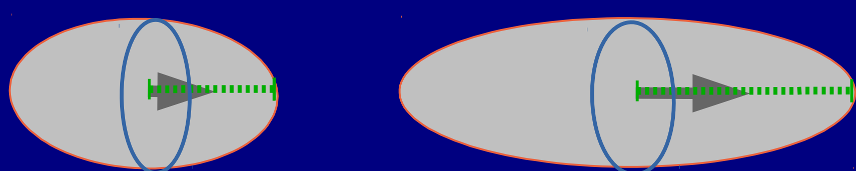

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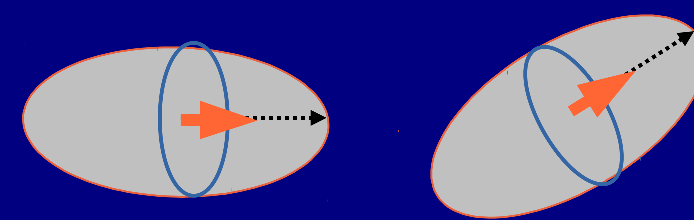
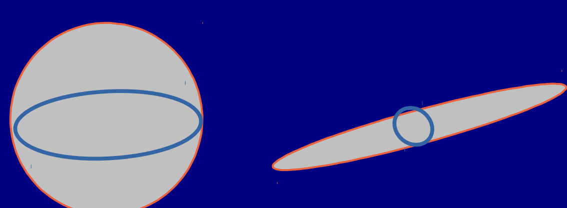


e_1 e_1

Fractional anisotropy, FA
(stdev of eigenvalues)



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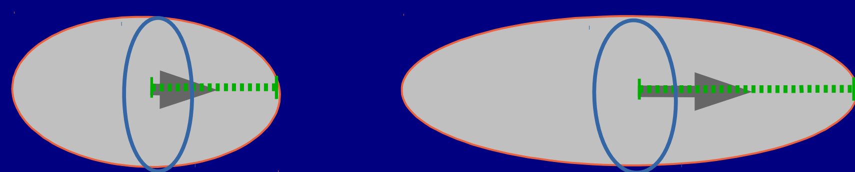

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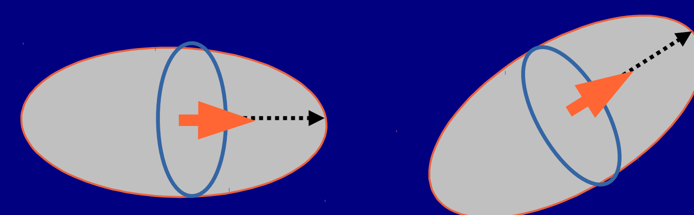

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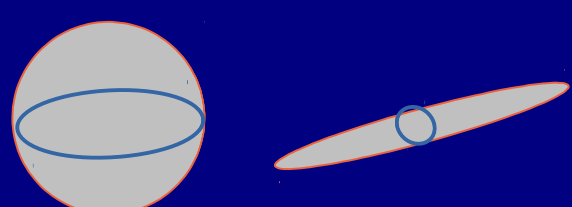

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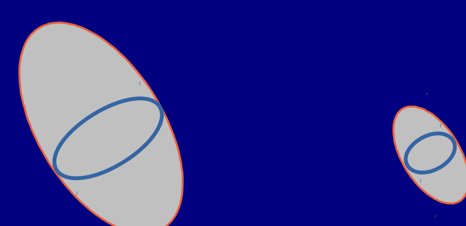
Mean diffusivity, MD
(mean of eigenvalues)



MD_1 > MD_2

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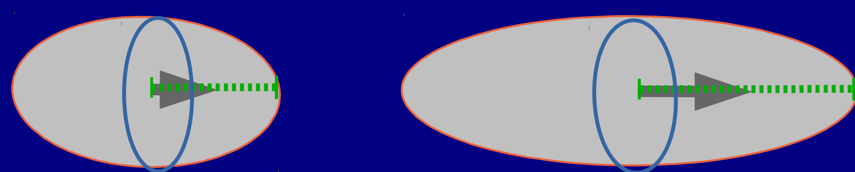

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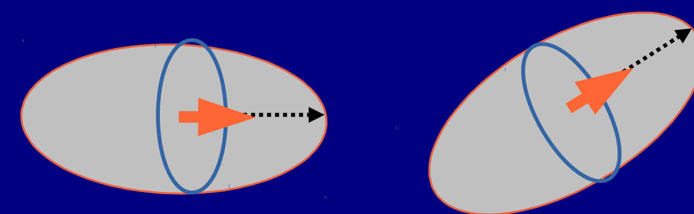
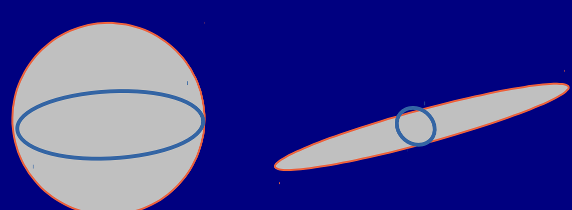


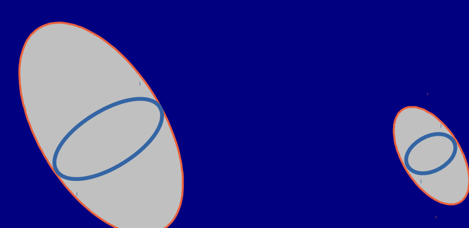
e_1 e_1

Fractional anisotropy, FA
(stdev of eigenvalues)



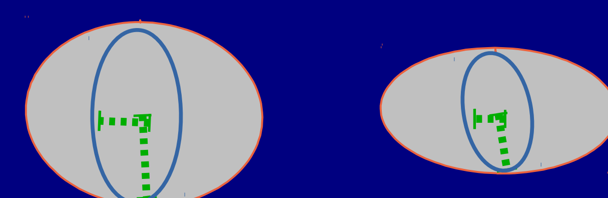
FA≈0 FA≈1

Mean diffusivity, MD
(mean of eigenvalues)



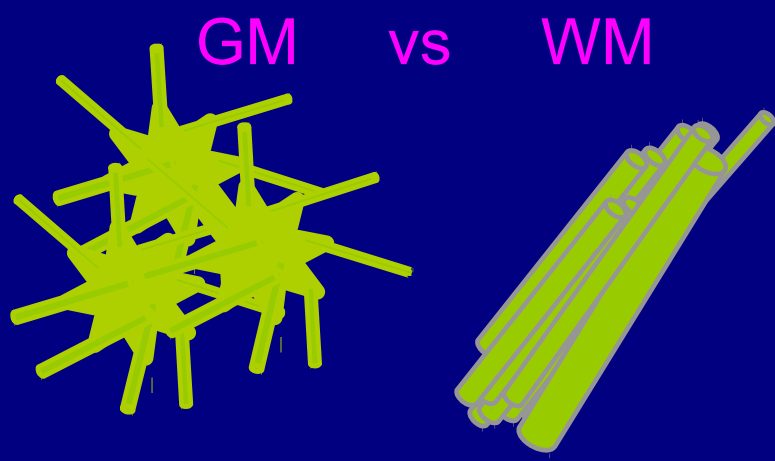
MD_1 > MD_2

Radial diffusivity, RD
(= $(\lambda_2+\lambda_3)/2$)



RD_1 > RD_2

Cartoon examples: white matter ↔ FA



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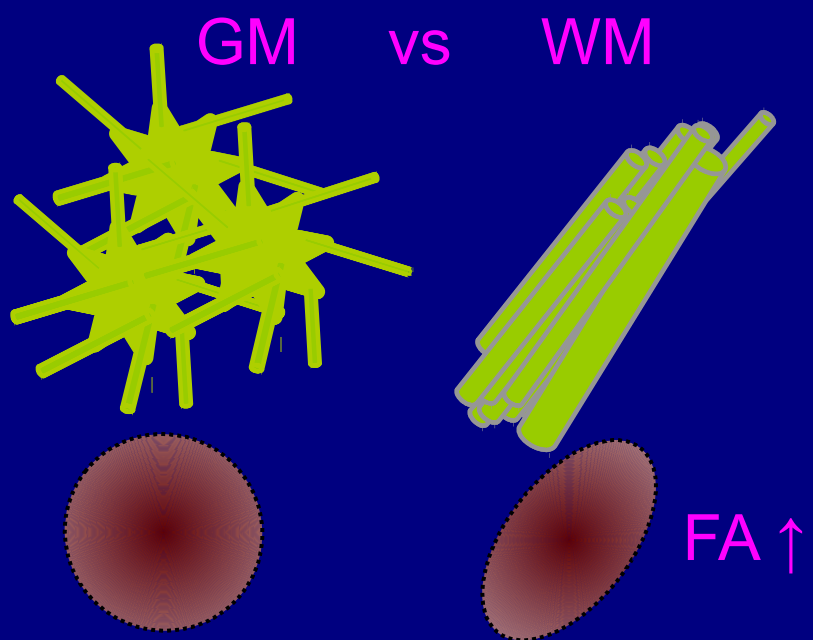

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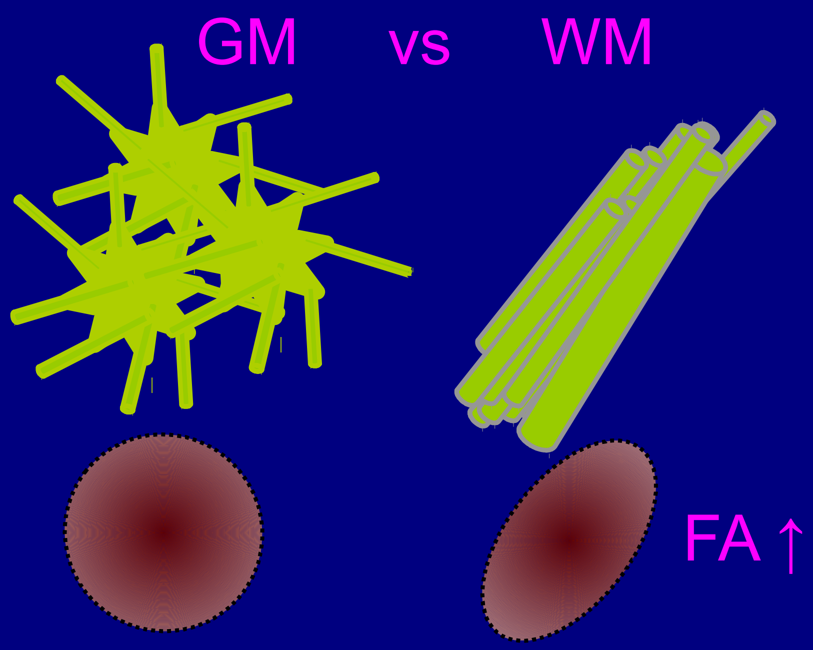

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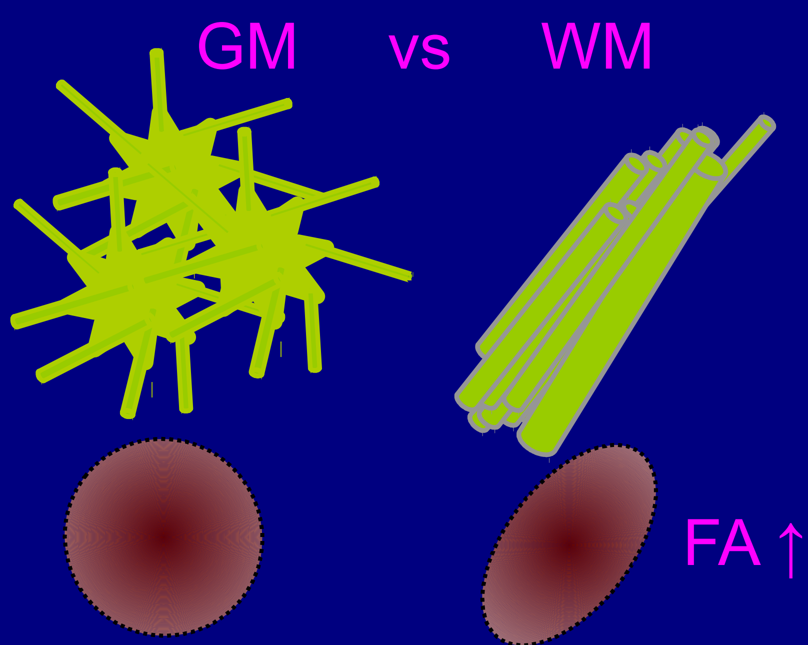

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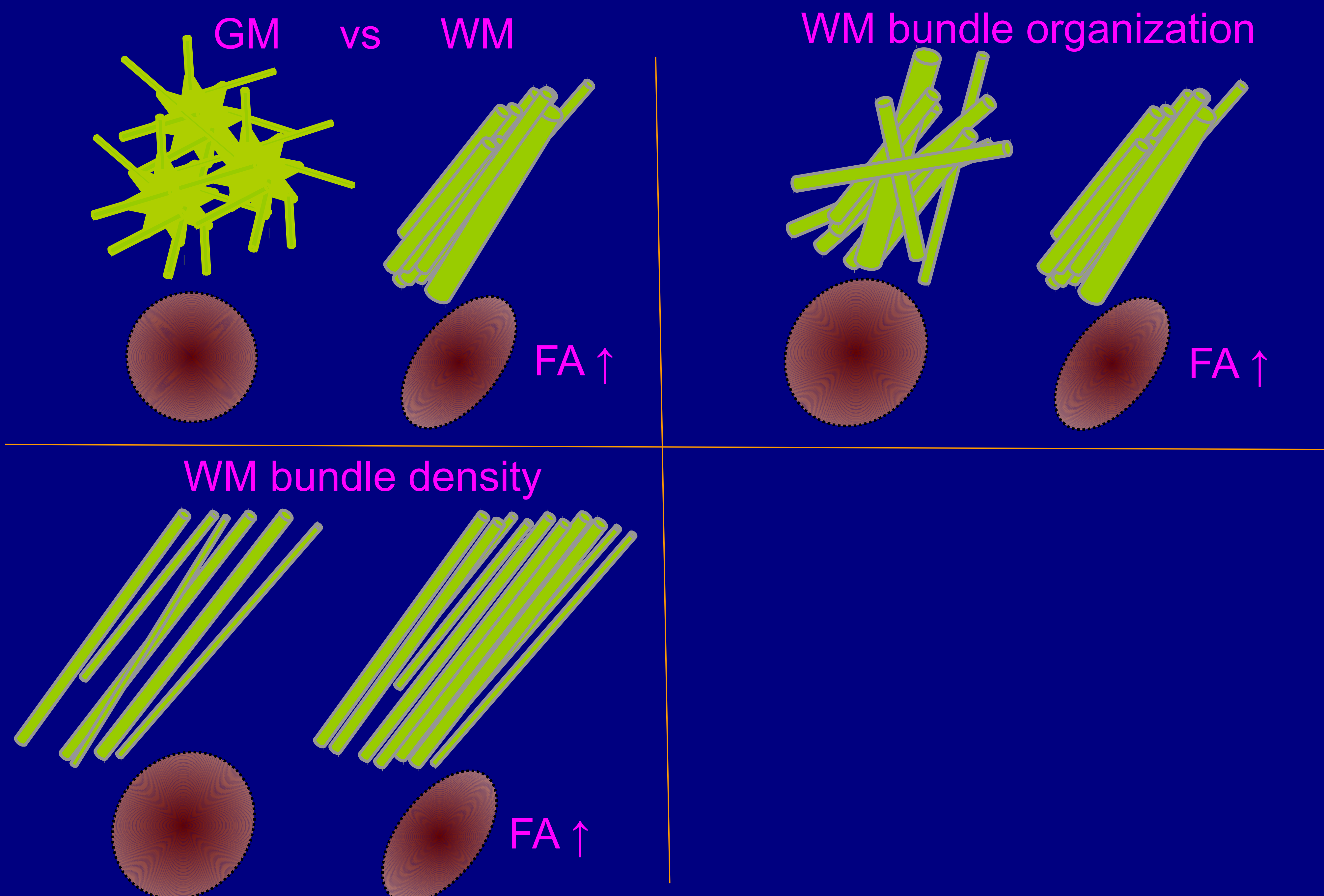

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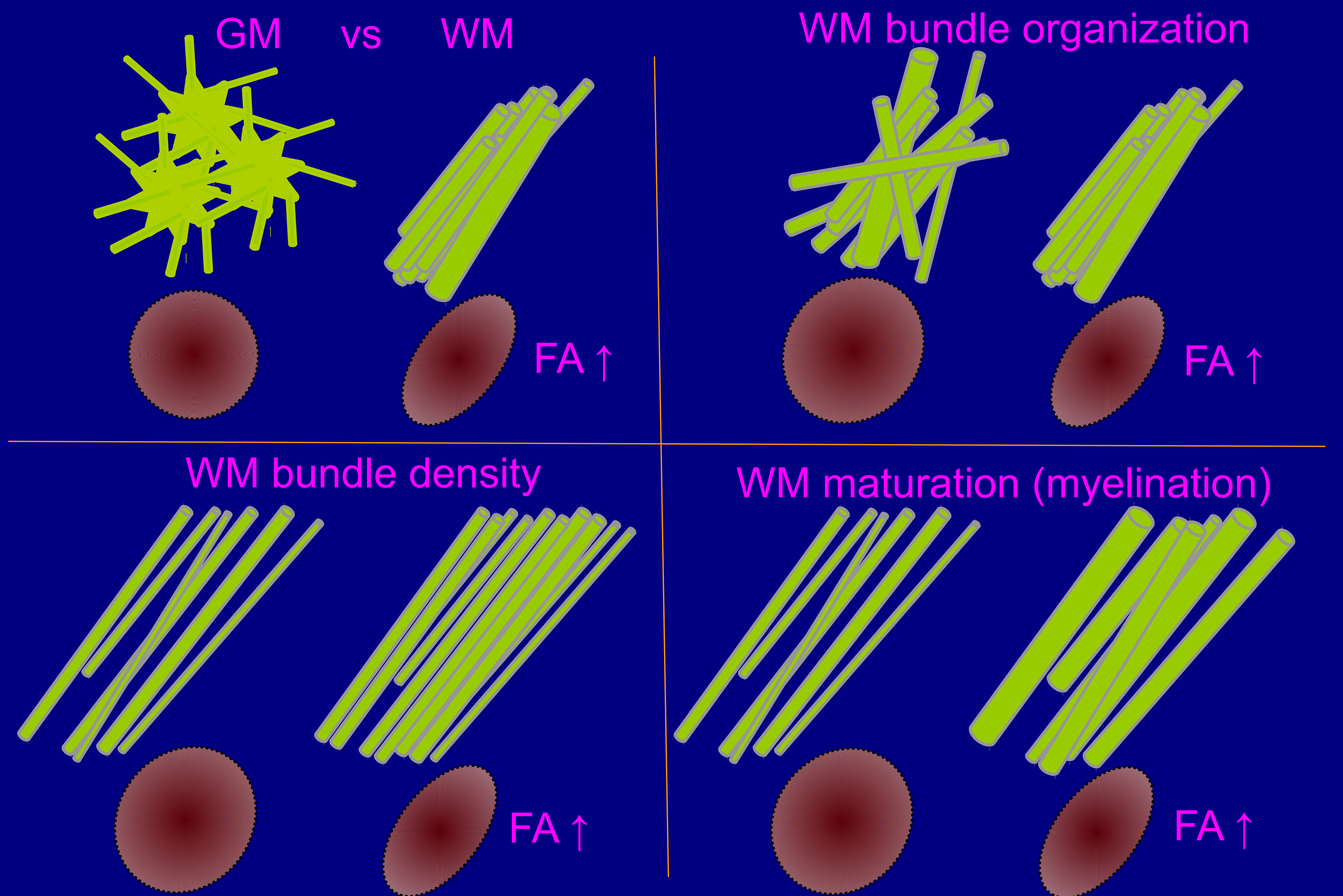

