THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

Diffusion Tensor Processing and Visualization

Martin Styner UNC

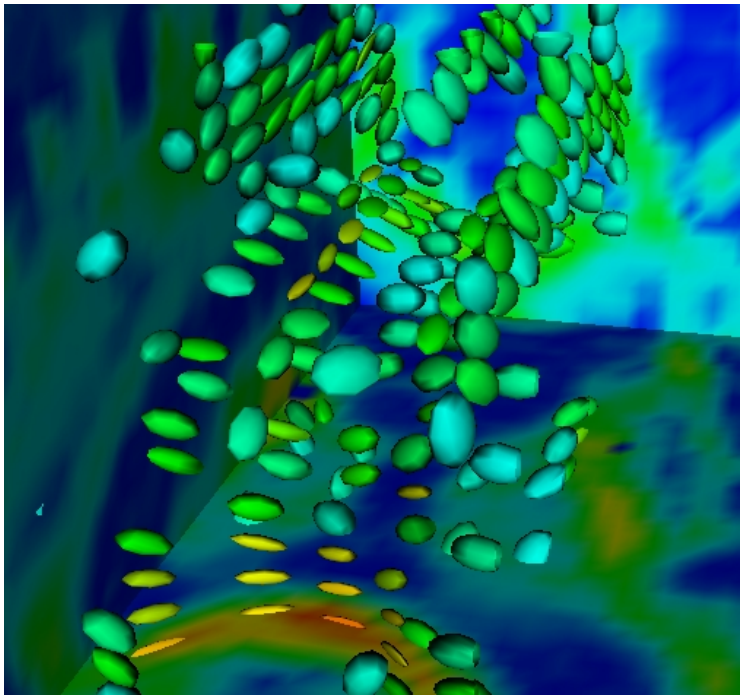
Thanks to Guido Gerig, UUtah

NAMIC: National Alliance for Medical Image Computing

And many, many folks

TOC & Acknowledgment

- Intro DTI
- Tensors & Scalars
- Visualization
- Tractography
- Analysis Approaches



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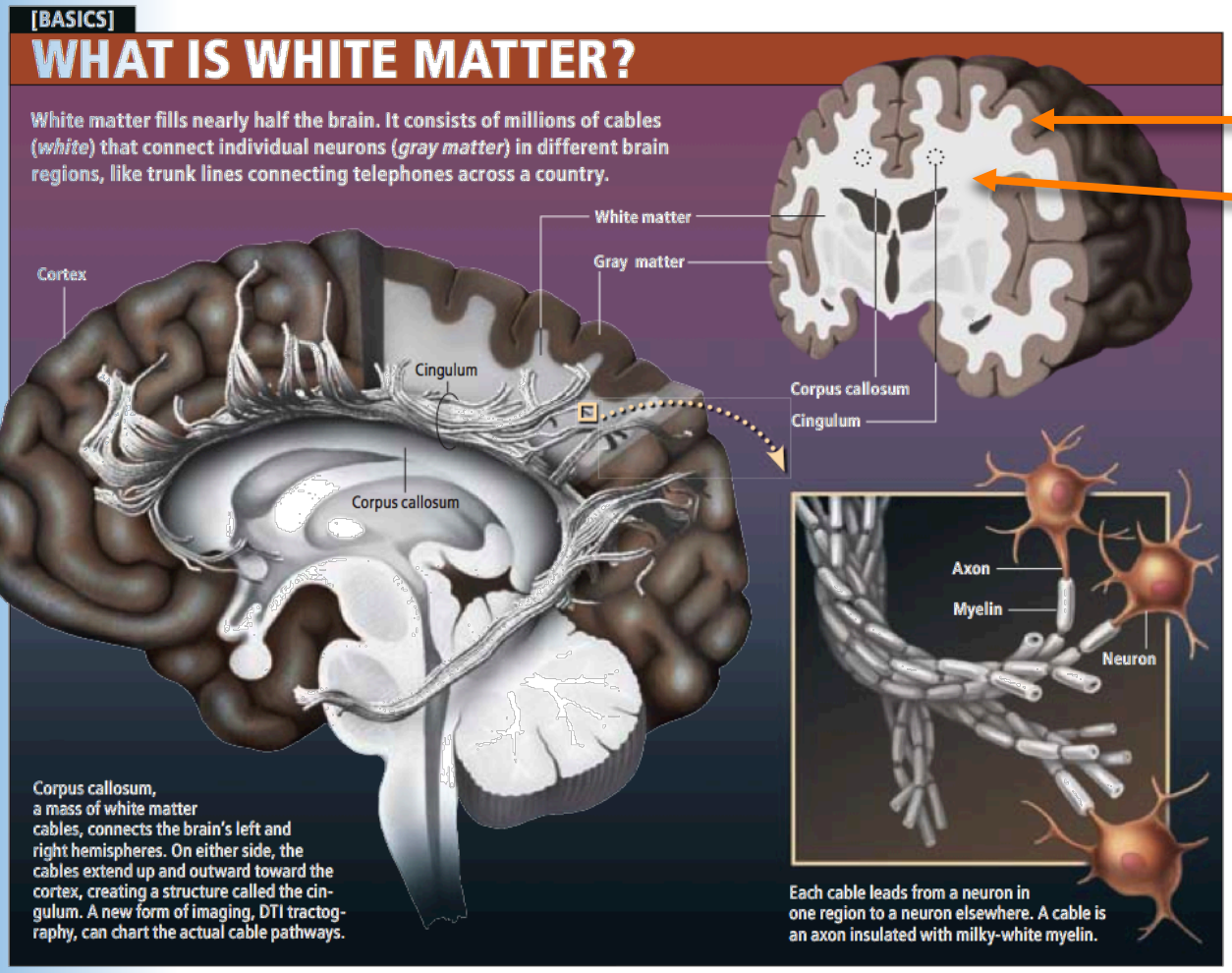
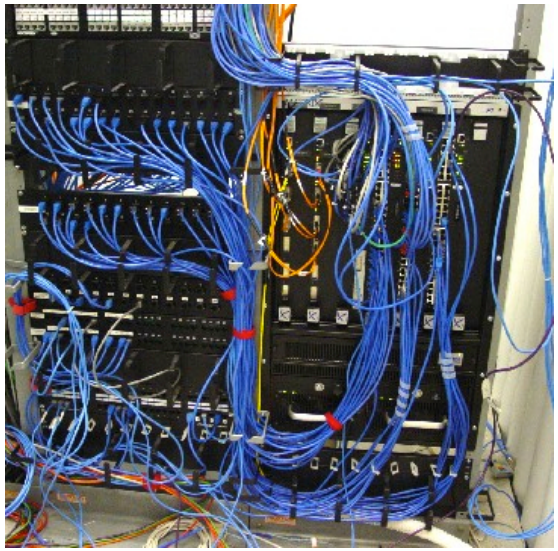
National Alliance for Medical Image Computing (NIH U54EB005149), Autism Center of Excellence HD-055741, P50 MH 064065, P50 MH070890, P30 HD03110, R01 MH091645, P01-DA022446