Interpreting DTI parameters

General literature:

FA: measure of fiber bundle coherence and myelination

- in adults, FA>0.2 is proxy for WM

MD, L1, RD: local density of structure

e_1: orientation of major bundles

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e_1: orientation of major bundles

Cautionary notes:

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

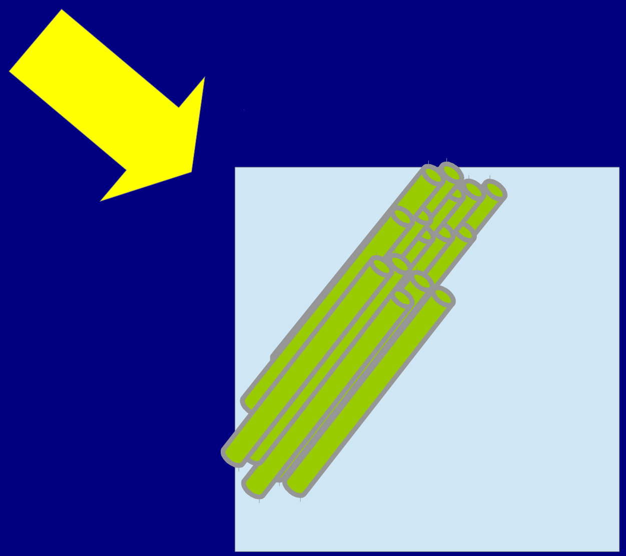
Acquiring DTI data:

diffusion weighted gradients in MRI

Diffusion weighted imaging

For a given voxel, observe relative diffusion along a given 3D spatial orientation (gradient)

DW gradient
$\mathbf{g_i} = (g_x, g_y, g_z)$



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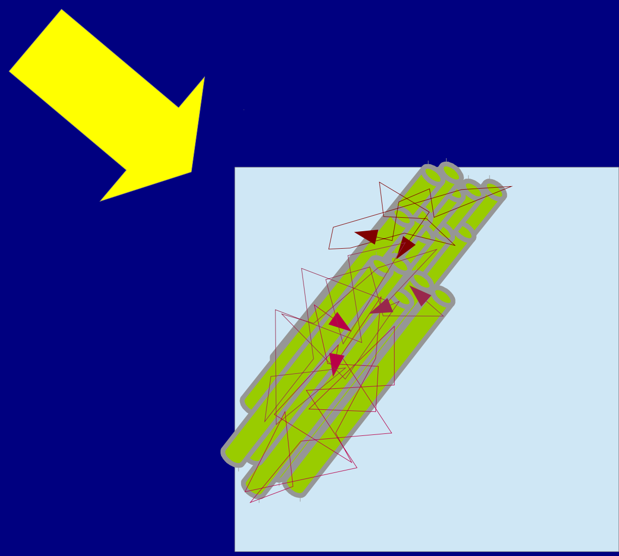

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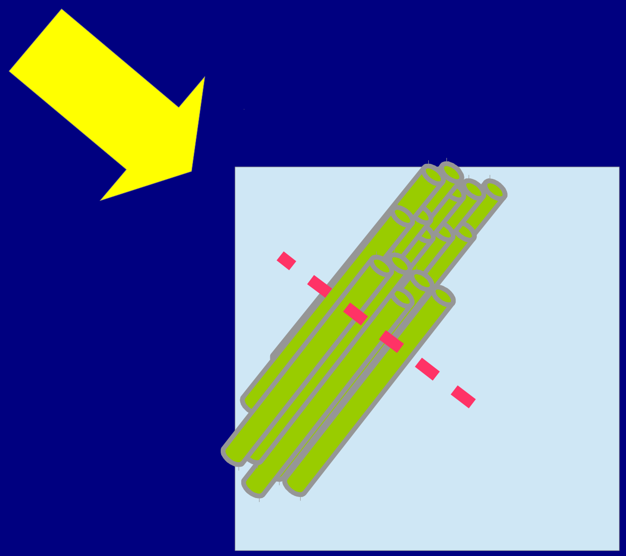

MR signal is attenuated by diffusion throughout the voxel in that direction:

$$S_i = S_0 \, e^{-b \, \mathbf{g}_\mathbf{i}^T \, \mathbf{D} \, \mathbf{g}_\mathbf{i}}$$

→ ellipsoid equation of diffusion surface: $C = \mathbf{r}^T \, \mathbf{D}^{-1} \, \mathbf{r}.$

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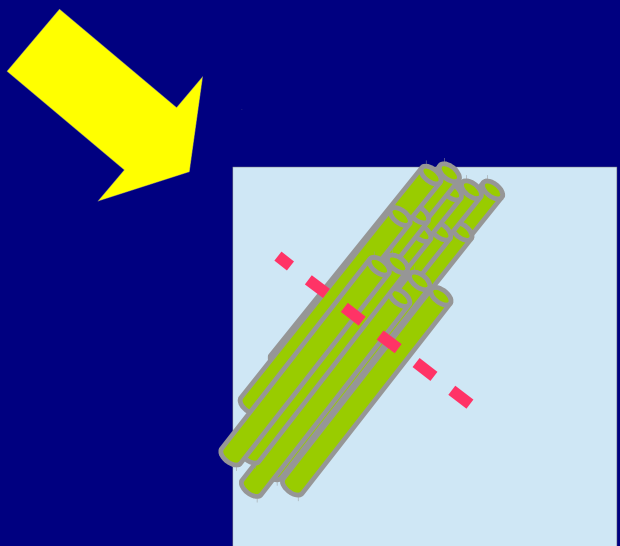
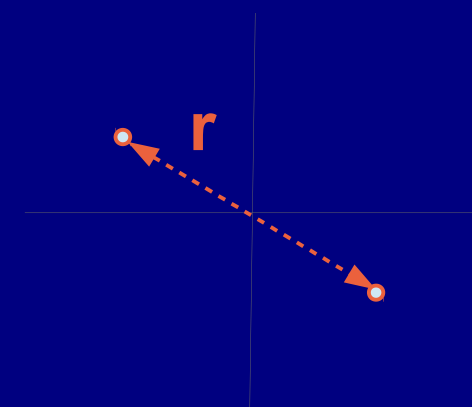


diffusion motion ellipsoid:

$C_2 = \mathbf{r}^T \mathbf{D}^{-1} \mathbf{r}.$



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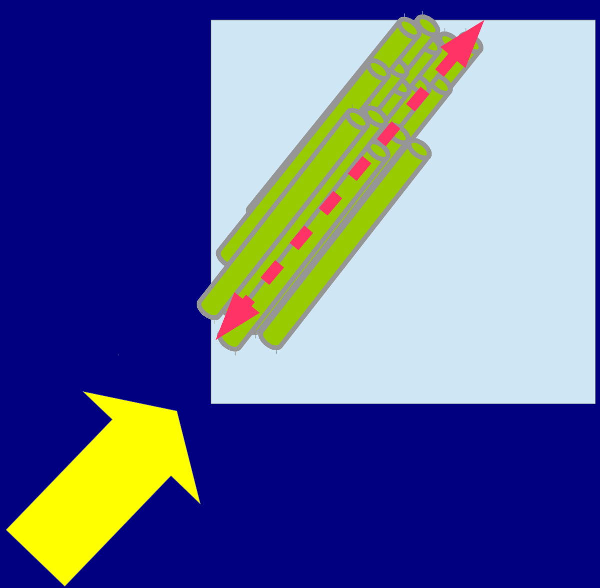

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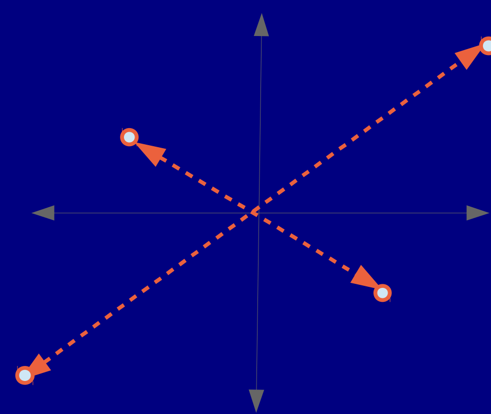

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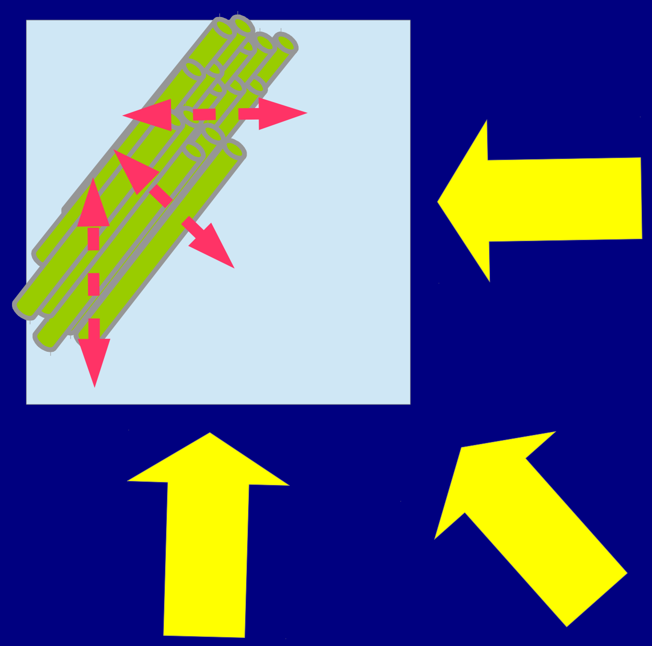

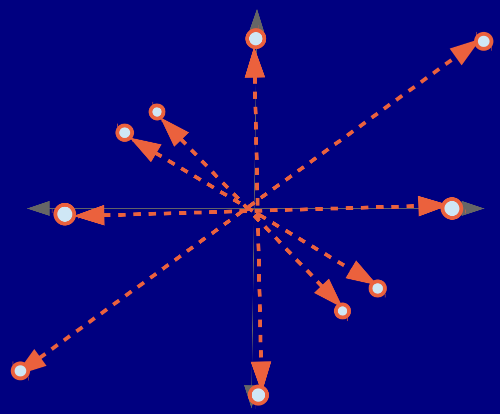

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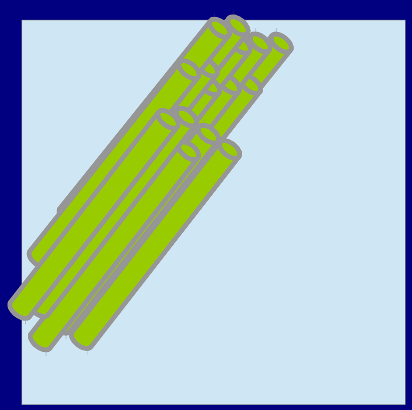
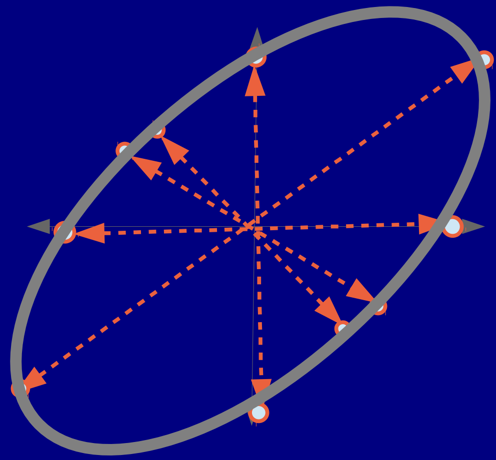
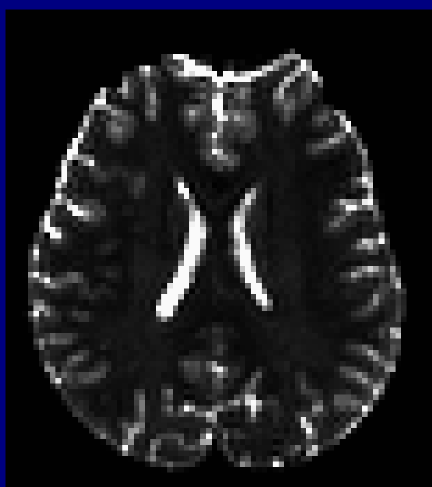




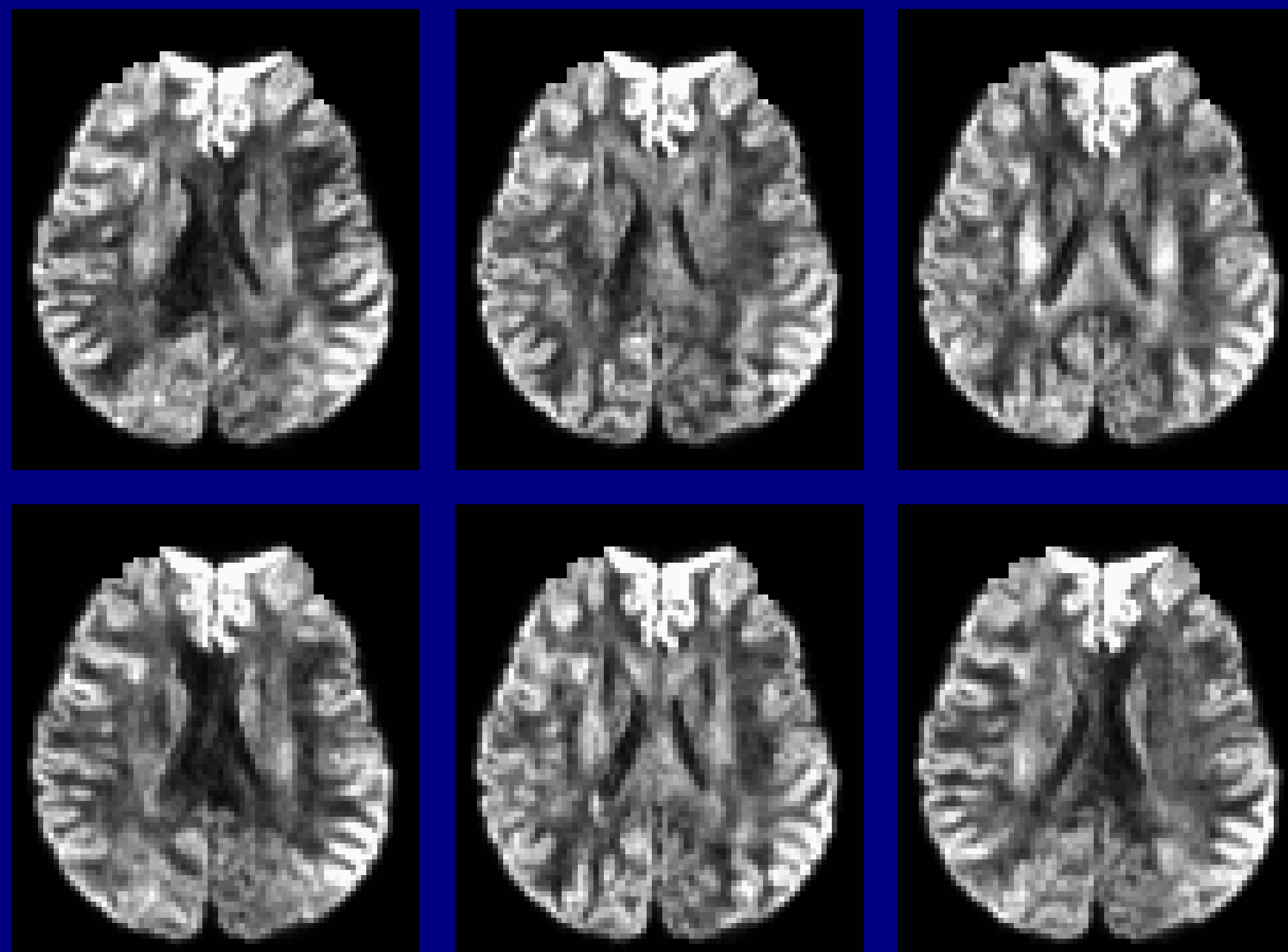
Individual points → Fit ellipsoid surface
Individual signals → Solve for **D**

Sidenote: what DWIs look like

Unweighted reference
$b=0\ s/mm^2$



Diffusion weighted images
(example: $b=1000\ s/mm^2$)



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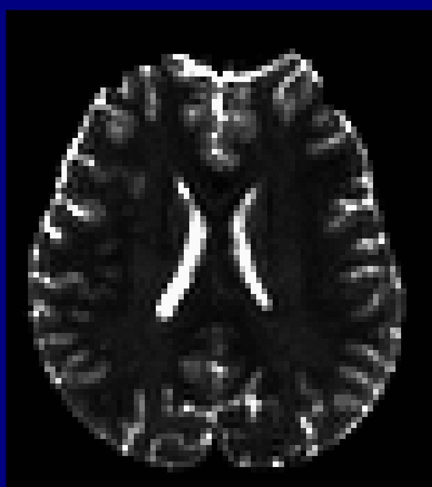

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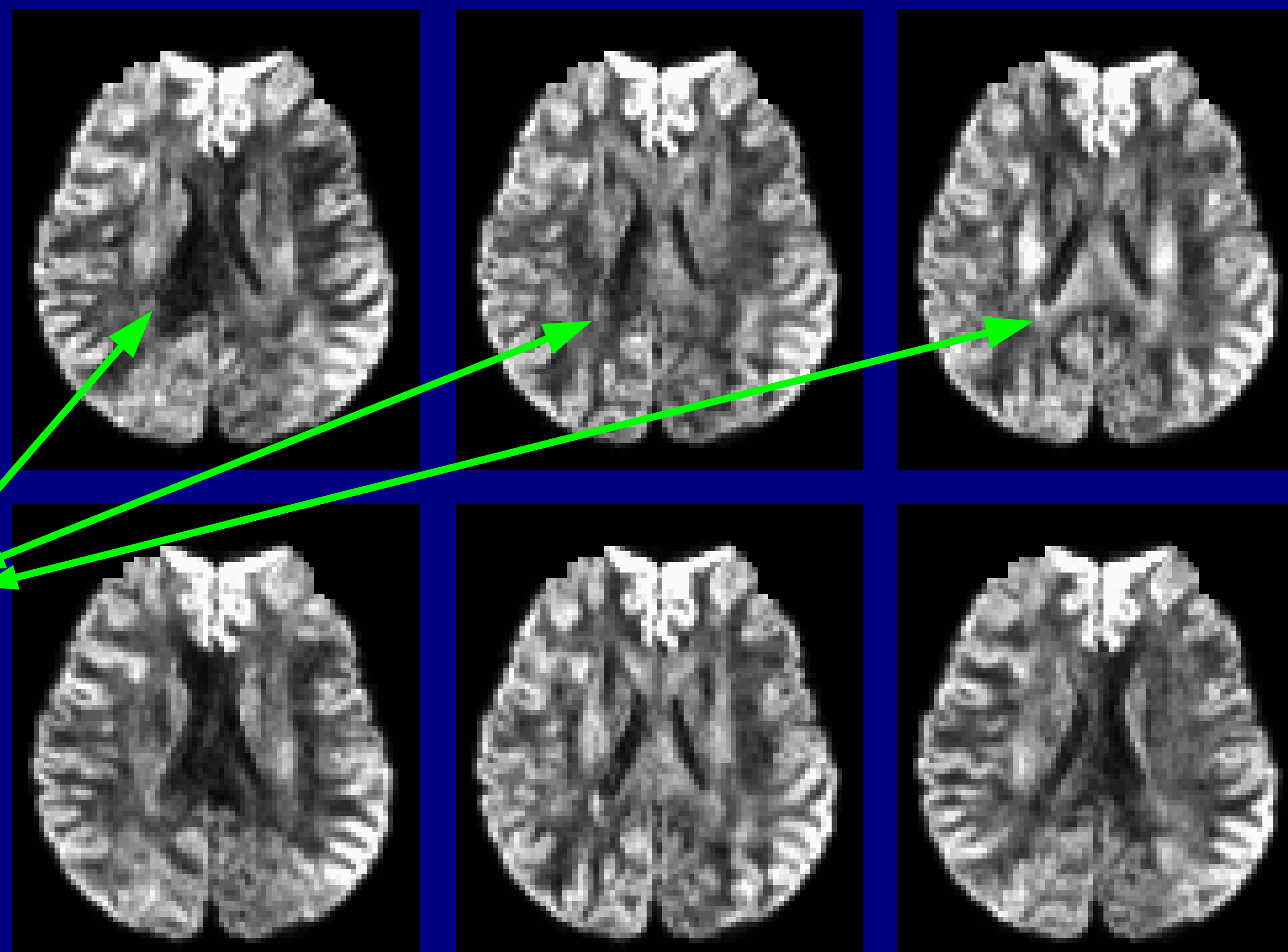

(Each DWI has a different brightness pattern: viewing structures from different angles.)