Brain White & Gray Matter



CPU's

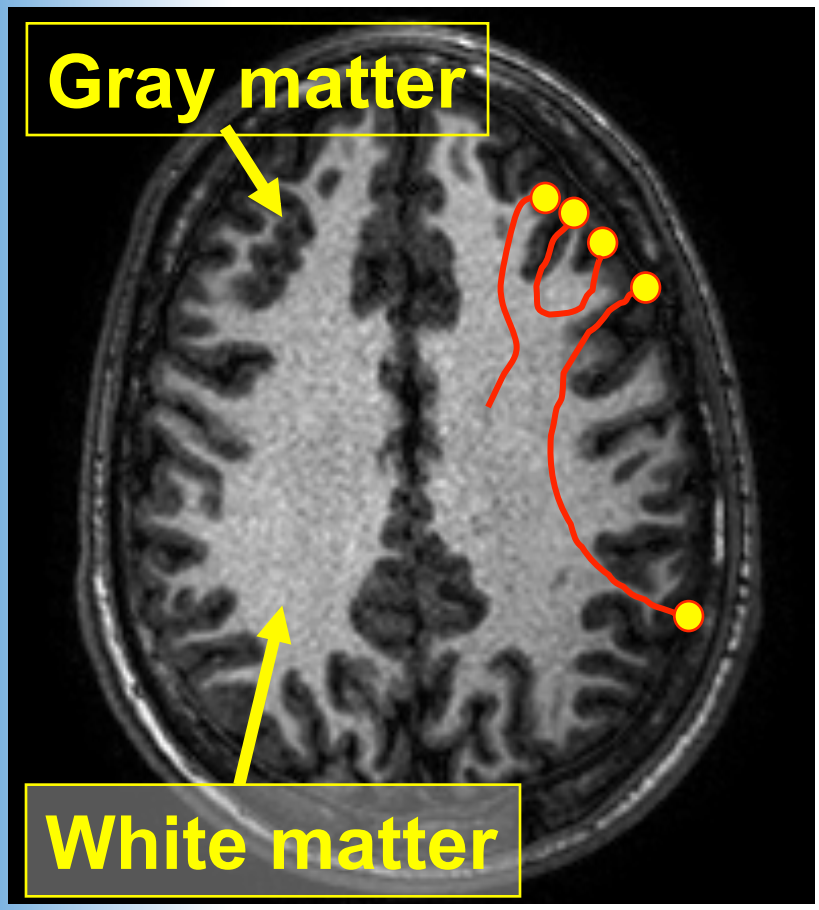
Network

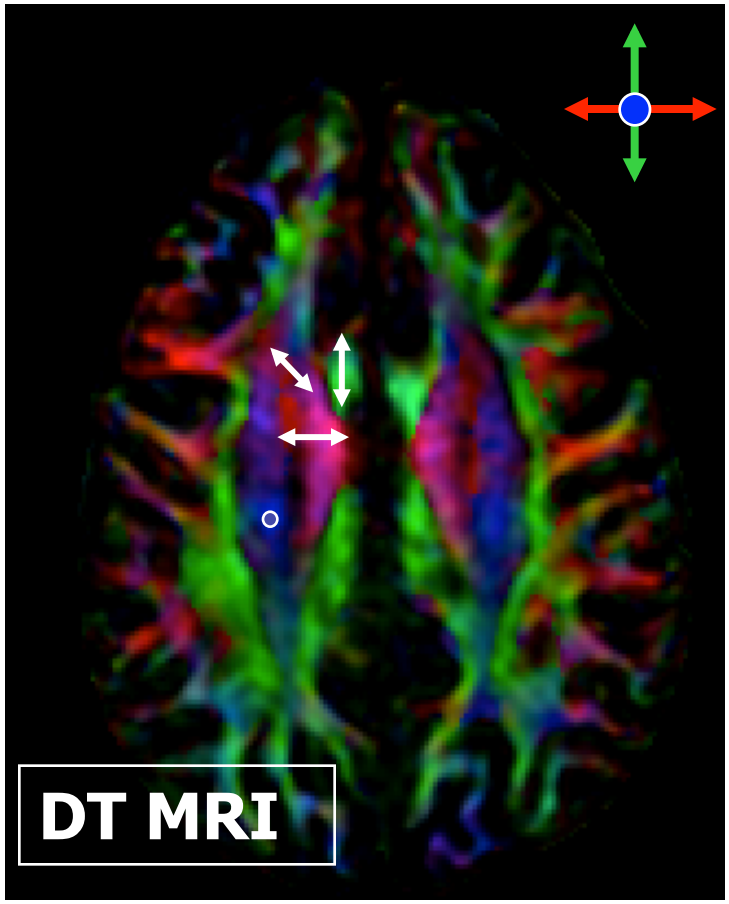


UNC CS: Network cabinet

Fields, Scientific American, 2008

Diffusion Tensor Imaging (DT MRI) reveals White Matter Structure

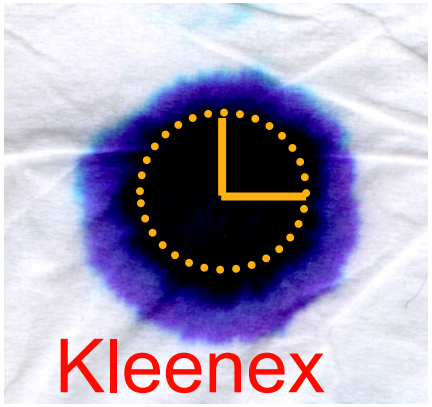


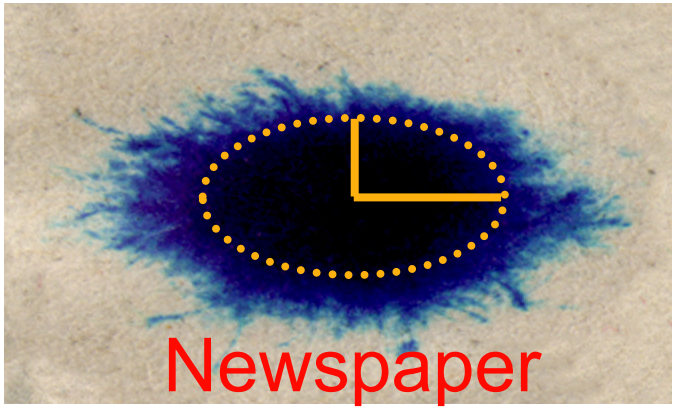


Susumu Mori, JHU

Diffusion in Biological Tissue

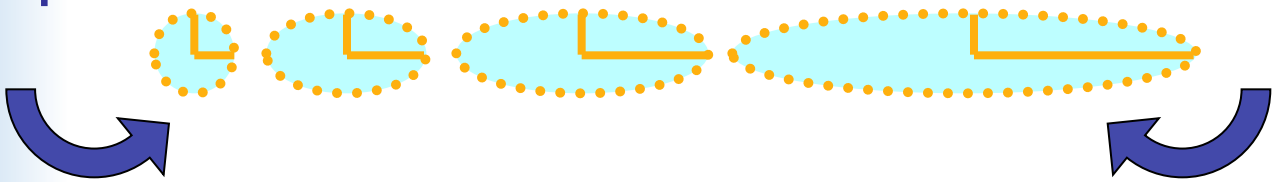
- Brownian motion of water through tissue





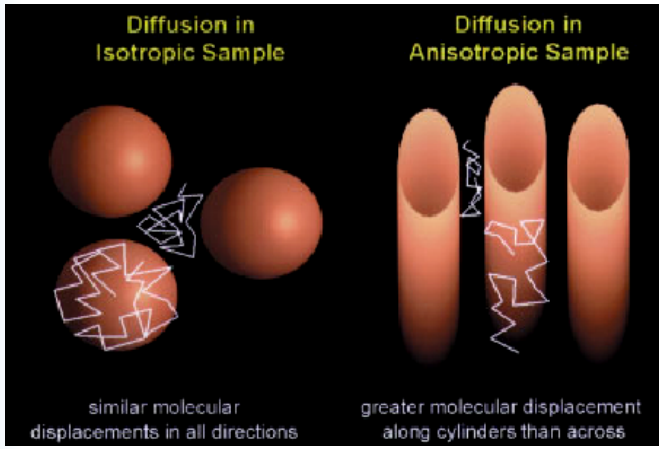
- Anisotropy: diffusion rate depends on direction

isotropic anisotropic



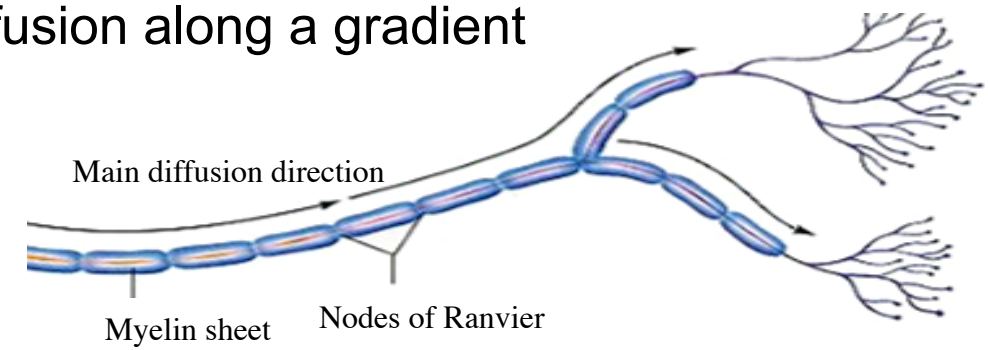
G. Kindlmann

Diffusion in White Matter



From Beaulieu[02]

- Reflects the underlying structure of the tissues
  - Water diffusion anisotropy to track fibers, estimate white matter integrity
  - Faster diffusion along fibers than perpendicular to them
- DTI measures diffusion along a gradient



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The Physics of Diffusion

- Density of substance changes (evolves) over time according to a differential equation (PDE)

$$\frac{\partial \mu}{\partial t} = \nabla \cdot D \nabla \mu$$

Change in density

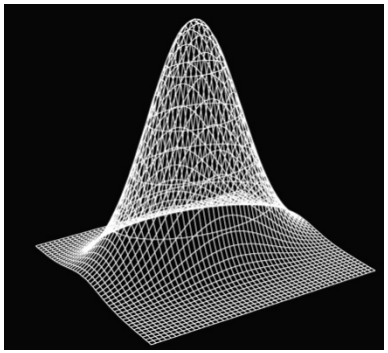
Diffusion – matrix, Tensor (2x2 or 3x3)