Noise in DW signals

MRI signals have additive noise

$$S_i = S_0\, e^{-b\, \mathbf{g}_i^T \mathbf{D}\, \mathbf{g}_i} + \varepsilon,$$

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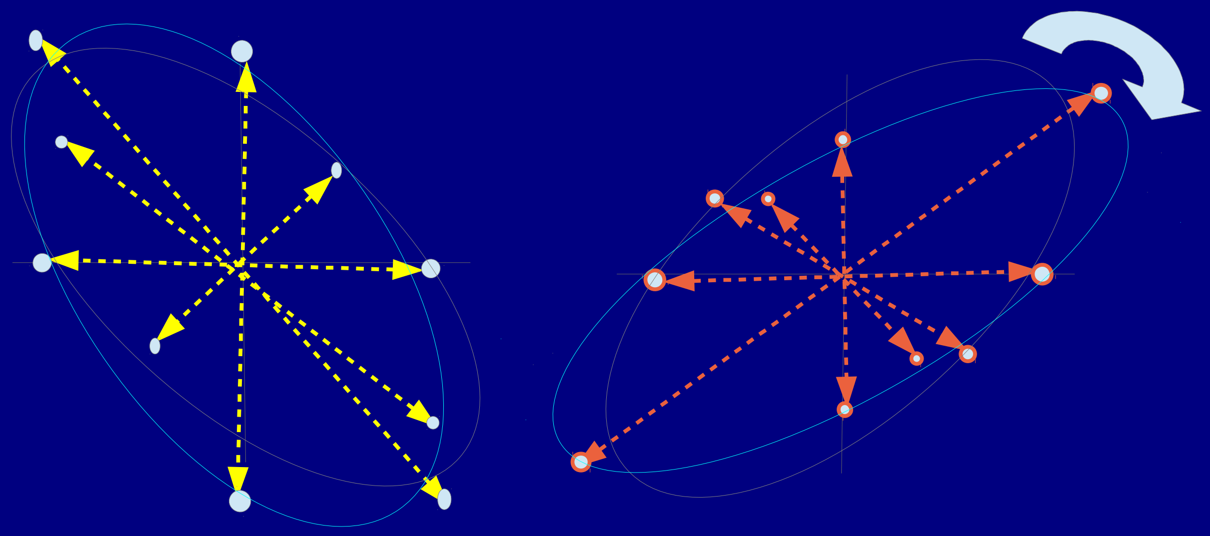
→ Leads to errors in surface fit, equivalent to *rotations* and *rescalings* of ellipsoids:



'Un-noisy' vs perturbed/noisy fit

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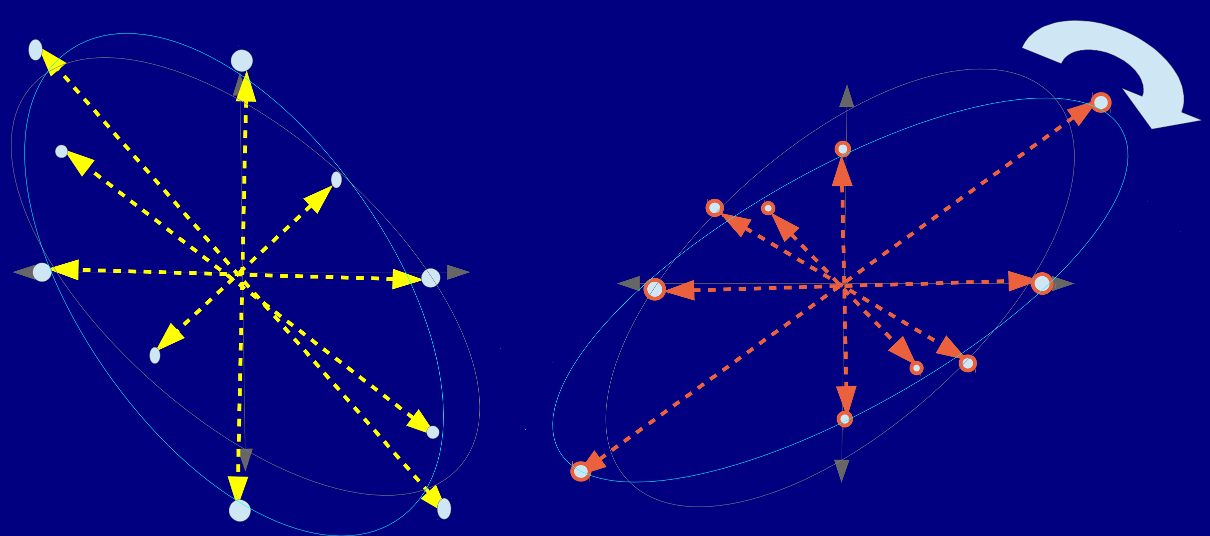


<u>Leads to standard:</u>

+ 30 DWs (~12 clinical)
+ repetitions of b=0
+ DW *b* chosen by: MD * *b* ≈ 0.84
+ nonlinear fitting

'Un-noisy' vs perturbed/noisy fit

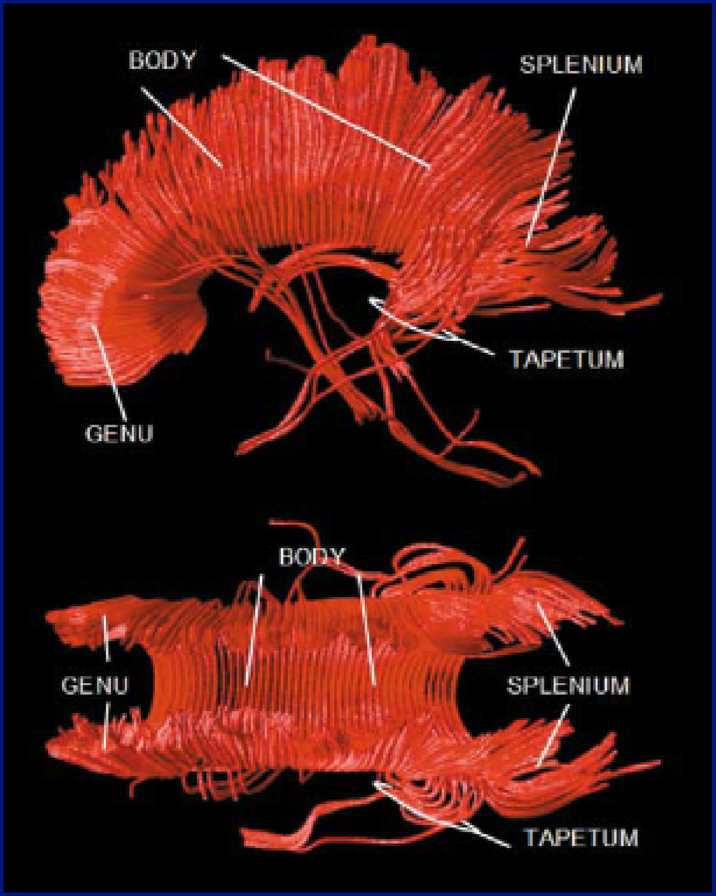
Now discuss using *local* structure information
to generate/estimate *nonlocal* structures:
WM tractography

Tractography in brief

old, invasive

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

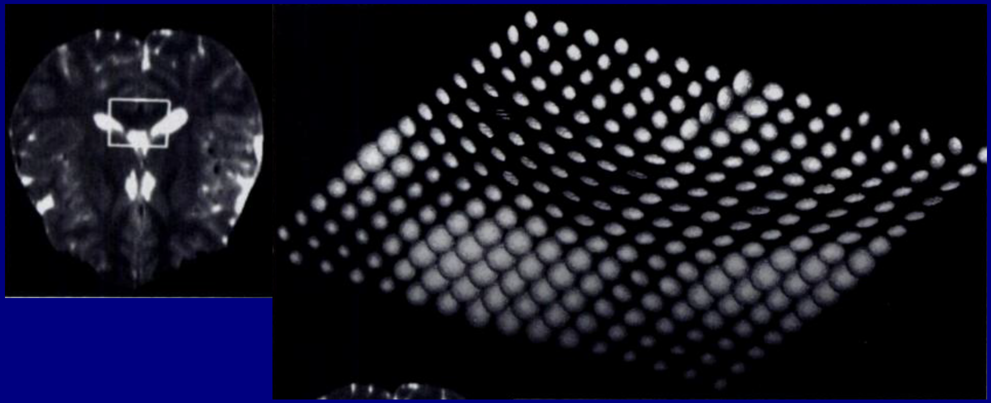
new(er), theoretical



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

Local DTs $\longrightarrow$ extended tracts

Field of local diffusion parameters



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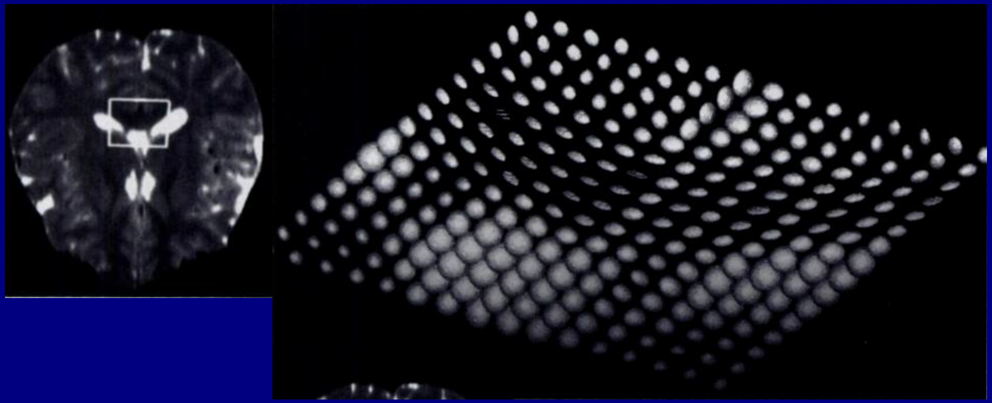


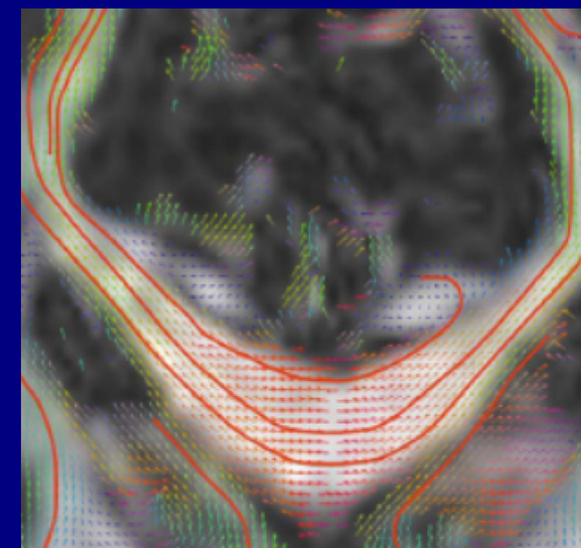
$\longrightarrow$ individual ellipsoids

Local DTs $\longrightarrow$ extended tracts

Field of local diffusion parameters

$\longrightarrow$ individual ellipsoids

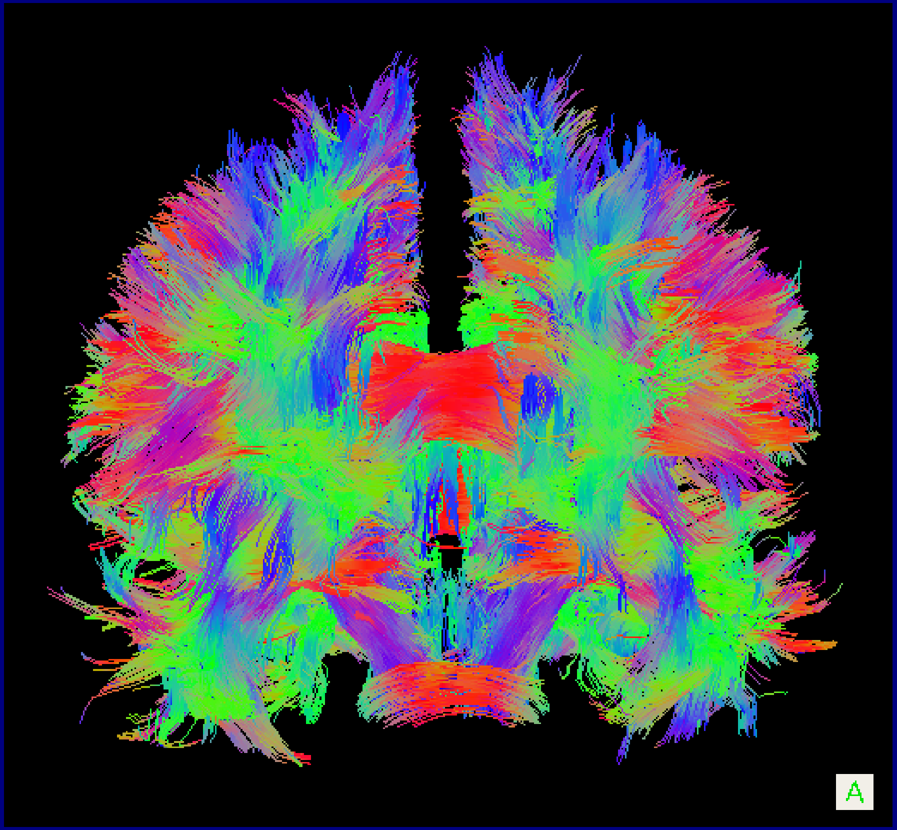
Connect to form extended tracts



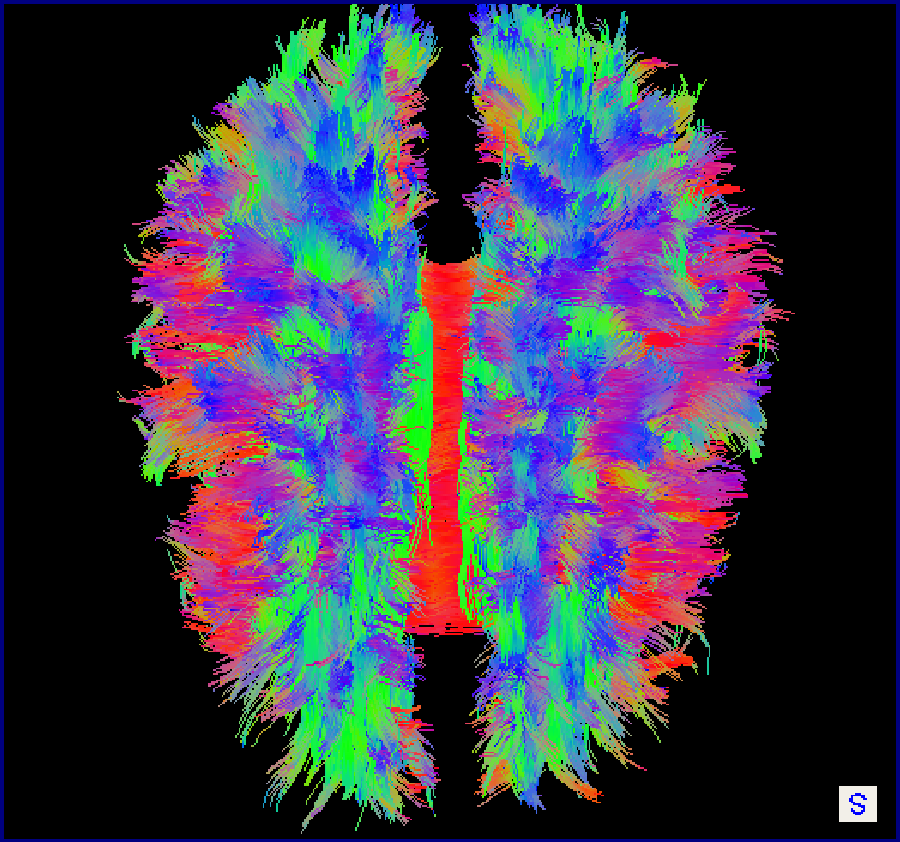
$\longrightarrow$ linked structures

Tractography: connecting the brain

(looking at you)

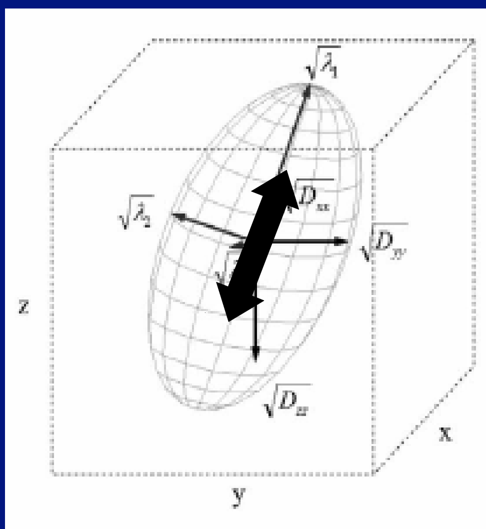


(looking downward)



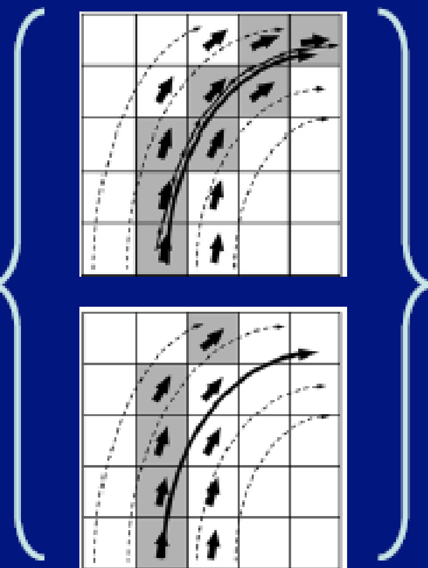
Tractography

Estimate WM structure (fiber tract locations)



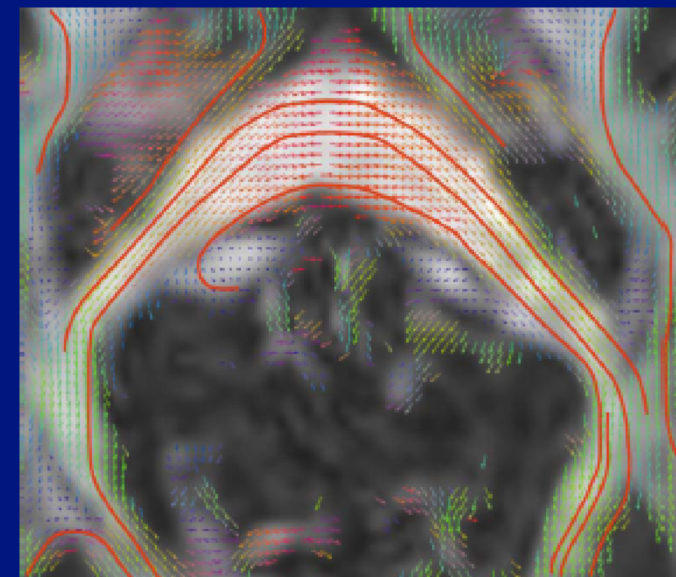
ellipsoid measures (~*smoothing of real structures*)

+



some kind of algorithm for connecting

=



estimate spatial extents of WM ‘tracts’ in vivo

(images from Bammer et al. 2003)

Diversity in tractography

Series of (mostly) logical, simple rules for estimating tracts
→ *<u>many</u>* methods/algorithms and kinds of parameters to choose:
(Mori et al., 1999; Conturo et al. 1999; Weinstein et al. 1999; Basser et al. 2000; Poupon et al. 2001; Mangin et al. 2002; Lazar et al. 2003; Taylor et al. 2012; ….)