Derivatives (gradients) in space

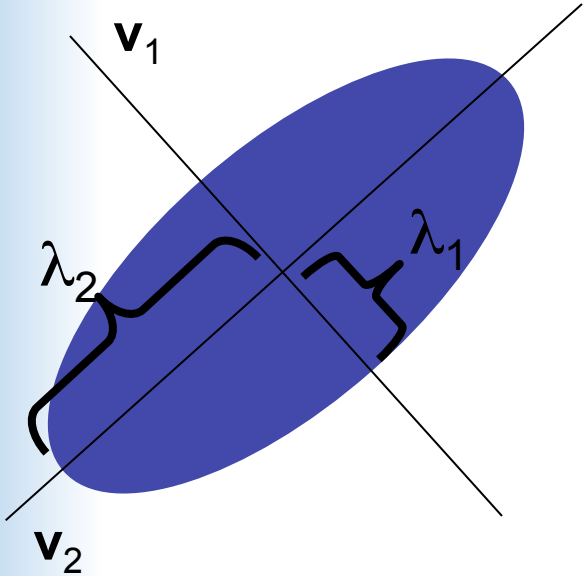
Solutions of the Diffusion Equation

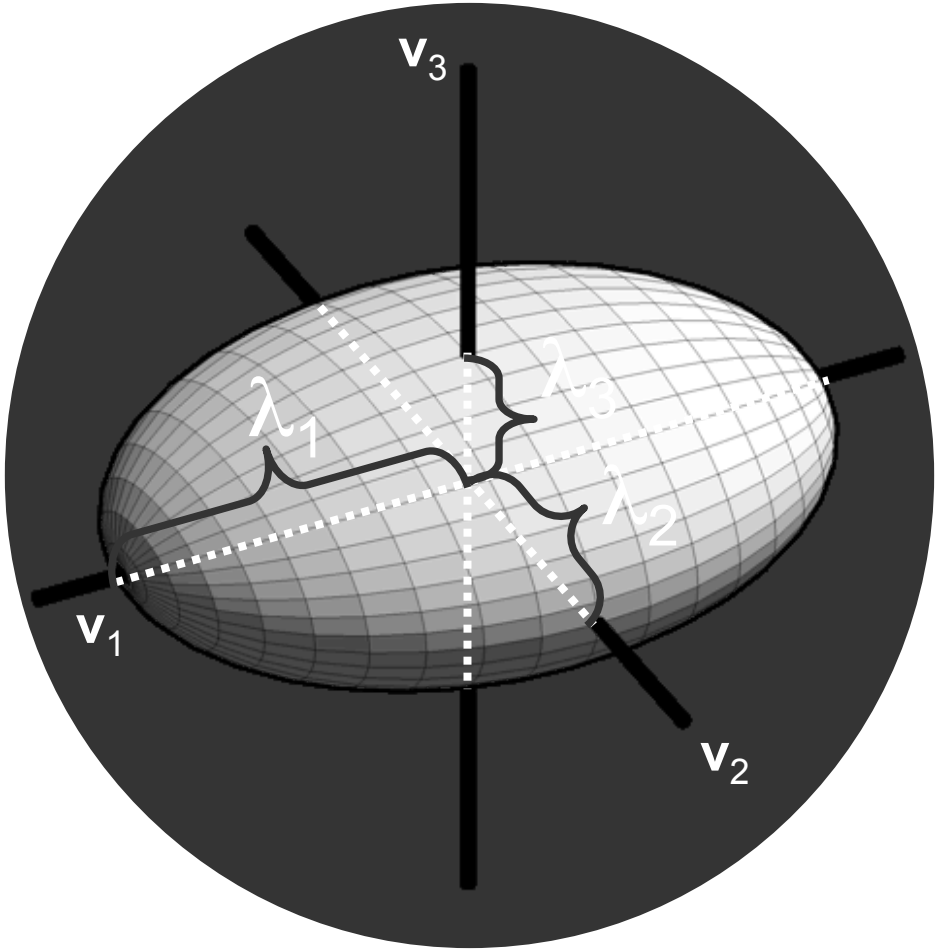
$$\frac{\partial \mu}{\partial t} = \nabla \cdot D \nabla \mu$$

- Simple assumptions
  - Small dot of a substance (point)
  - D constant everywhere in space
- Solution is a multivariate Gaussian
  - Normal distribution
  - “D” plays the role of the covariance matrix
- This relationship is not a coincidence
  - Probabilistic models of diffusion (random walk)

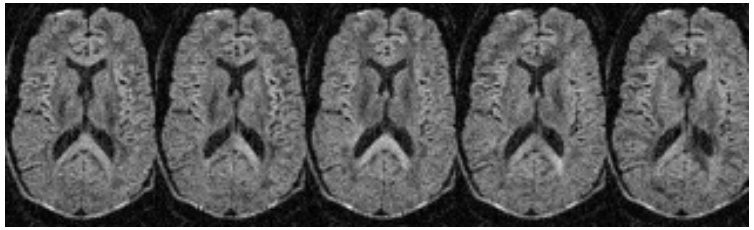


Tensors: Eigen Directions and Values (Principle Directions)





Tensors From DW-MRI



- Diffusion weighted images
- Tensor: Big assumption
  - voxel scale of DW-MRI: 2x2x2mm => 100,000+ axons
  - Diffusion of water is approximated by Gaussian
- Stejskal-Tanner equation
  - Relationship between the DW images and tensor D

$$S_k = S_0 e^{-b g_k^T D g_k}$$

Physical constants
Strength of gradient
Duration of gradient pulse
Read-out time

k^{th} DW Image

Base image

Gradient direction

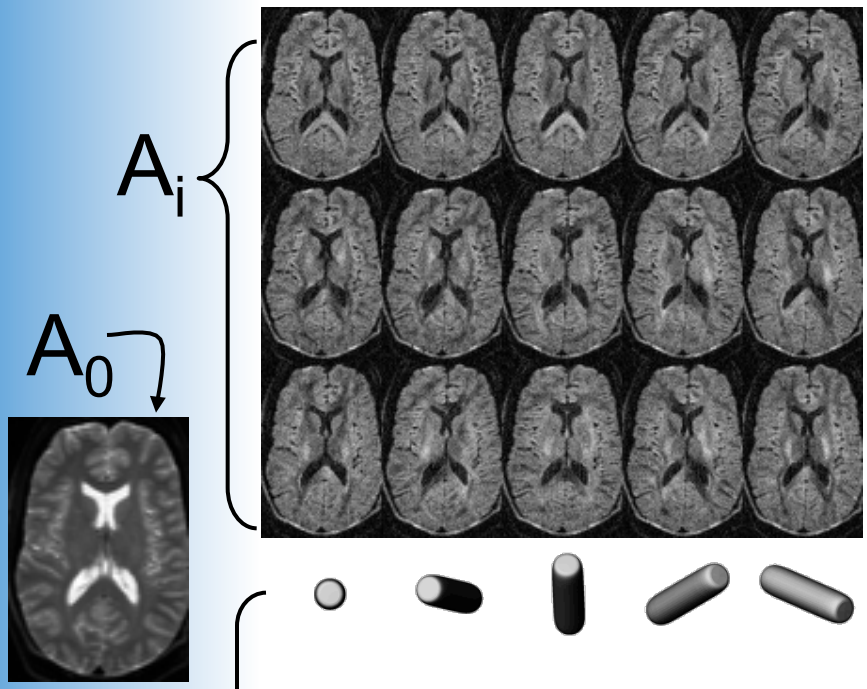
DWI summary: Model

Single Tensor Model (Basser 1994)

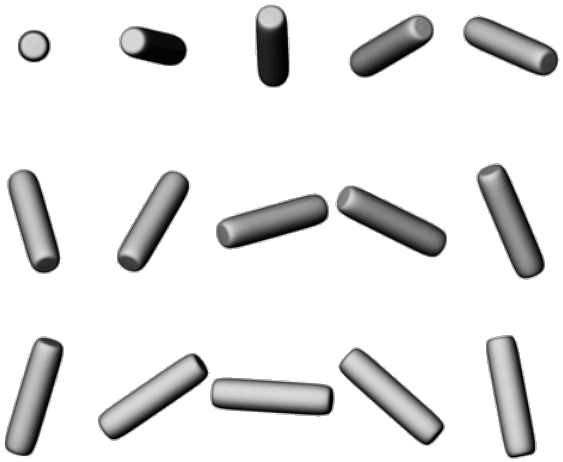
$$A_i = A_0 e^{-b\mathbf{g}_i^T \mathbf{D} \mathbf{g}_i}$$