Propagation via, e.g.:
smoothing diffusion vectors and solving differential equations; deflecting propagating tracts; allowing tracts themselves to 'diffuse'; solving for global minimum energy of connections…

To date, no single 'best' algorithm, work continues:
- histology can't give perfect answers.
- some test models (phantoms) exist, but not brain-complex

So, first question for using tractography in a study:

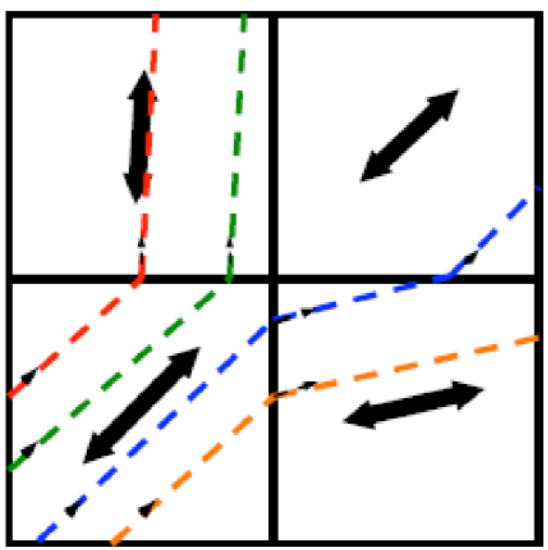
Which algorithm to choose?

Popular technique: FACT

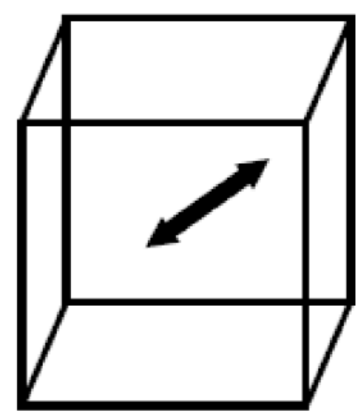
- FACT = Fiber Assessment by Continuous Tracking (Mori et al. 1999) [used more than 200 times in past 1.5 yrs]
  - Start in voxel with FA>0.2 (proxy definition for WM)
  - Follow 1st eigenvector/greatest diffusion direction to next voxel
  - Continue if FA stays>0.2 and angle between $\mathbf{e}_1$s is <45 deg

Ex.:

FACT (in 2D)



FACT (in 3D)



Very simple, but actually, gives some decent results, e.g.many known tracts

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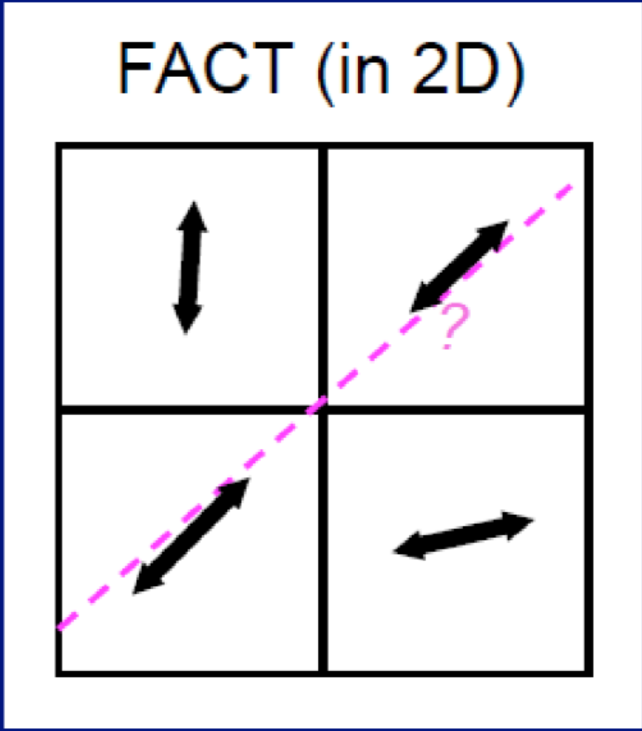

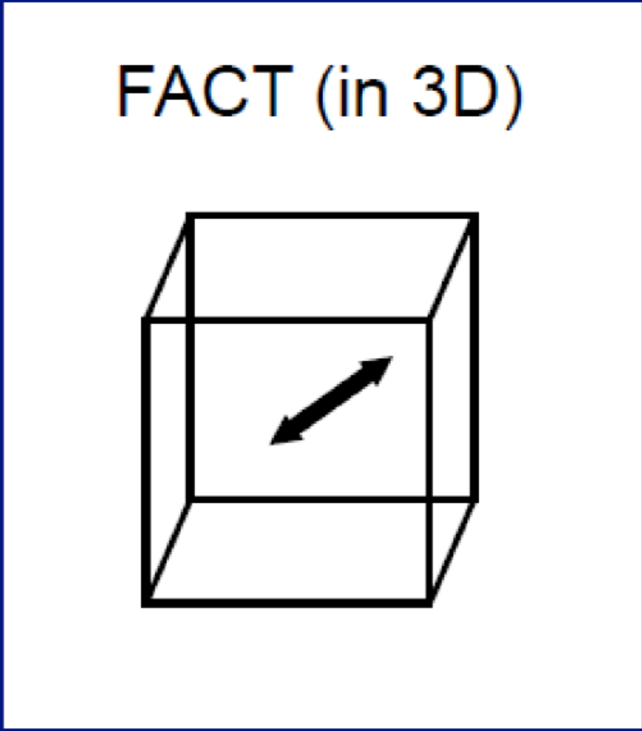

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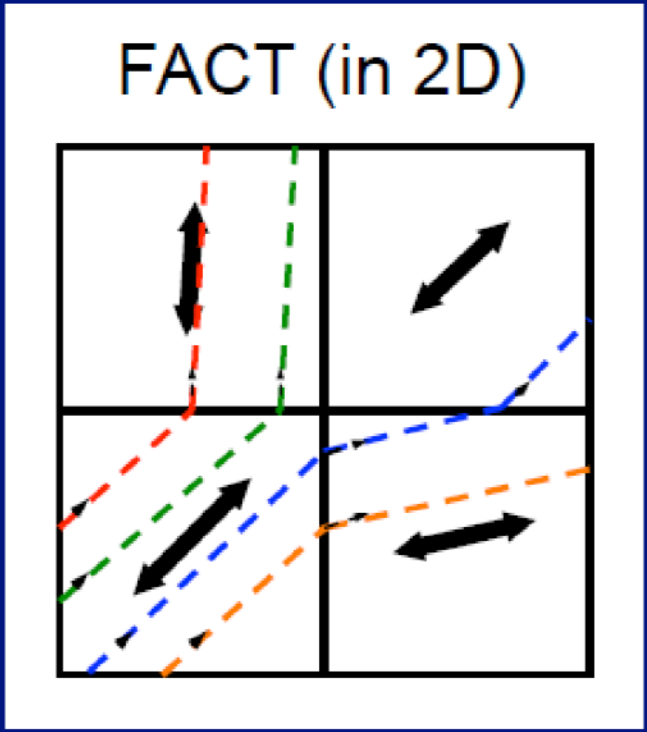

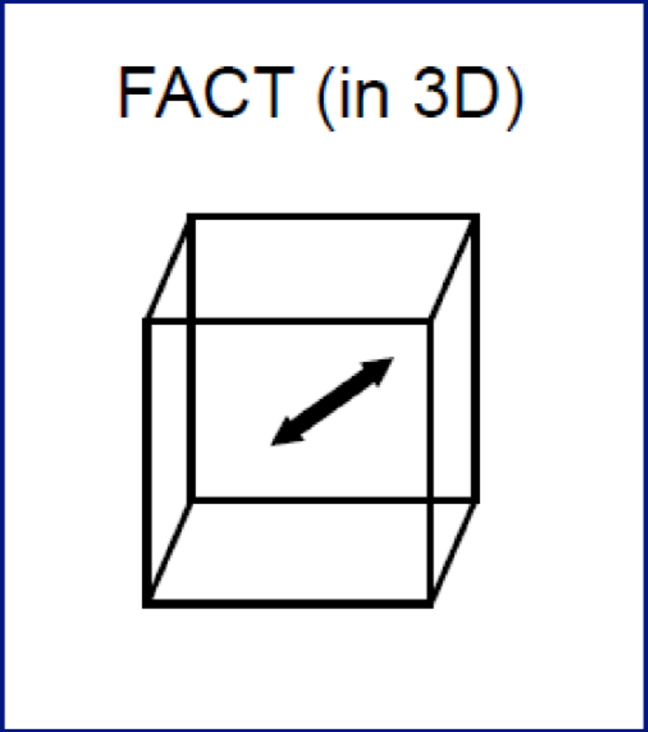

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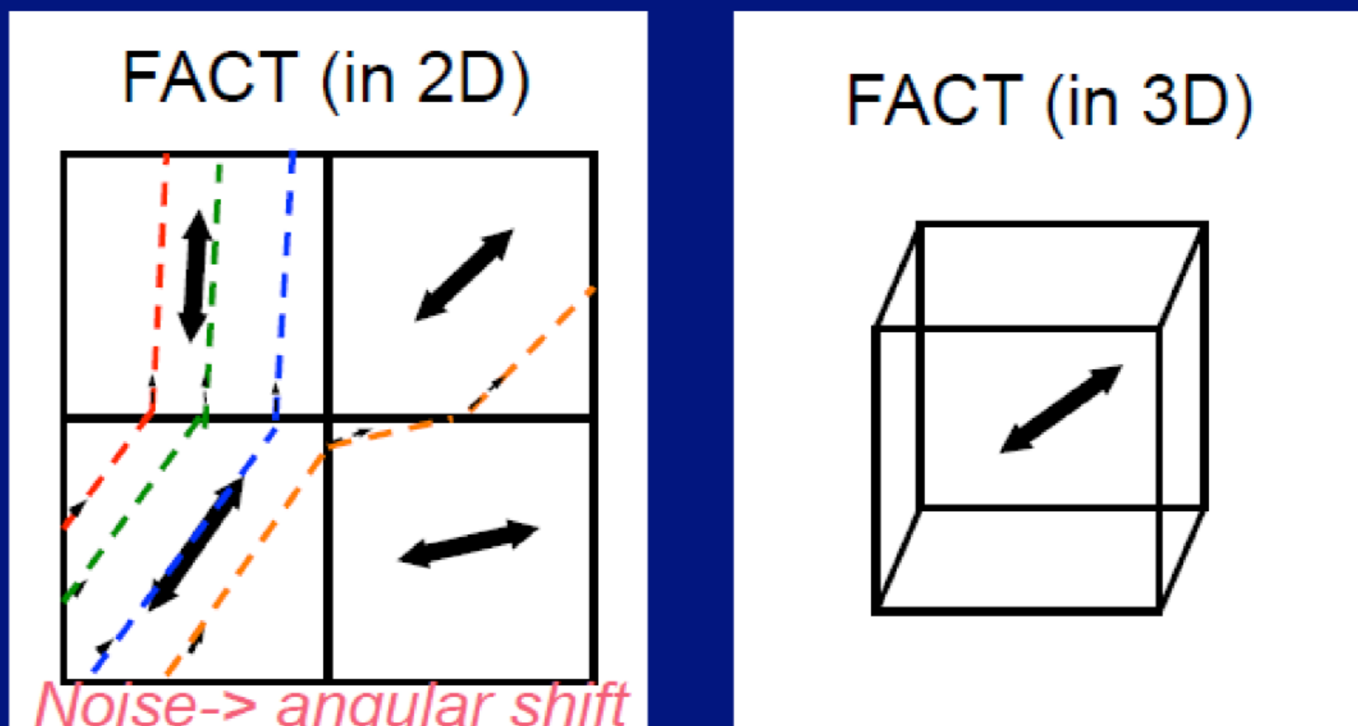

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Improving FACT->

- Start by thinking: what properties a ‘good’ algorithm should have?
  1) Should be independent of coordinate axes (i.e., results invariant to rotation of data set)
  2) Should improve with spatial resolution (convergence in resolution)
     e.g., like in calculus, diagonals are better approximated with small grid steps
  3) Should improve with SNR (converge in SNR)
  4) Should not have strong instability with or dependence on noise

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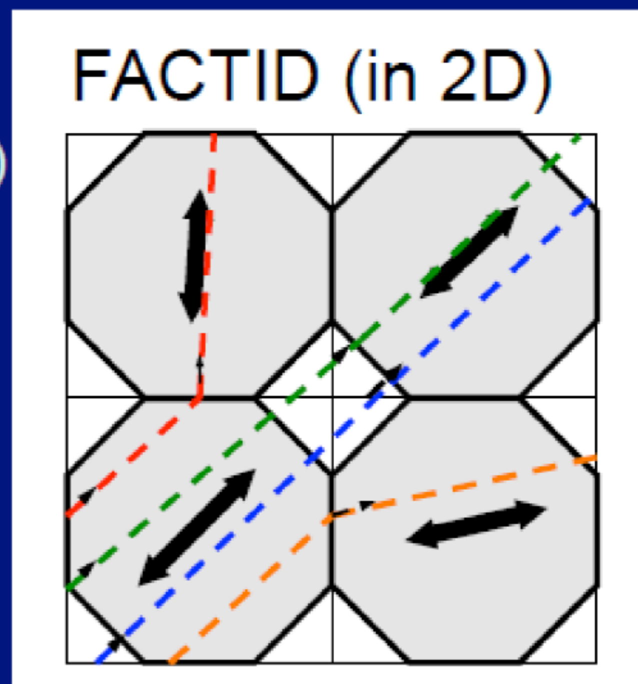
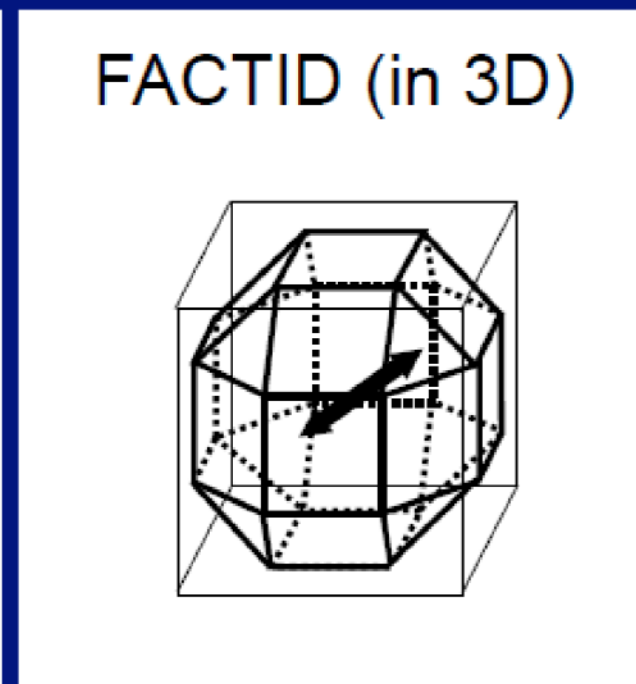
Posit: including diagonal (ID) propagation helps 1 and 4, check about other props.

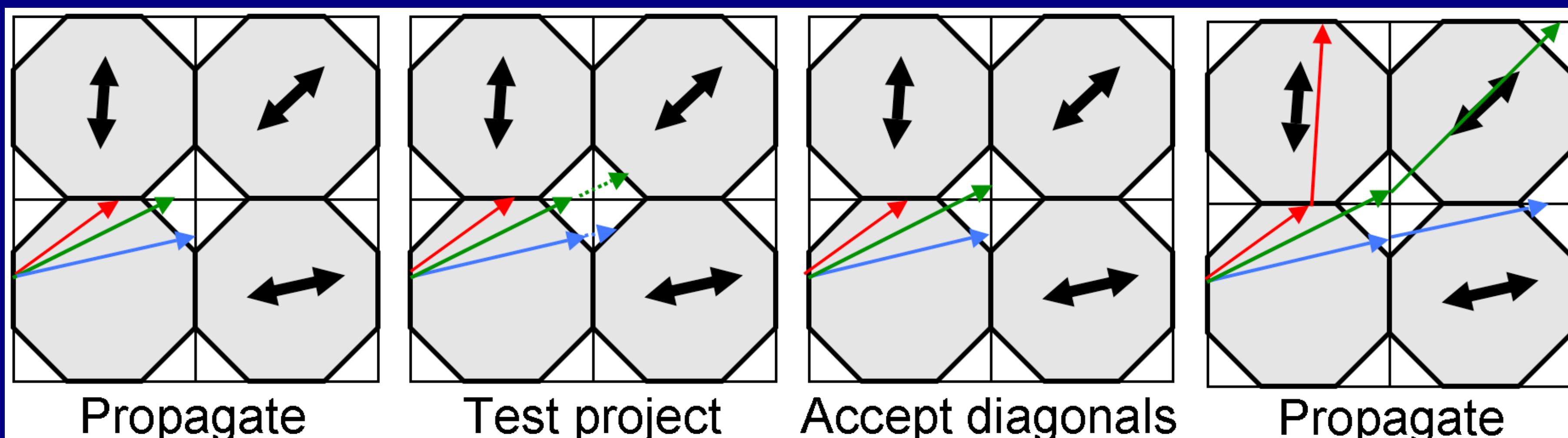




FACTID (FACT Including Diagonals):

+ Utilize simple check for diagonals.