A_i

A_0

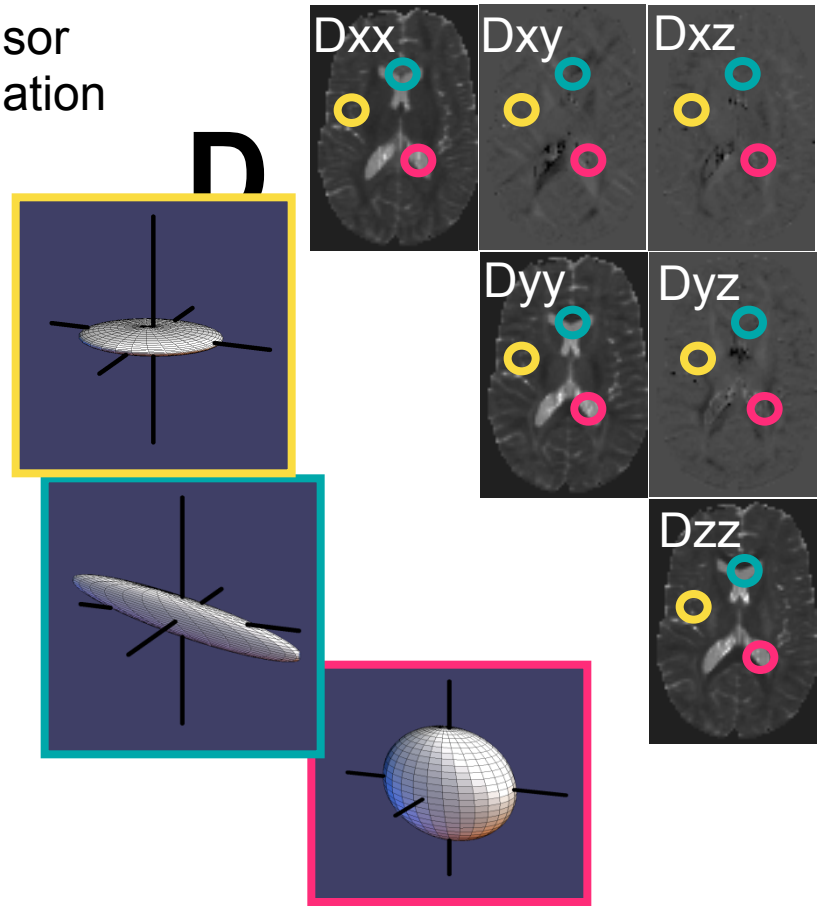


$\mathbf{g}_i$



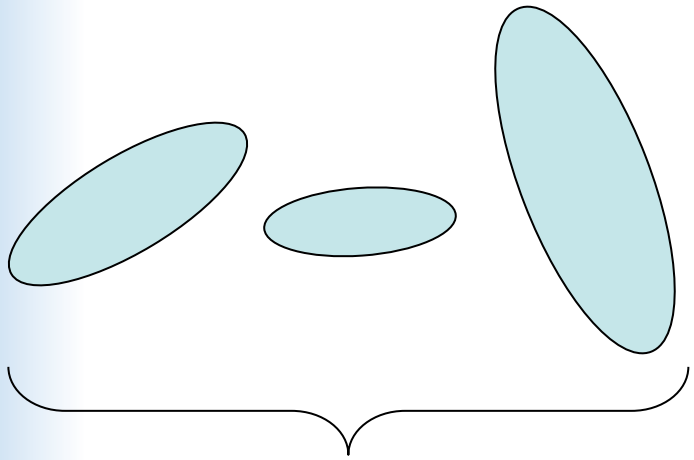
Tensor estimation

$\mathbf{D}$

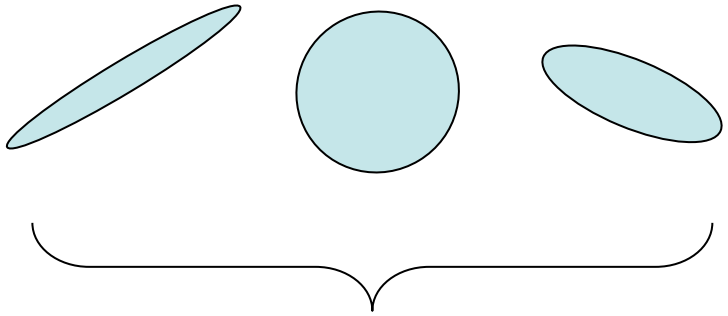


Shape Measures on Tensors

- Represent or visualization shape
- Quanitfy meaningful aspect of shape
- Shape vs size



Different sizes/orientations



Different shapes

Measuring Tensor "Size"

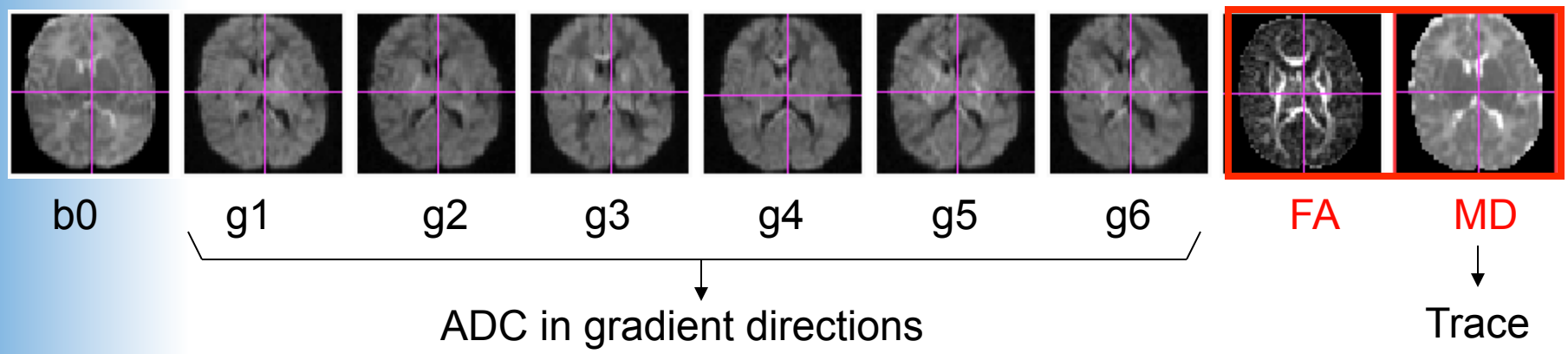
- Length: (1) $(\lambda_1 + \lambda_2 + \lambda_3)/3$
  (2) $(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)^{1/2}$
- Area – $(\lambda_1 \lambda_2 + \lambda_1 \lambda_3 + \lambda_2 \lambda_3)$
- Volume – $(\lambda_1 \lambda_2 \lambda_3)$