(2D) Schematic:



(Taylor, Cho, Lin & Biswal, 2012)

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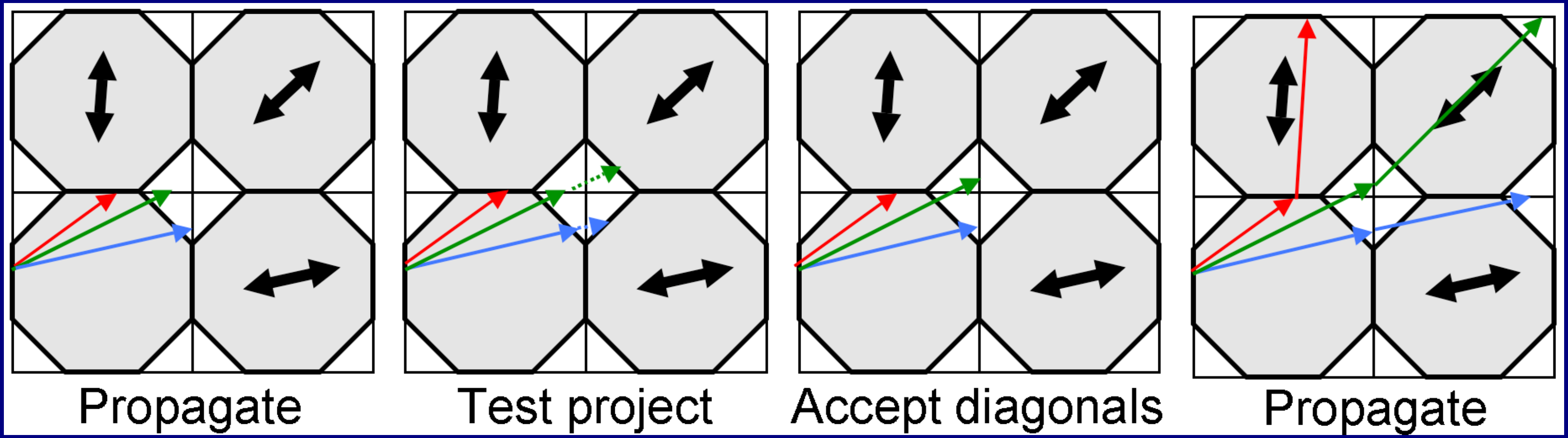
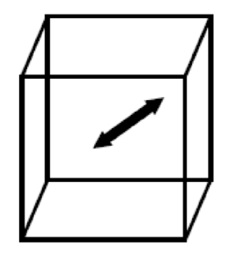
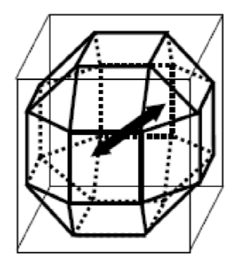


NB that in (3D) FACT, a single voxel has 6 neighbors for propagation, while in FACTID, a voxel has 26 neighbors propagation.



vs

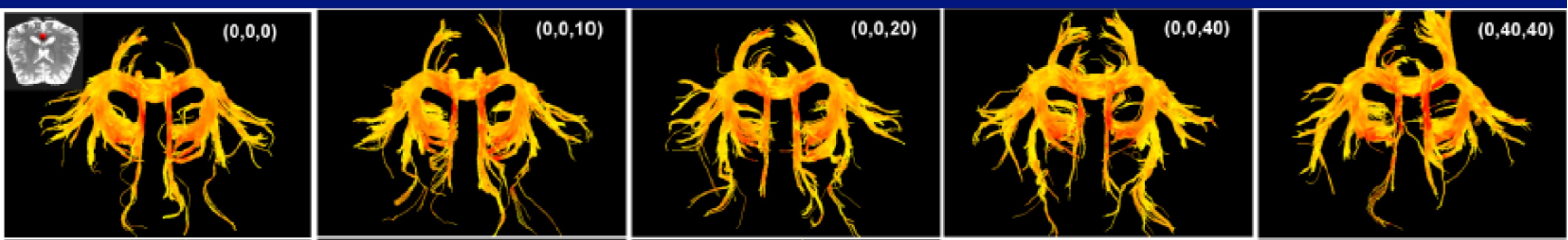


(Taylor, Cho, Lin & Biswal, 2012)

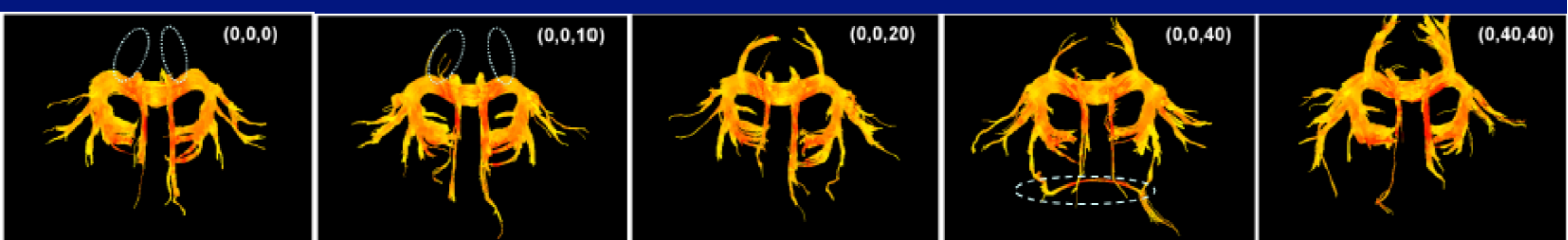
Test 1: Rotational invariance

A test for consistency of results when axes of data have been rotated; here, using data from a real subject (scan axes rotated)

FACTID

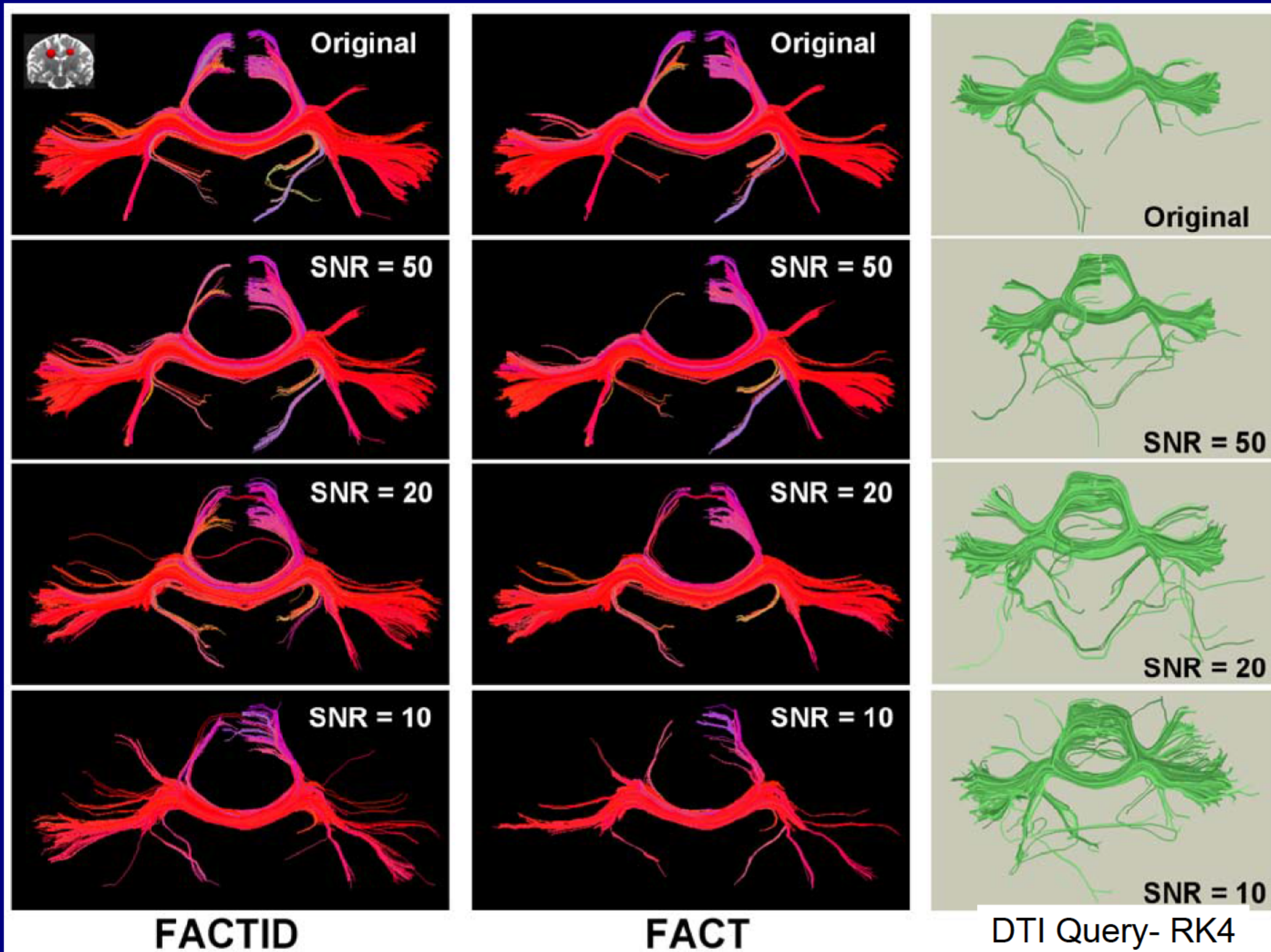


FACT



(Taylor, Cho, Lin & Biswal, 2012)

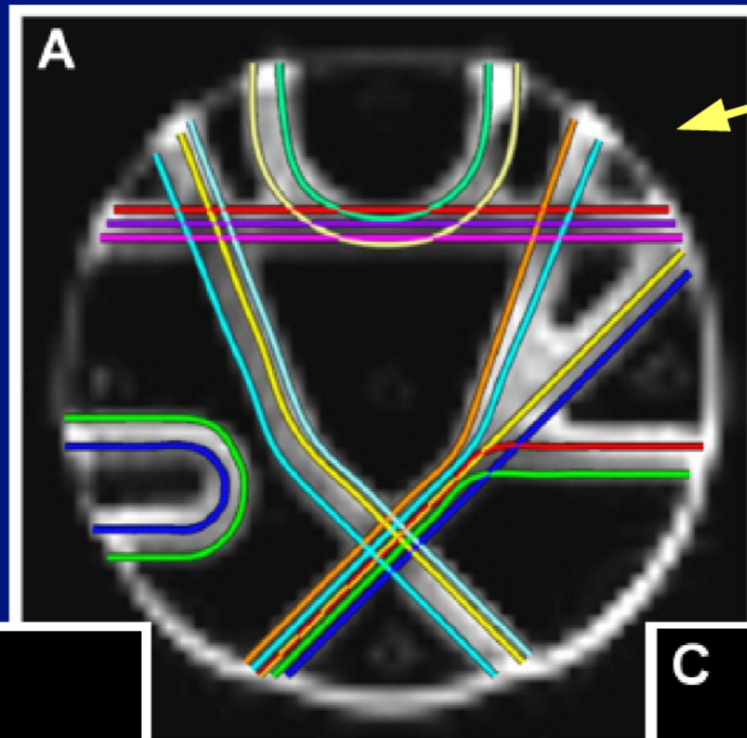
Test 3: Noise sensitivity



(Taylor, Cho, Lin & Biswal, 2012)

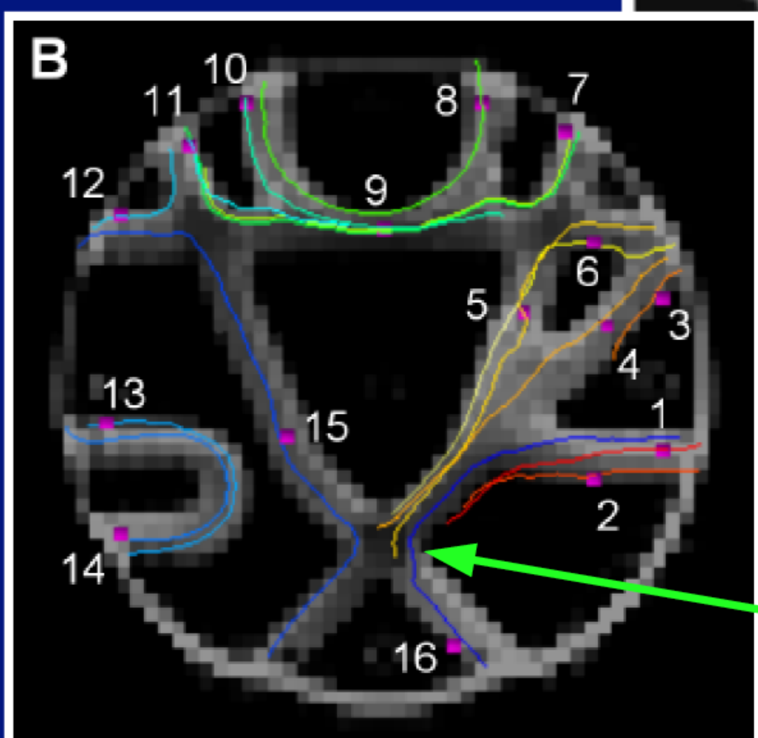
Test 5: Phantom Set

Fillard et al. (2011, NI) test phantom

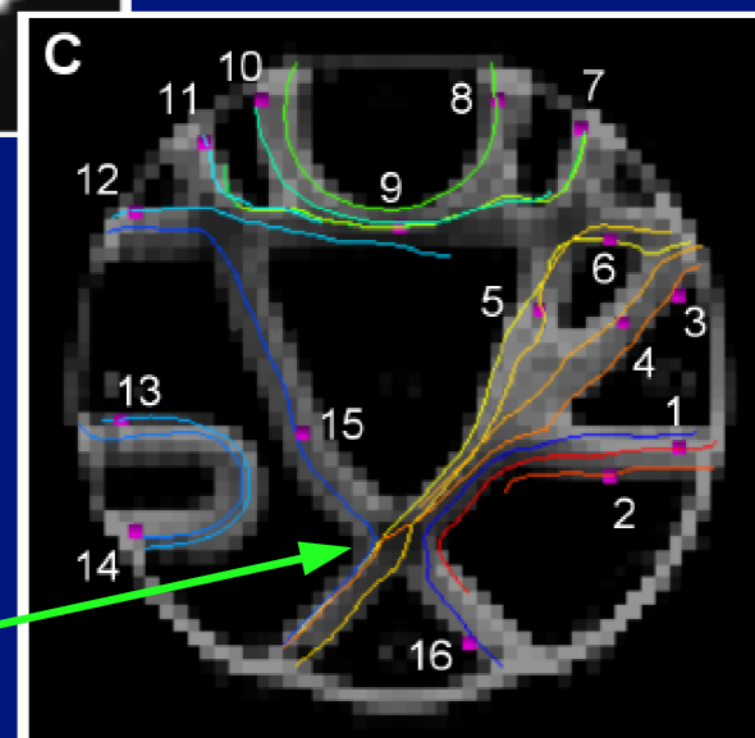


“ANSWER”

FACT



FACTID



(Taylor, Cho, Lin & Biswal, 2012)

e.g. compare

In addition to tracking algorithms, (great) care also has to be taken in pre-processing the diffusion data.

Importance of being processed (in earnest)

NB words of wisdom from wikipedia GIGO entry:

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

—Charles Babbage, Passages from the Life of a Philosopher

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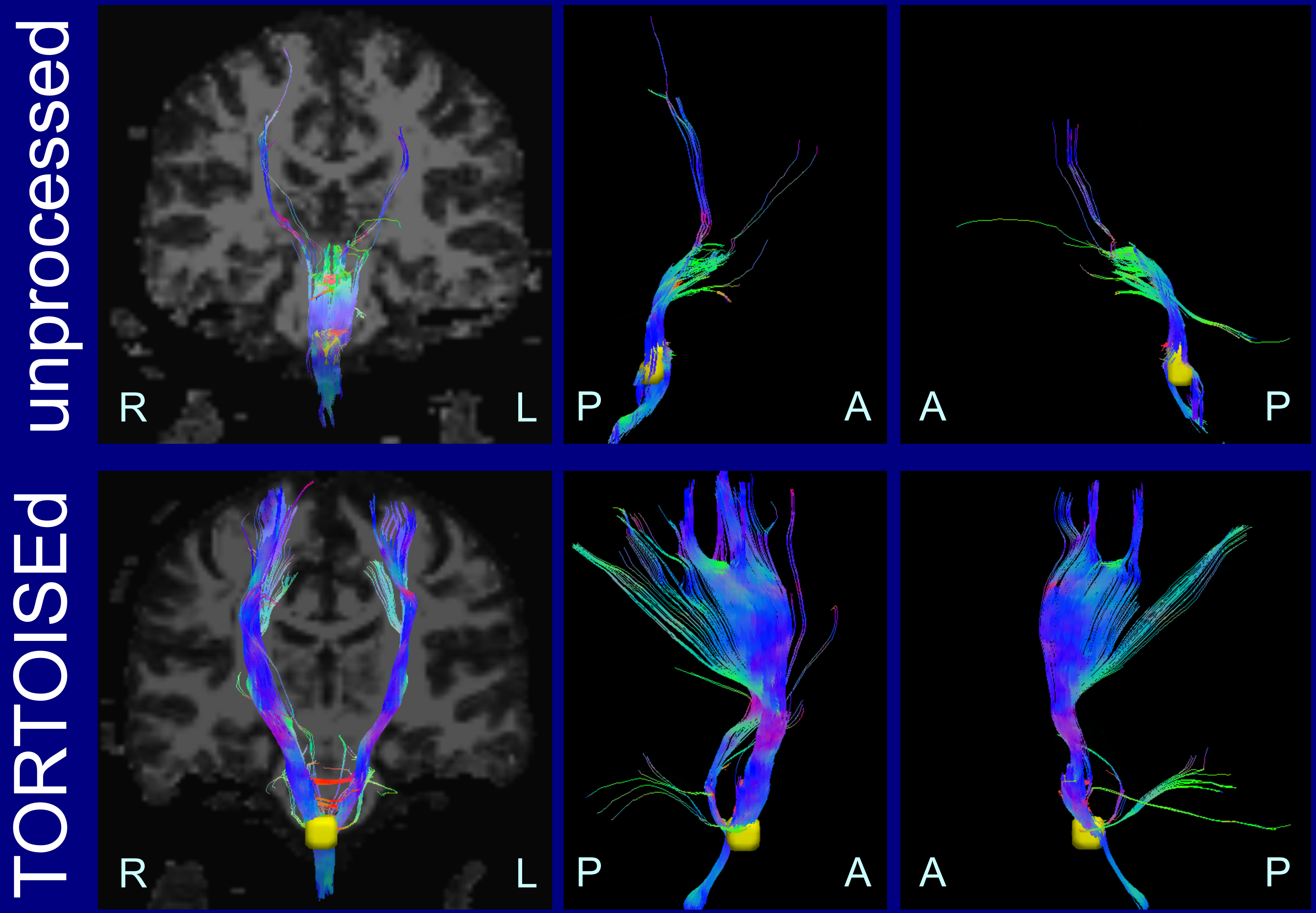
In addition to the tracking algorithm, the quality of data acquisition and preparation matter quite a bit

→ see the *TORTOISE* tool (Pierpaoli et al., 2010)

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

Importance of being processed (in earnest)



Data from the morning session, same target ROI in brainstem.

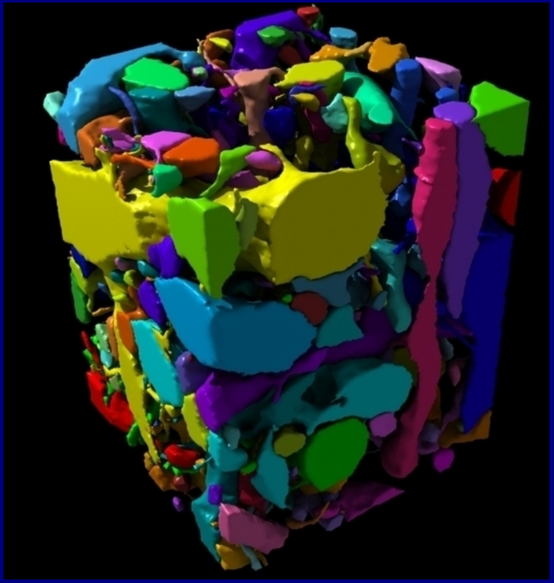
Consider reach of tracts, symmetry, physiology, etc.

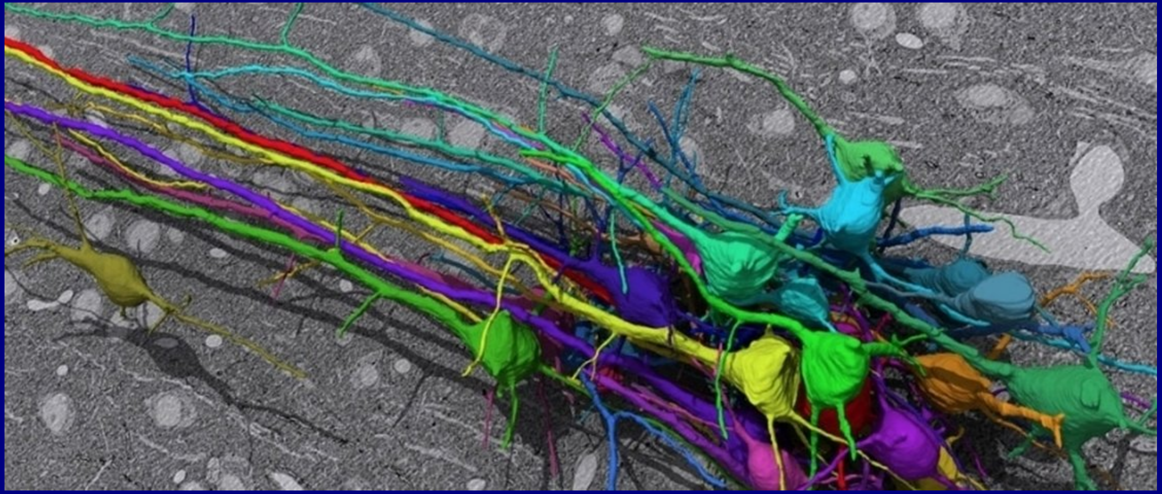
Cinematic side note:

La Belle et la Bête of tractography

Known Challenges for Tracking

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

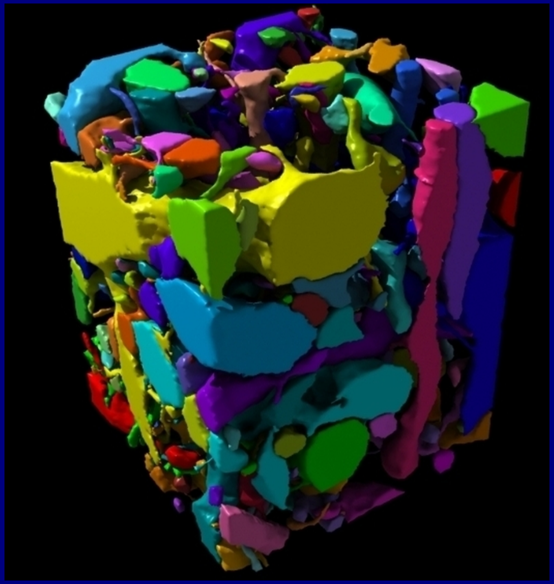


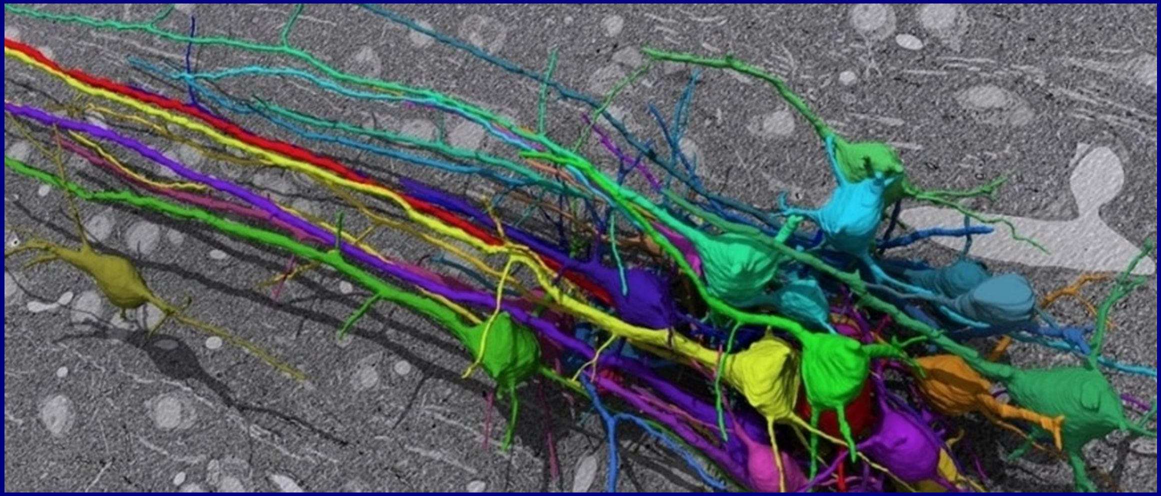


(images of Eyewire data via NPR website)

Known Challenges for Tracking

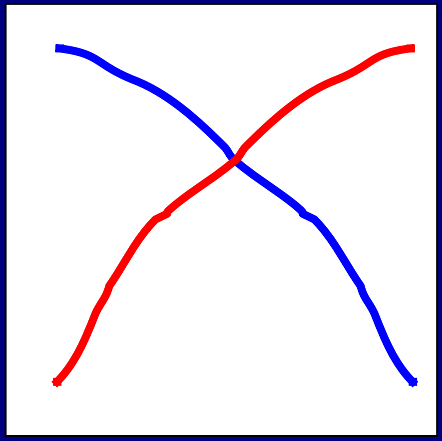
+ Axon diameters are of order a few micrometers
+ MRI voxel size is of order millimeters

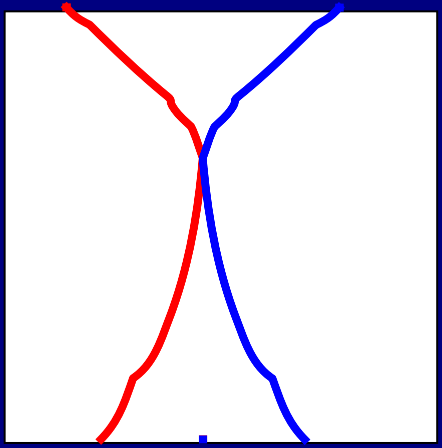




(images of Eyewire data via NPR website)

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

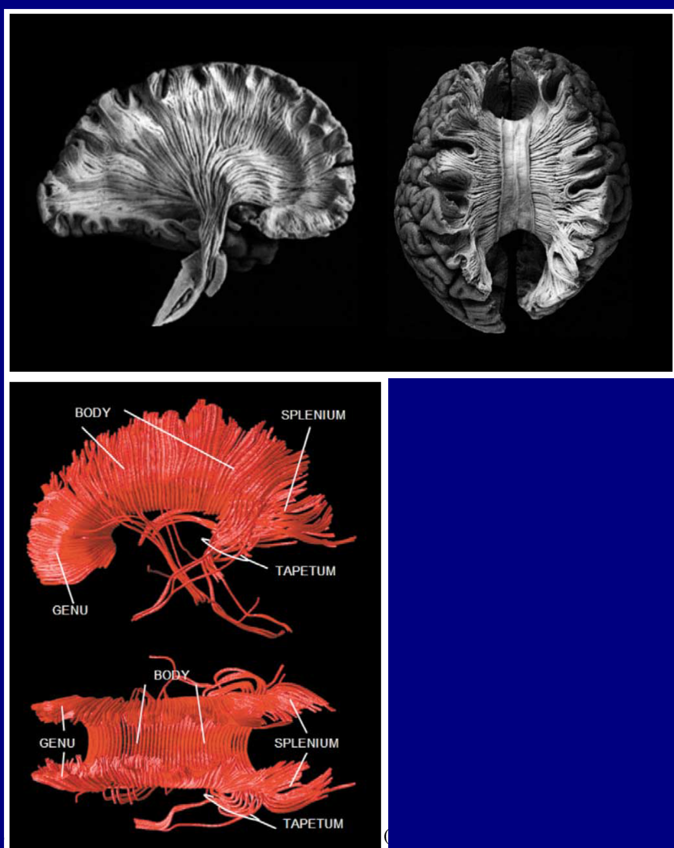




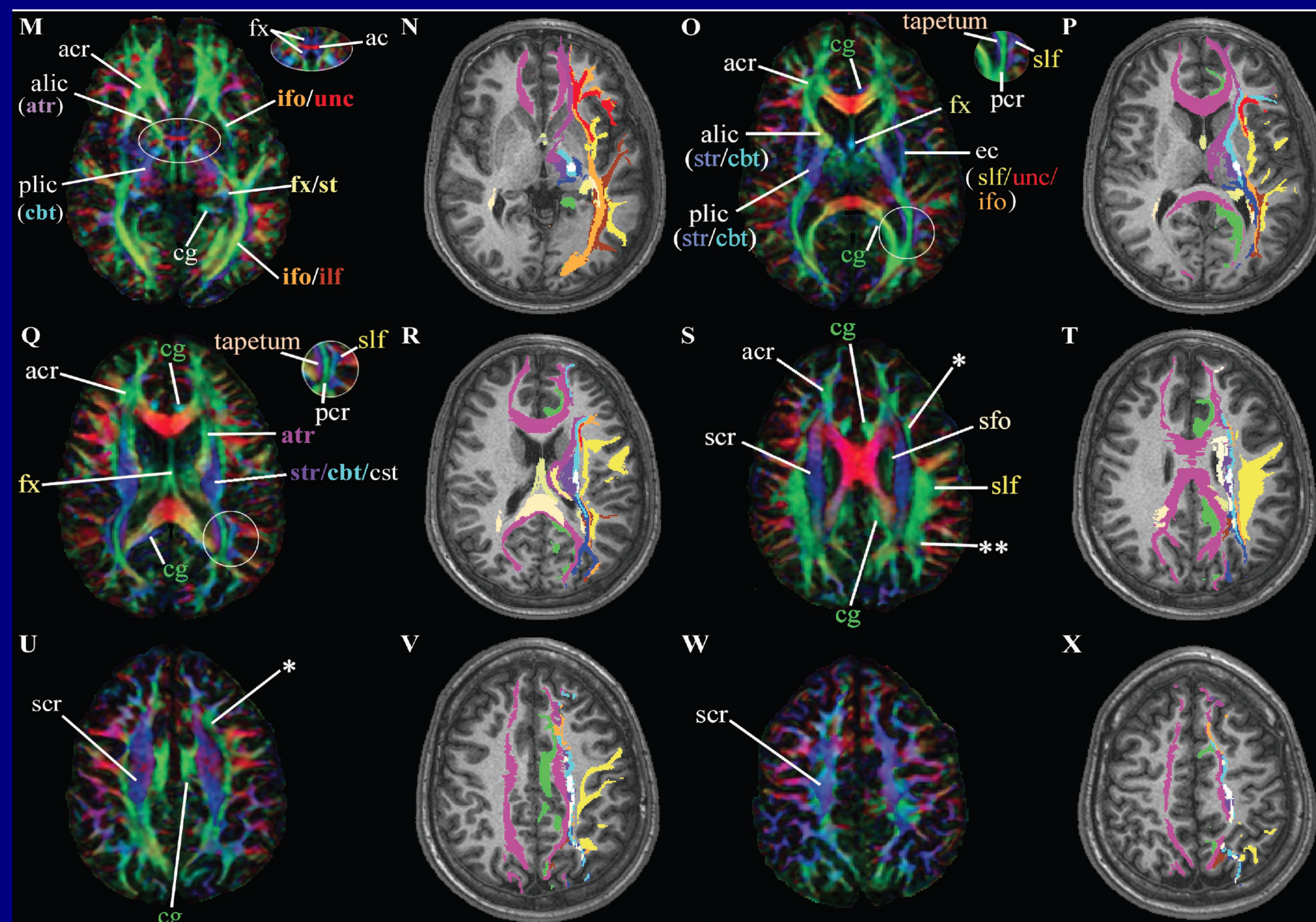
Crossing/kissing fibers can:
- Lower FA (stop tracking)
- Redirect (or *not*) tracking incorrectly.

Achievements of Tracking

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



(Bammer et al., 2003)



(Wakana et al., 2004)

Light at the end of the tunnel?

Tractography seems useful and logically consistent as follows:

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

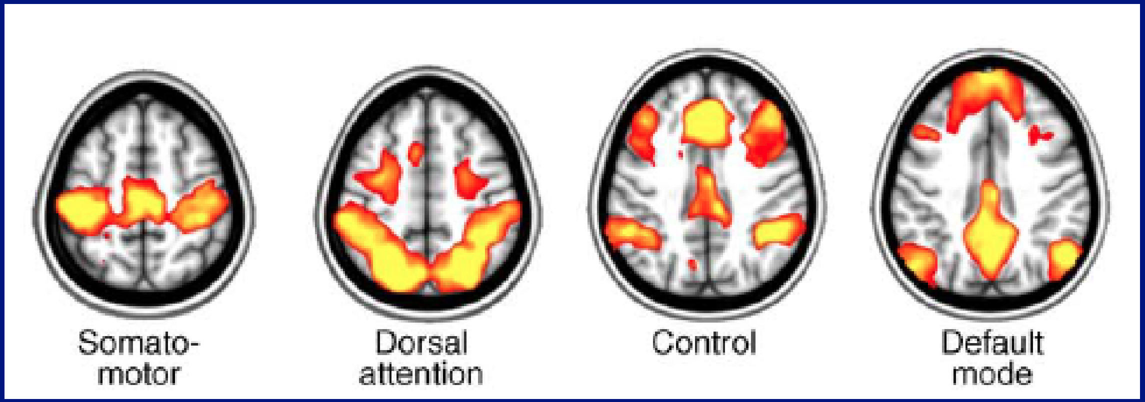
Applying tractography

Structure + Function

Simple example:

FMRI provides:
maps of (GM) regions working together

GM ROIs network:



Raichle (2010, TiCS)

Structure + Function

Simple example:

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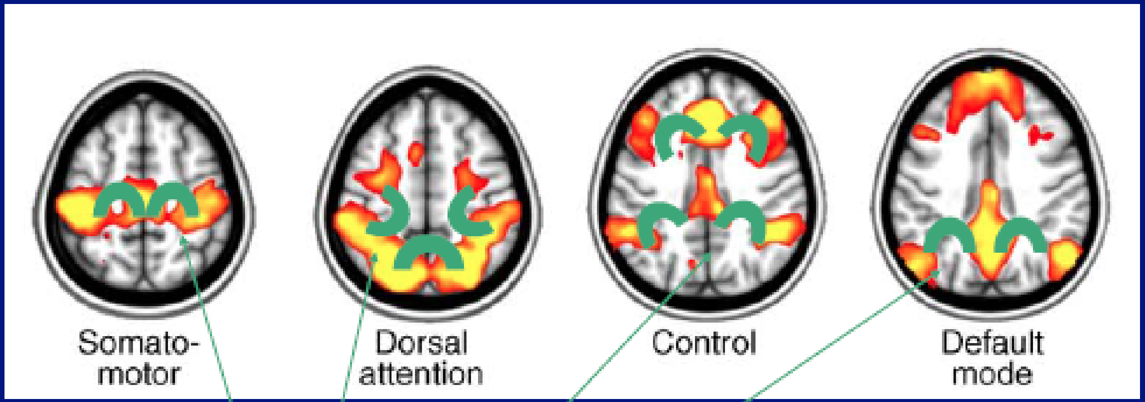

Raichle (2010, TiCS)

Associated WM ROIs

Structure + Function

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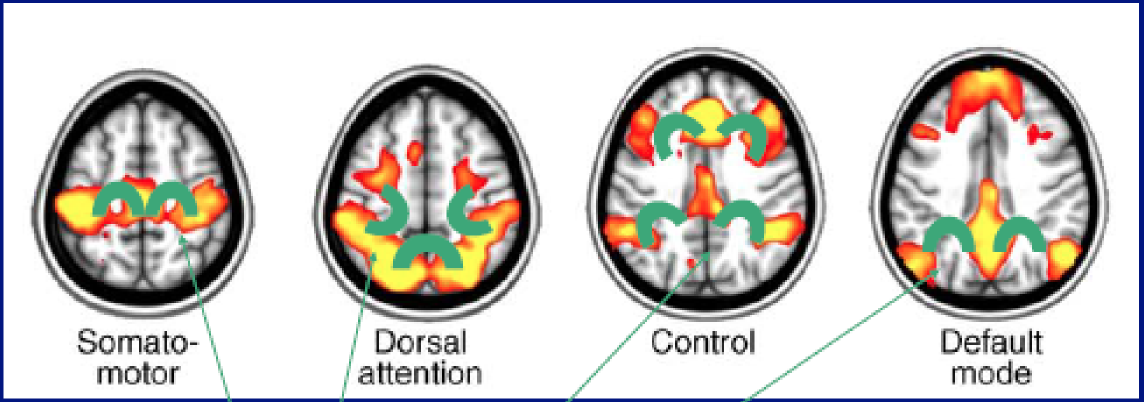


Raichle (2010, TiCS)

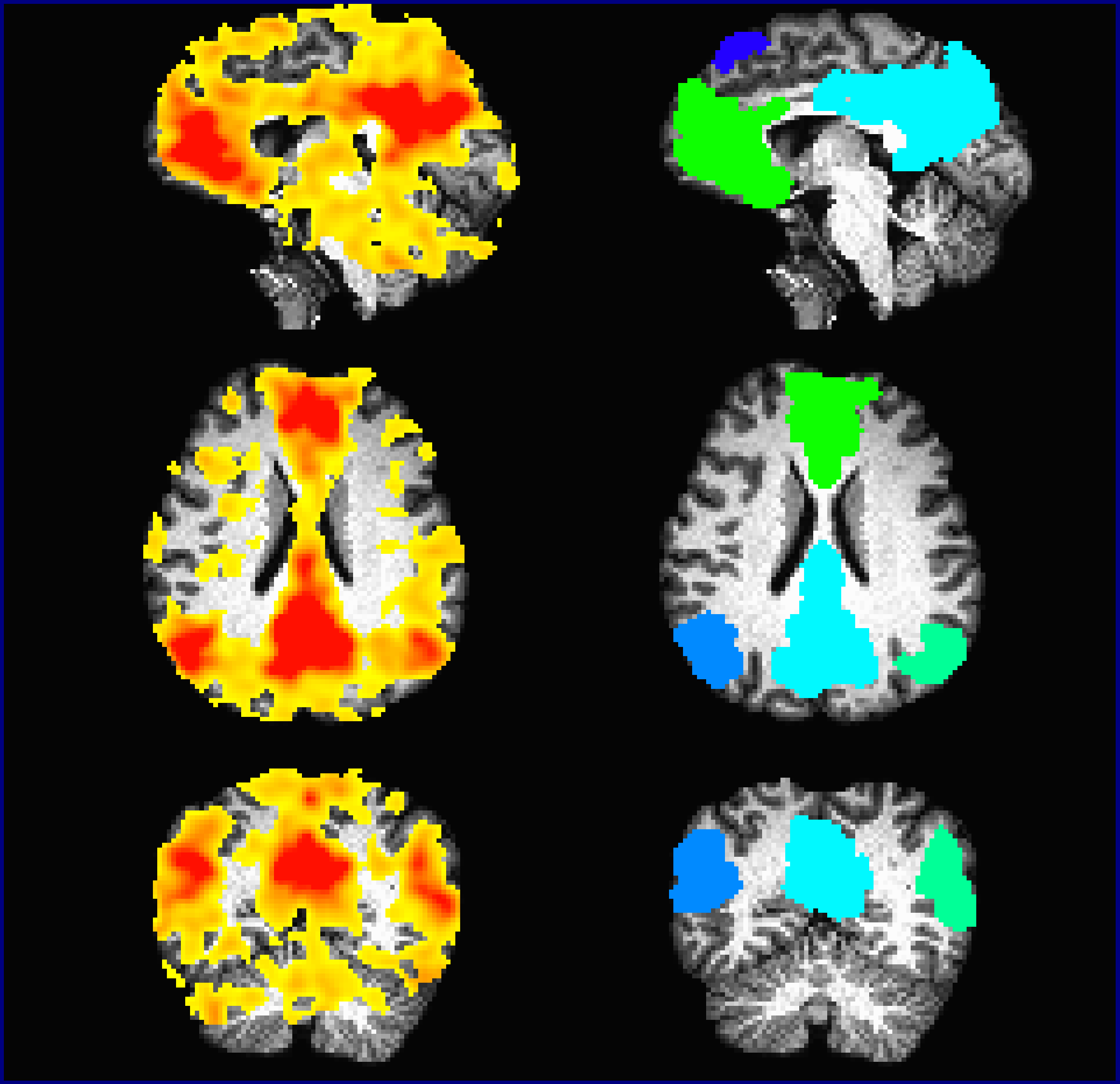
Associated WM ROIs

Our goal for tractography->
estimate likely/probable locations of WM associated with GM, and relate ROI quantities with functional/GM properties