(2) Sometimes used.
Also called:
"Root sum of squares"
"Diffusion norm"
"Frobenius norm"

(1) Generally used.
Also called:
"Mean diffusivity" <MD>
"Trace"

ADC vs Mean Diffusivity

- Apparent diffusion coefficient (ADC) measures diffusivity <u>in a specific direction</u>.
- Mean diffusivity (<MD>) is trace of diffusion tensor.
- Terms often not properly used, papers often cite ADC but actually mean <MD>

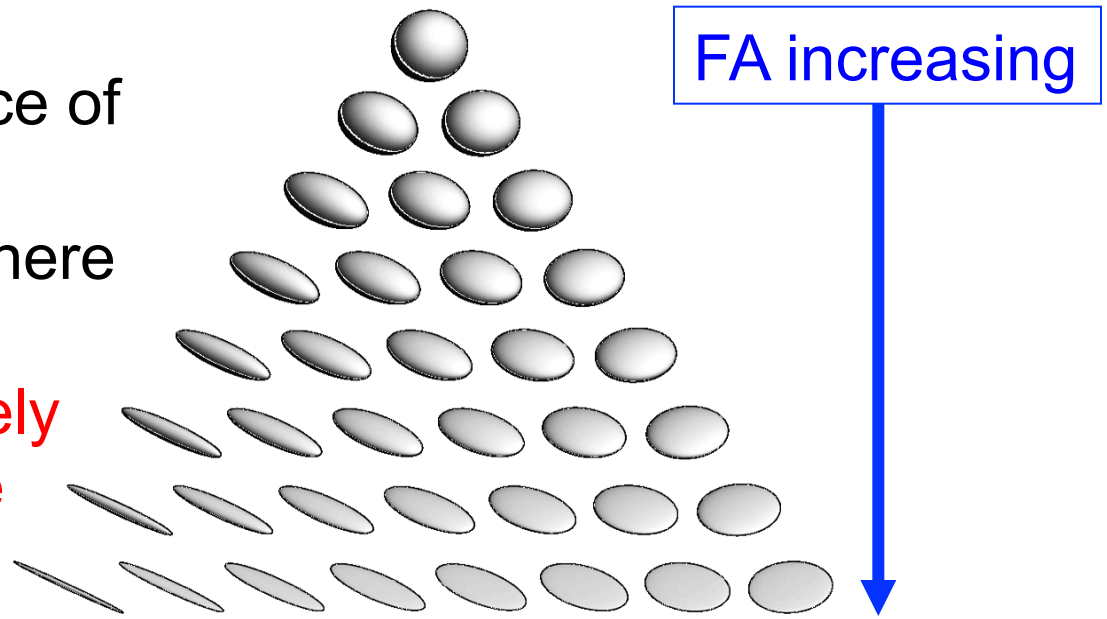


Reducing Shape to Scalar Number Fractional Anisotropy

$$FA = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{2}\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

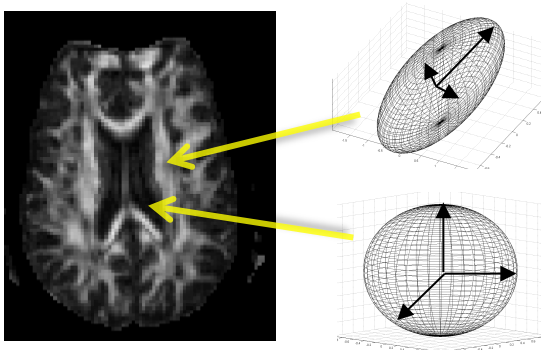
Properties:

- Normalized variance of eigenvalues
- Difference from sphere
- Invariant to size
- FA does not uniquely characterize shape

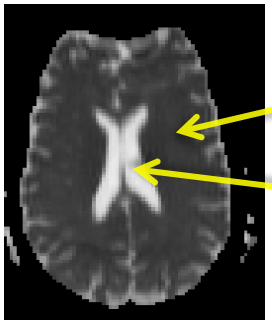


Diffusion Tensor Scalars

Fractional Anisotropy (Tensor shape), 0..1



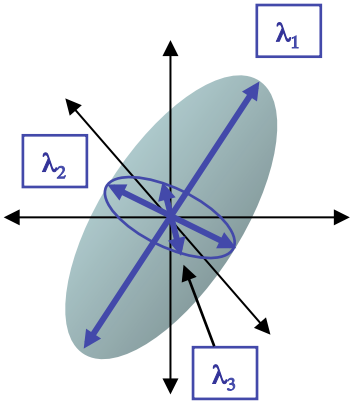
Mean Diffusion (Tensor volume)



Axial Diffusion

$$= \lambda_1 = \lambda_{||}$$

In WM: Diffusion parallel to axon



Radial Diffusion

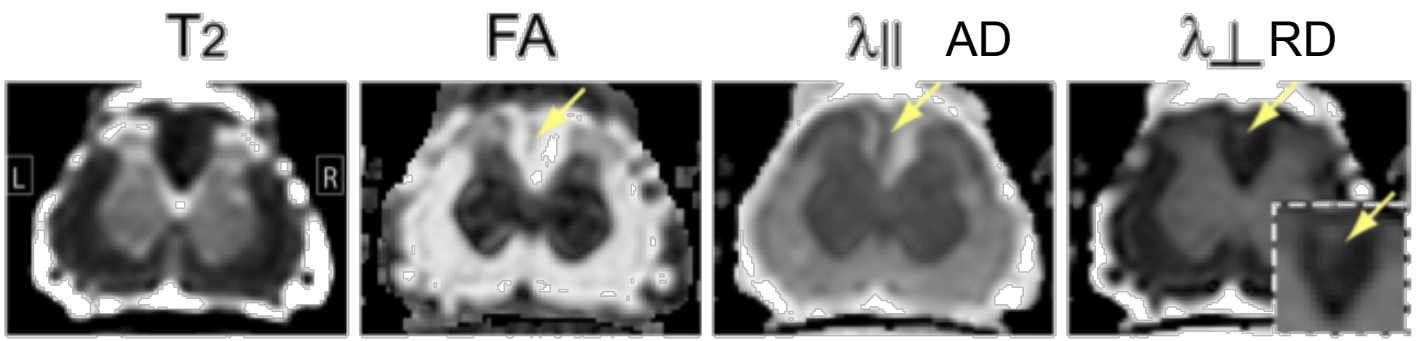
$$= \frac{(\lambda_2 + \lambda_3)}{2} = \lambda_\perp$$