Example: Tractographic selections of WM

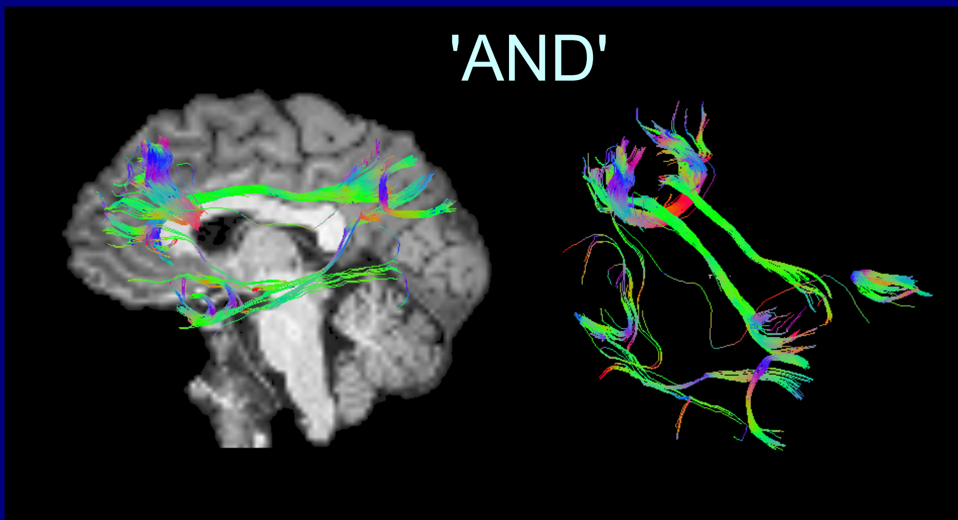
1) Start with FMRI:
→ threshold to obtain
networks of GM ROIs

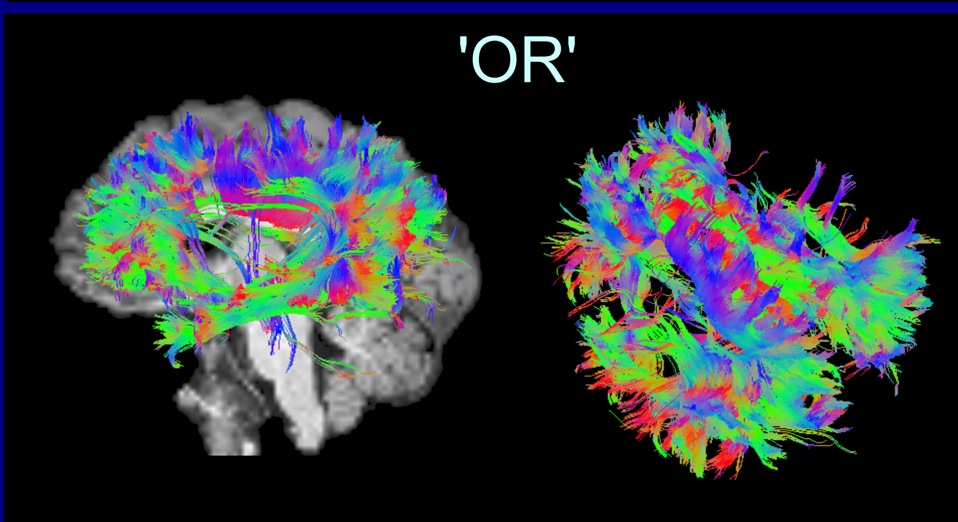
$Z>0$ (map) $\quad$ $Z>2.3$ (mask)

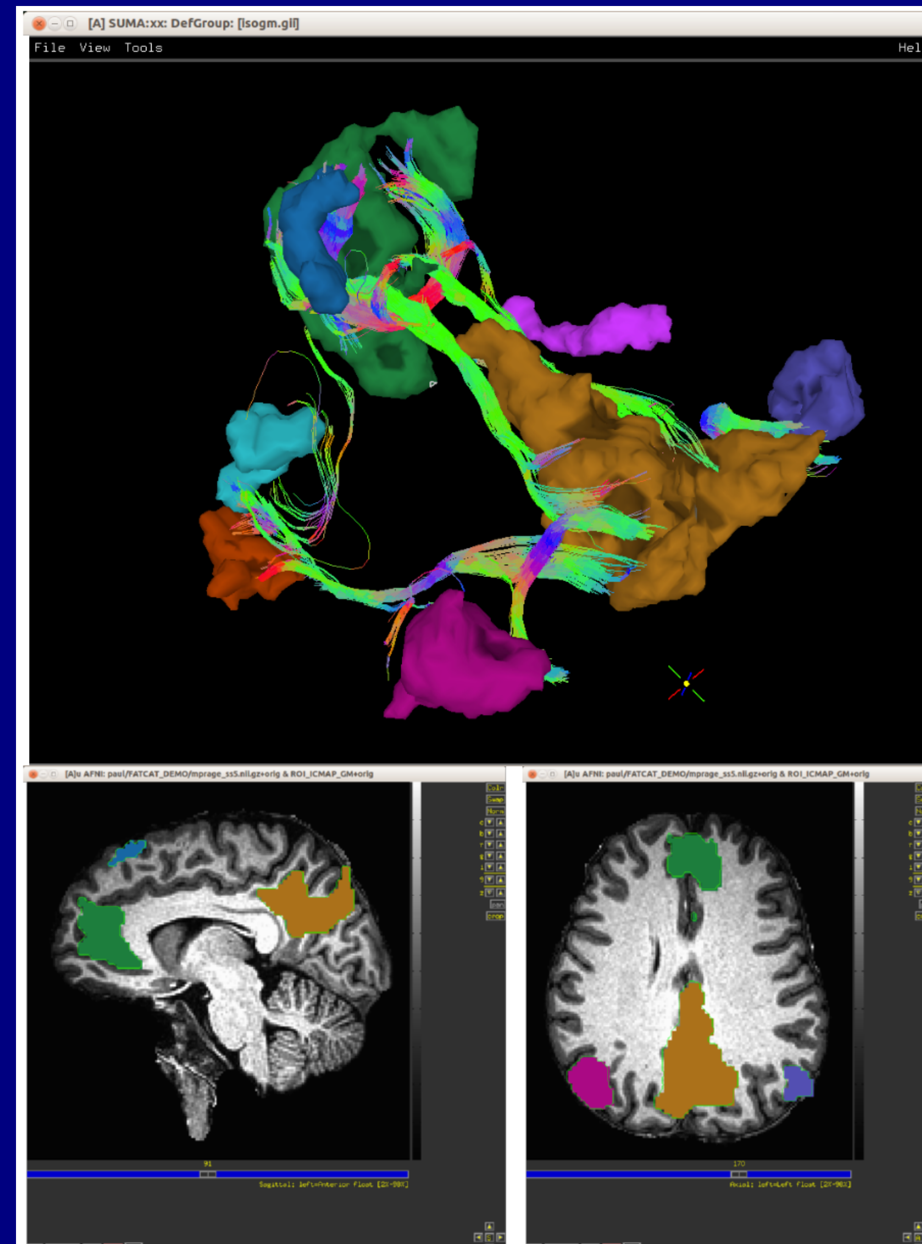


Example: Tractographic selections of WM

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





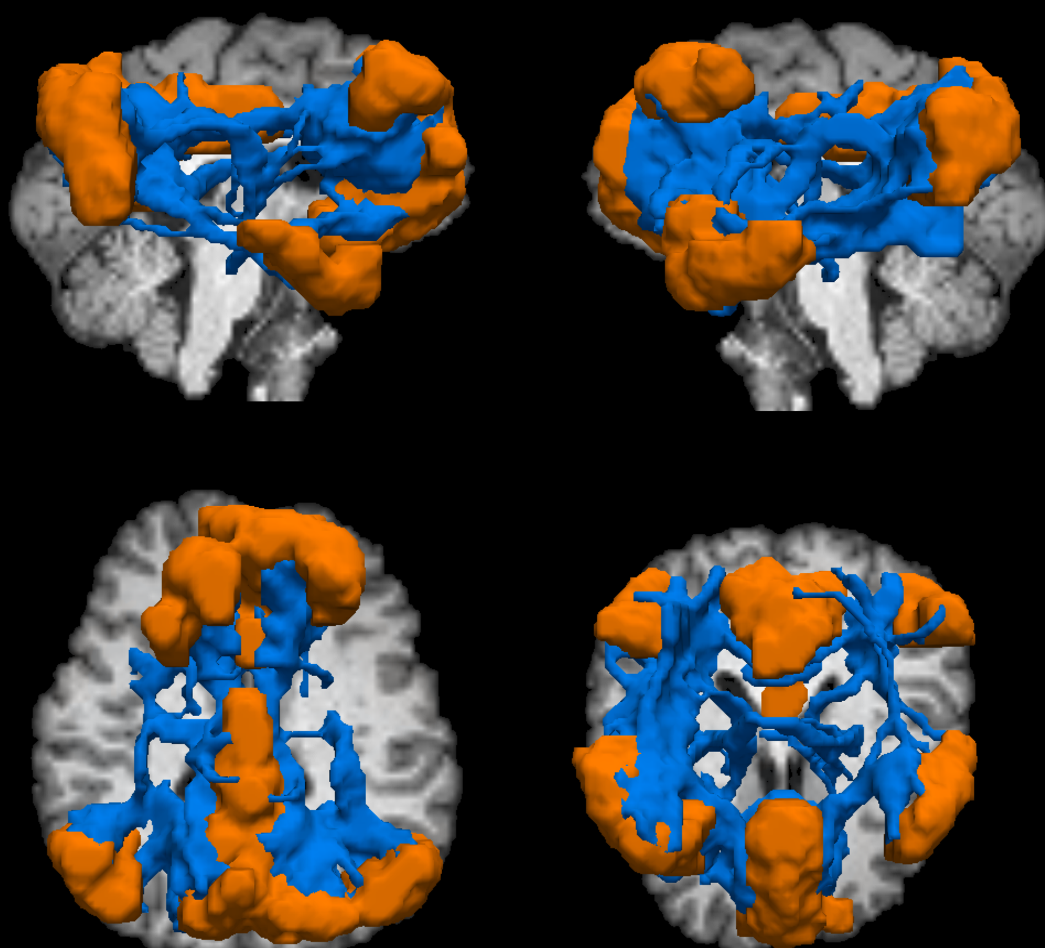


(Deterministic tracking using publicly available AFNI-FATCAT software)

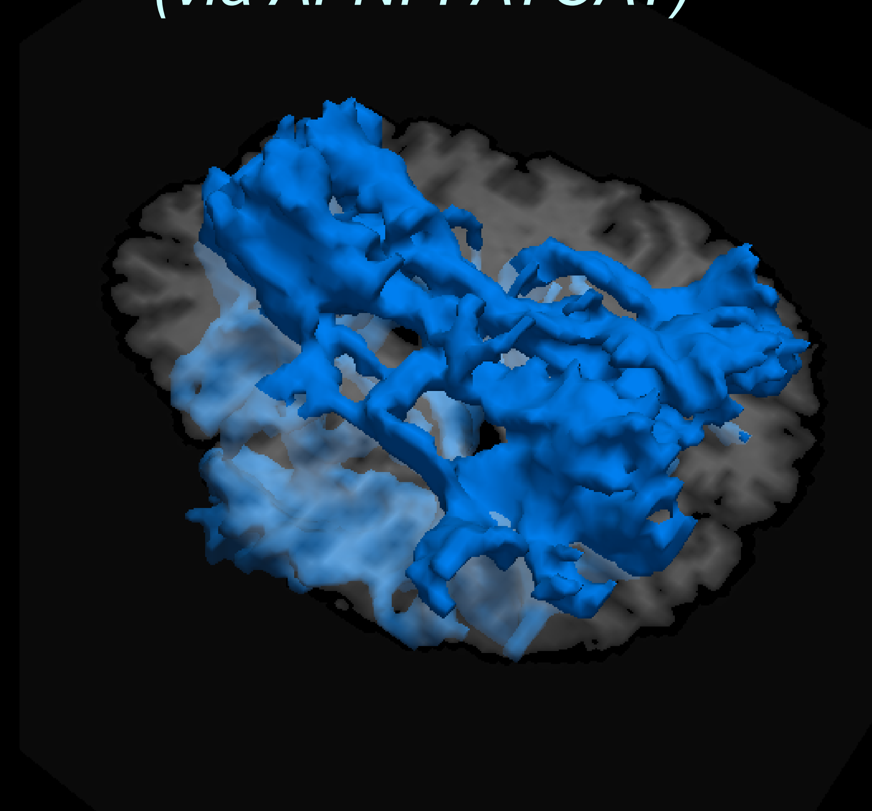
Example: Probabilistic tractography

More robust tracking method (many Monte Carlo iterations)

→ '***most likely***' locations of WM



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



Brings up next question for doing tractography:

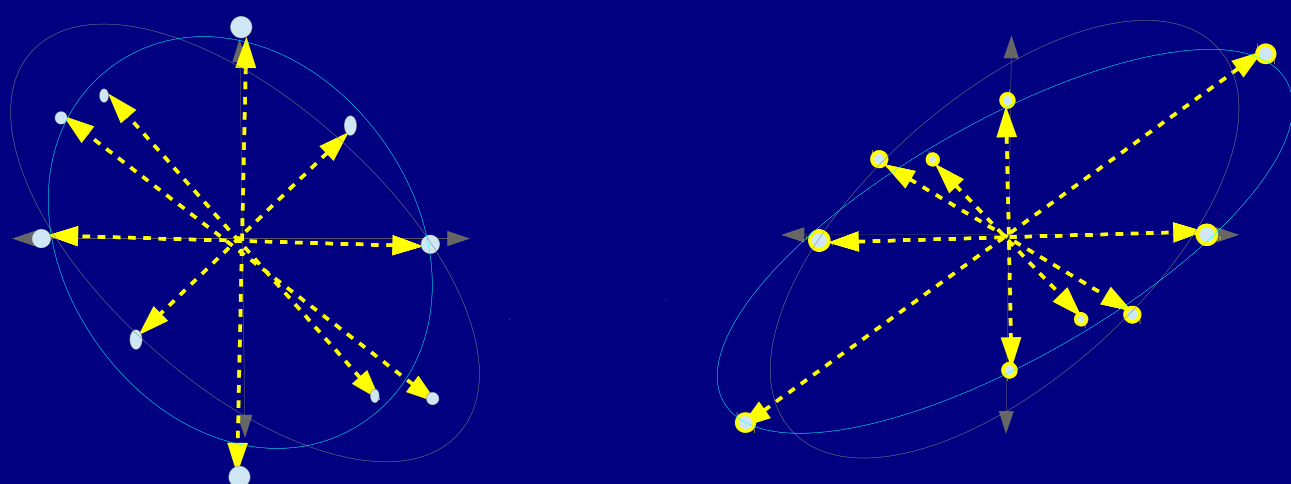
How do we estimate tensor parameter noise/uncertainty?

Noise in DW signals

MRI signals have additive noise

$$S_i = S_0\, e^{-b\, \mathbf{g}_i^T \mathbf{D}\, \mathbf{g}_i} + \varepsilon,$$

where ε is (Rician) noise, with the effect of leading to errors in surface fit, equivalent to *rotations* and *rescalings* of ellipsoids:



'Un-noisy' vs perturbed/noisy fit

EPI distortions, subject motion, et al. also warp ellipsoids.

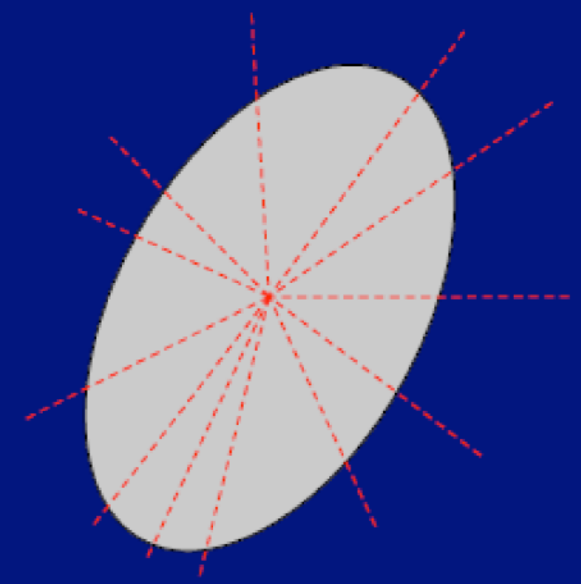
DTI Uncertainty

- We use jackknife resampling (e.g., Efron 1982)
  - Other studies have used bootstrapping (e.g., Jones 2003), or theoretical estimates (Jeong & Anderson 2008)
  - Jackknifing is efficient (just need one data set unlike bootstrap), simpler than theory, since, e.g., SNR is likely not constant across voxels

Jackknifing

- Basically, take M acquisitions

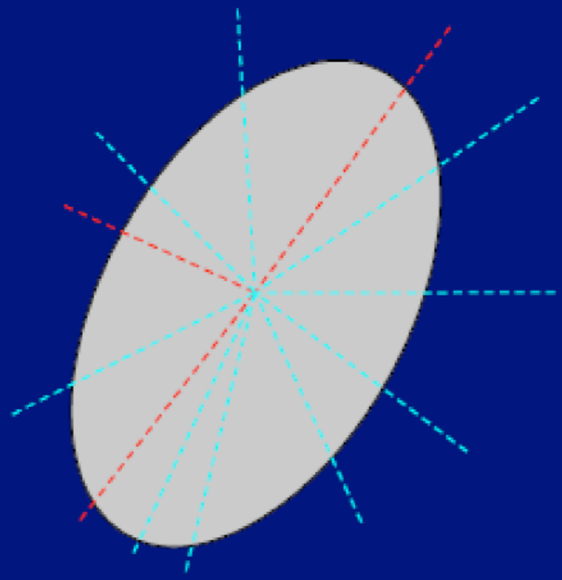
e.g., M=12



Jackknifing

- Basically, take M acquisitions
- Randomly select $M_J < M$ to use to calculate quantity of interest
  - standard nonlinear fits

e.g., $M=12$
$M_J=9$

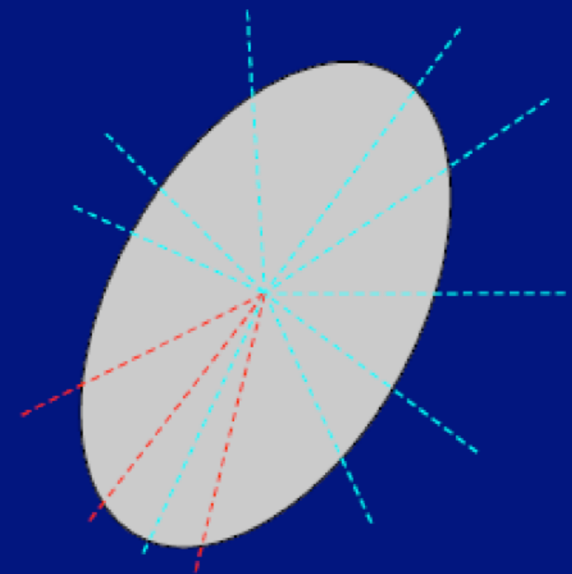


$$[D_{11} \;\; D_{22} \;\; D_{33} \;\; D_{12} \;\; D_{13} \;\; D_{23}] = \ldots$$

Jackknifing

- Basically, take M acquisitions
- Randomly select $M_J < M$ to use to calculate quantity of interest
  - standard nonlinear fits
- Repeatedly subsample large number (~10^3-10^4 times)

e.g., M=12
M_J=9



$$[D_{11}\ D_{22}\ D_{33}\ D_{12}\ D_{13}\ D_{23}] = \ldots.$$
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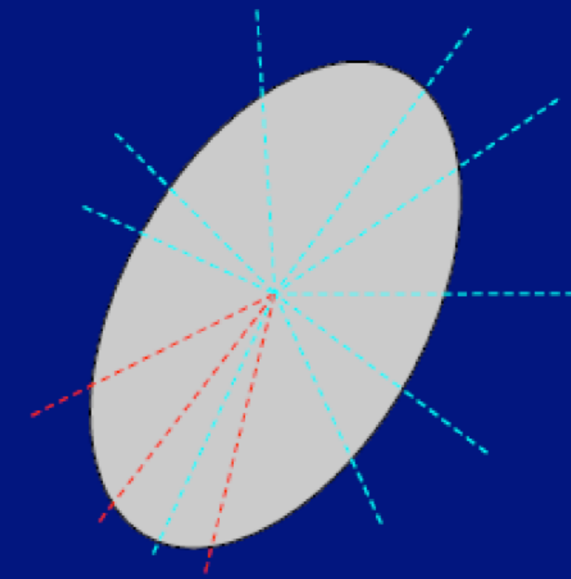
....