In WM: Diffusion orthogonal to axon

Example DTI Scalars

- DTI (AD/RD) & immunohistochemistry of Wallerian degeneration
- Unilateral L2–L4 dorsal axotomy in rat spine column
- DTI revealed dorsal lesion extending from lumbar to cervical cord

3 Days after axotomy

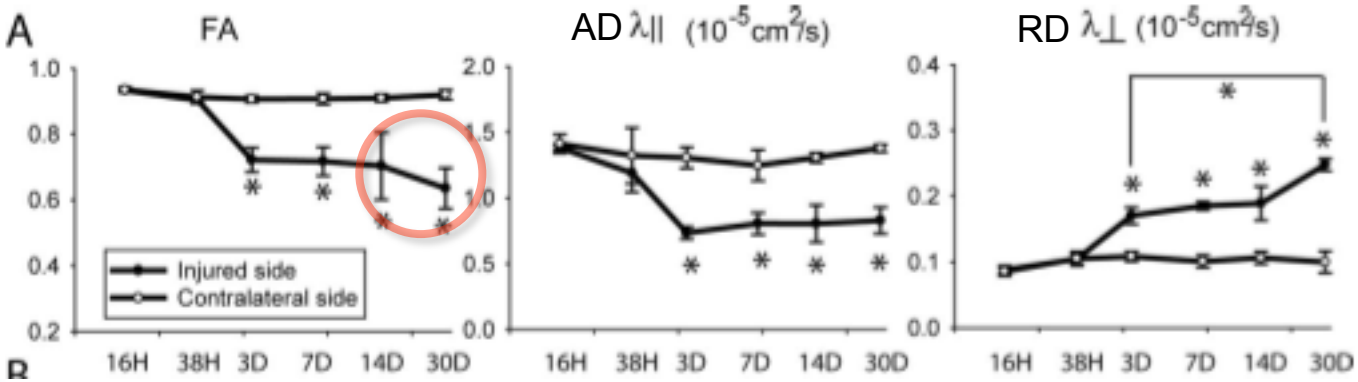


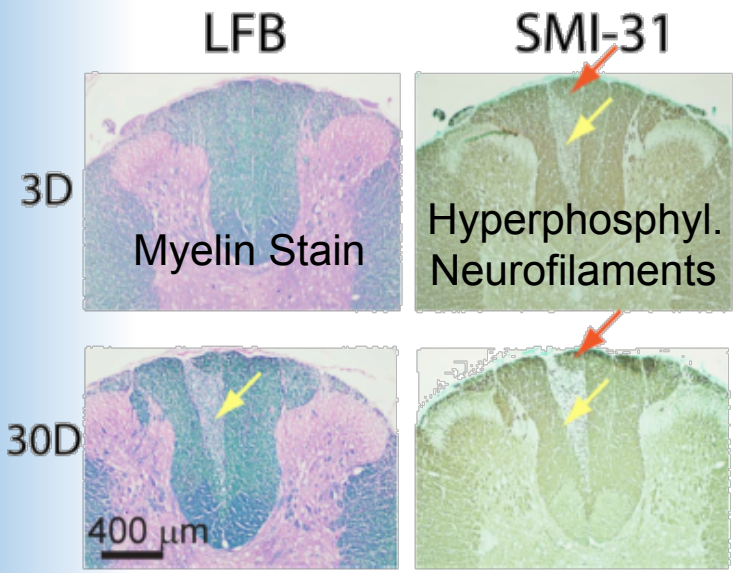
Neurobiology of Disease

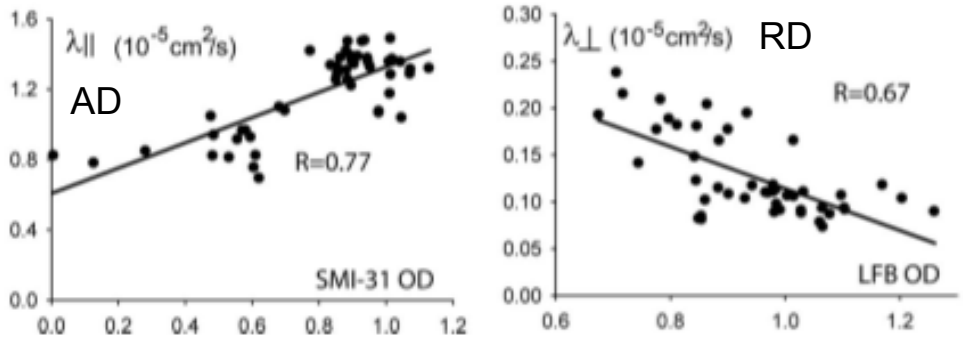
Diffusion Tensor Magnetic Resonance Imaging of Wallerian Degeneration in Rat Spinal Cord after Dorsal Root Axotomy

Jiangyang Zhang,[1] Melina Jones,[2] Cynthia A. DeBoy,[2] Daniel S. Reich,[1,2] Jonathan A. D. Farrell,[1,3,7] Paul N. Hoffman,[2,4] John W. Griffin,[2] Kazim A. Sheikh,[2] Michael I. Miller,[5,6] Susumu Mori,[1,7] and Peter A. Calabresi[2]

Immunohistochemistry







FA captures effects, no differentiation
RD correlates with myelin degeneration
AD correlates with loss of phosphorylated neurofilaments

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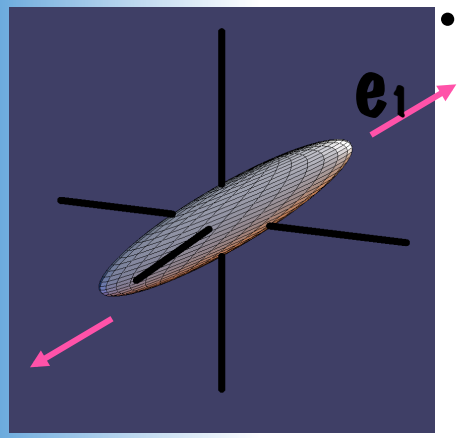
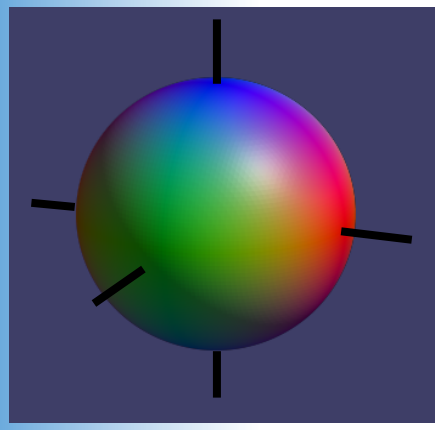
Visualizing Tensors: Direction and Shape