Jackknifing

- Basically, take M acquisitions
- Randomly select $M_J < M$ to use to calculate quantity of interest
  - standard nonlinear fits
- Repeatedly subsample large number ($\sim 10^3$-10^4 times)
- Analyze distribution of values for estimator (mean) and confidence interval
  - sort/%iles
    - (not so efficient)
  - if Gaussian, e.g. $\mu \pm 2\sigma$
    - simple

e.g., $M=12$

$M_J=9$



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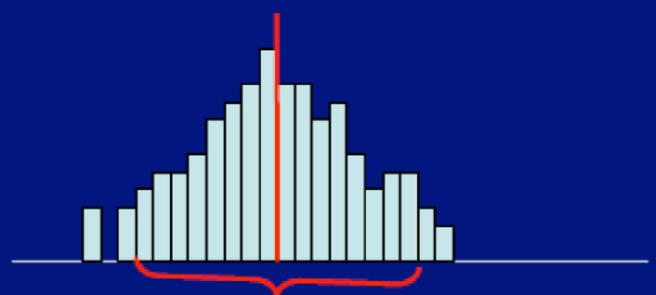
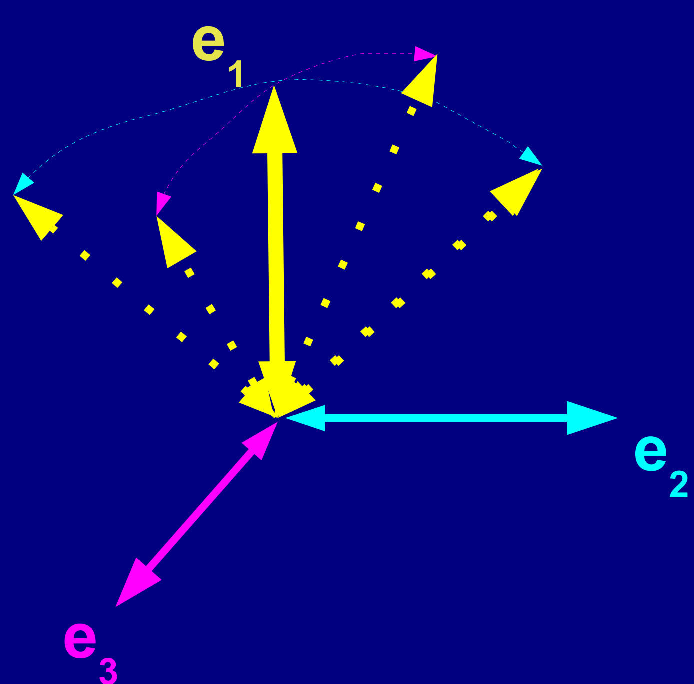
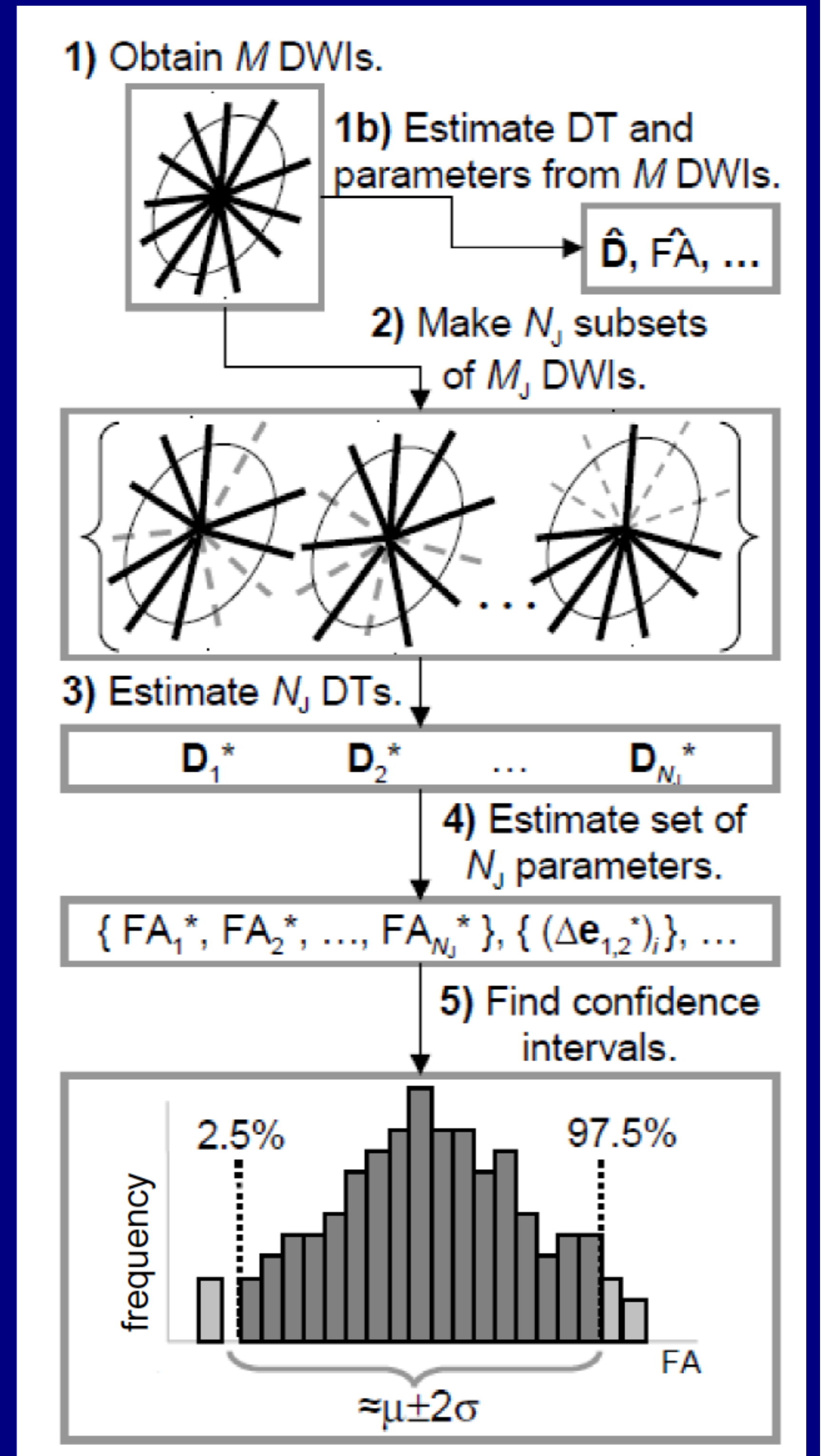
....



Uncertainty estimation

+ 3dDWUncert estimates bias and σ of first eigenvector $\mathbf{e}_1$ (main direction of diffusion), based on how much it could tip toward either $\mathbf{e}_2$ or $\mathbf{e}_3$:



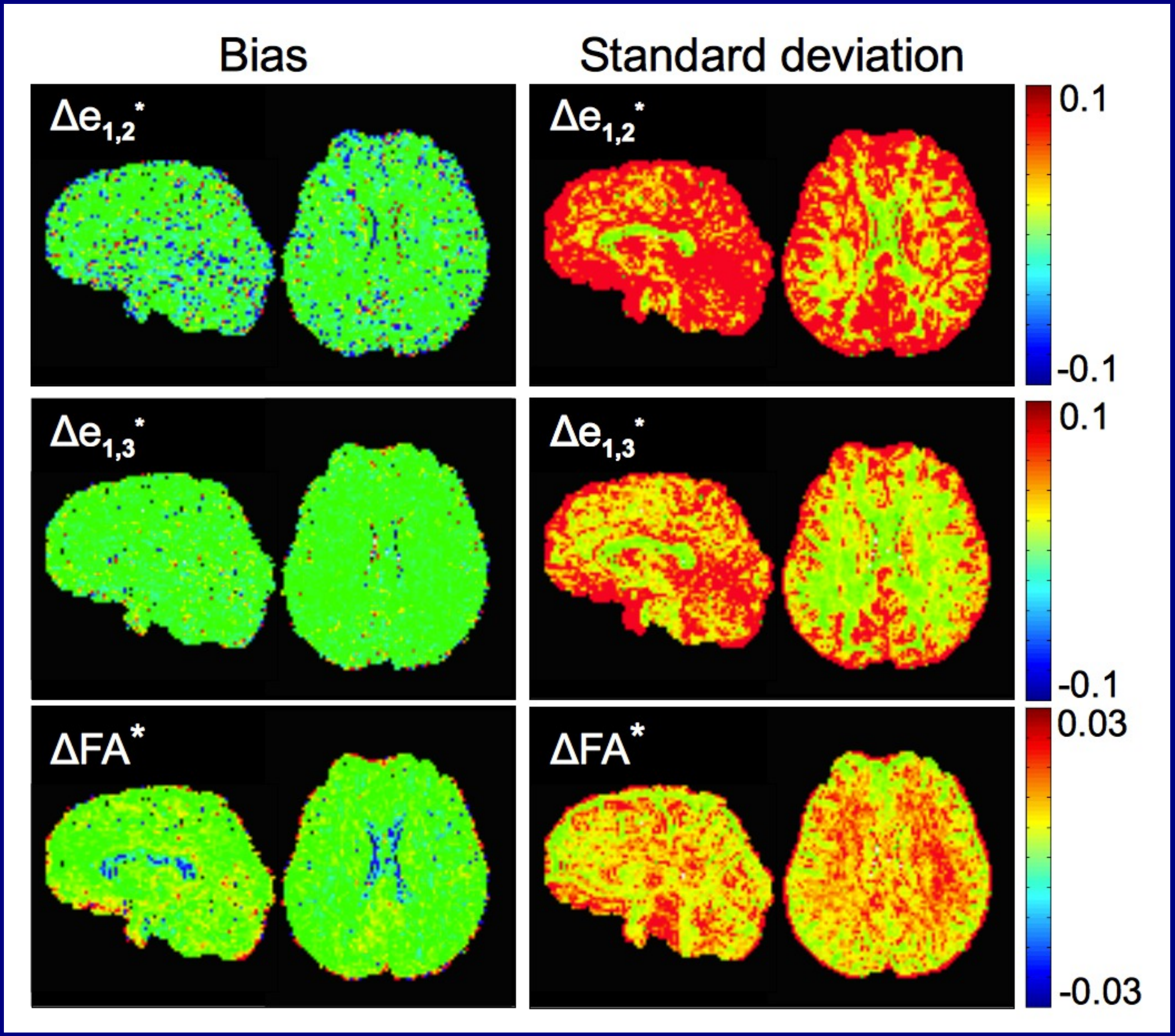


.... and the bias and σ of FA

Uncertainty example

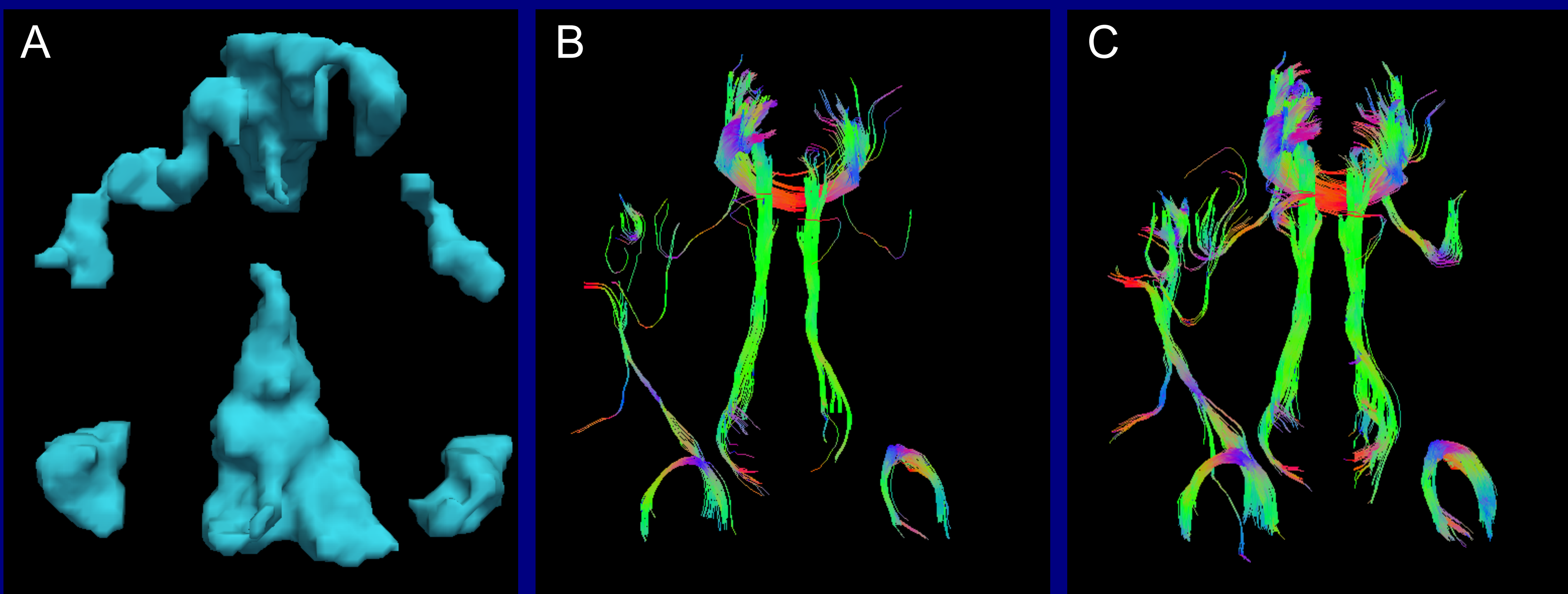
+ Can see difference in e1 uncertainty along e2 and e3

+ Tissue-dependent differences in FA uncertainty



Mini-Probabilistic Tracking

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



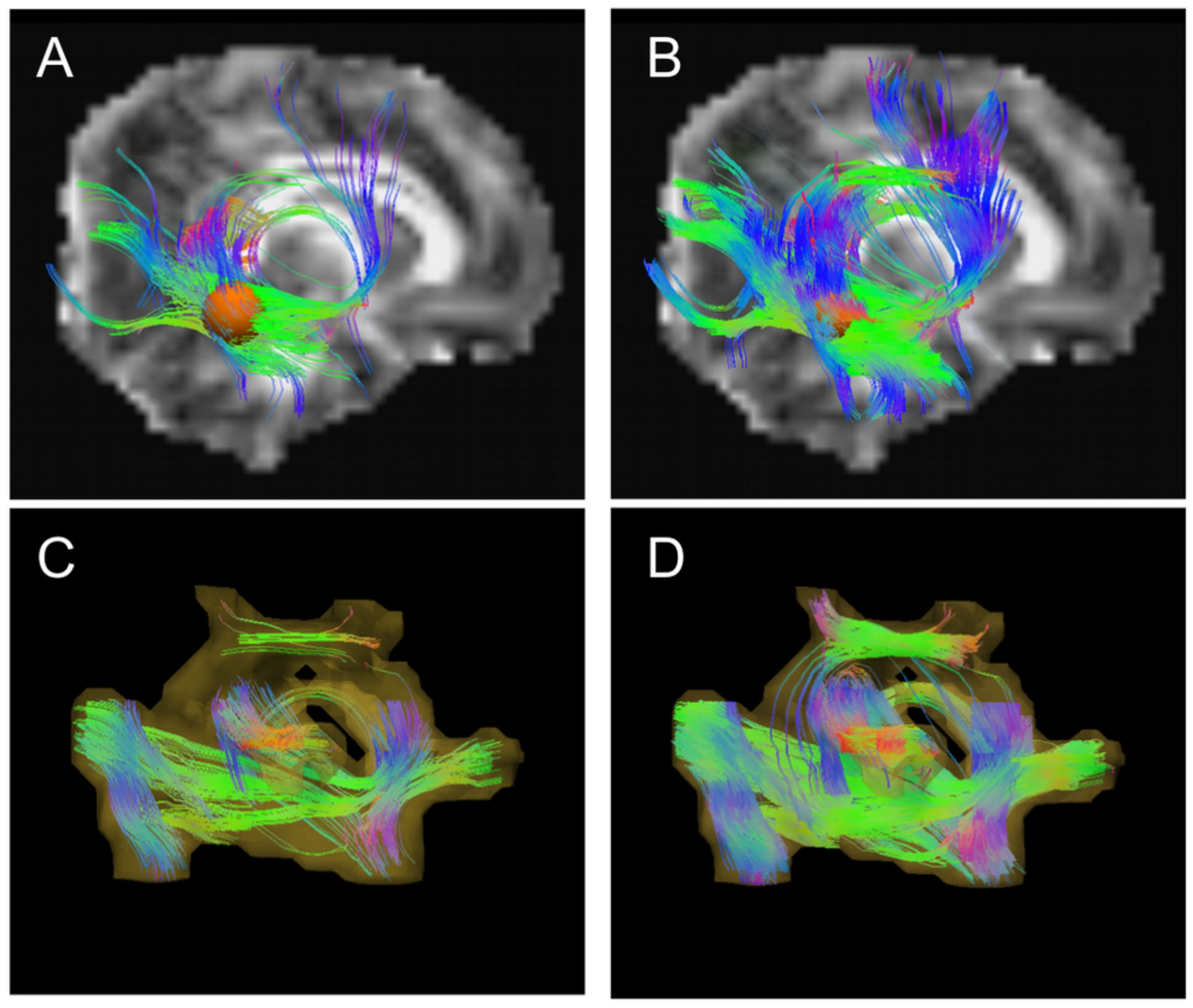
Deterministic (AND)   with `-mini_prob 7'

Mini-Probabilistic Tracking

Deterministic vs mini-Probabilistic

Through single ROI

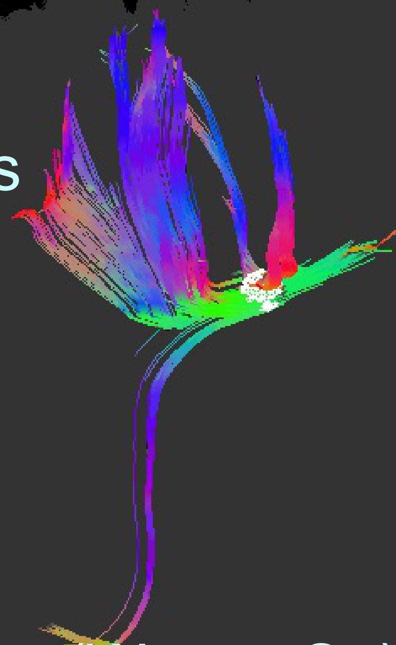
AND logic through network, cf with full-prob results



(Taylor et al., 2014)

Thanks

And thanks to collaborators:



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NJIT:
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