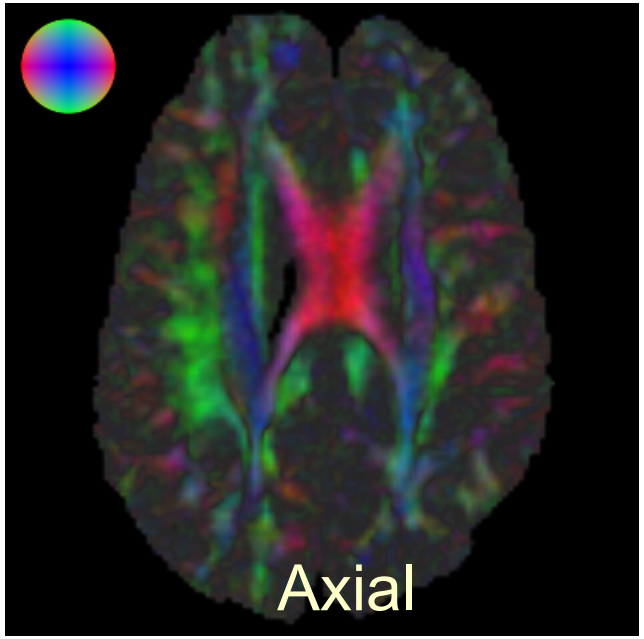
- Color mapping
- Glyphs

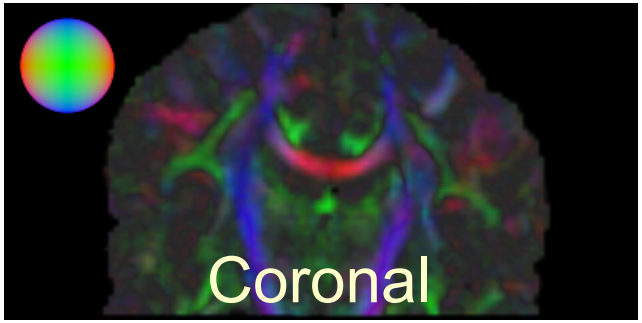
Coloring by Principal Diffusion Direction

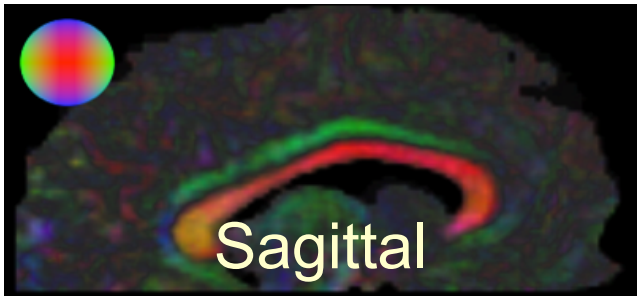




- Principal eigenvector, linear anisotropy determine color







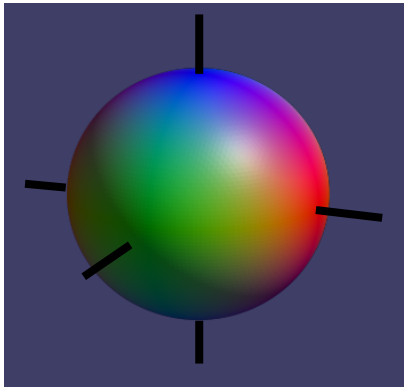
R=| $\mathbf{e}_1 \cdot x$ |
G=| $\mathbf{e}_1 \cdot y$ |
B=| $\mathbf{e}_1 \cdot z$ |

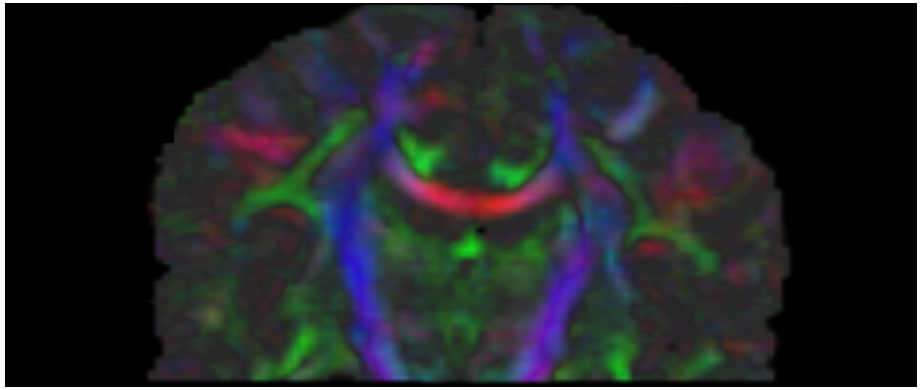
C. Pierpaoli, 1997

Slide G. Kindlmann

Issues With Coloring by Direction

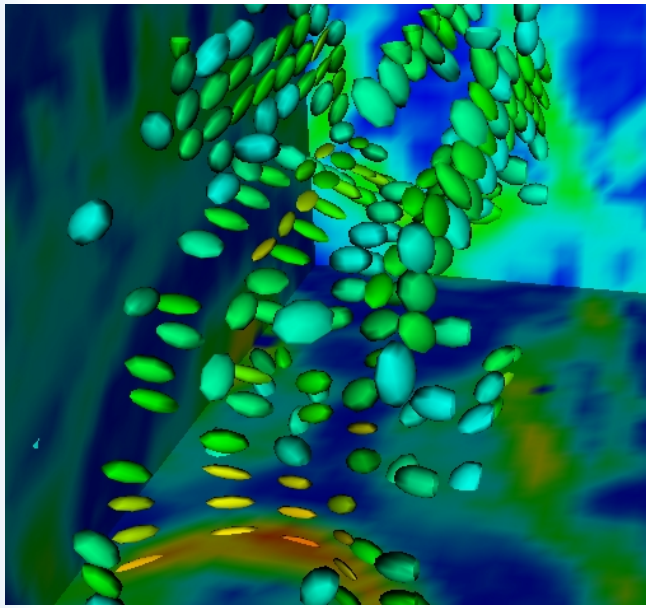
- Set transparency according to FA (highlight-tracts)
- Coordinate system dependent
- Primary colors dominate
  - Perception: saturated colors tend to look more intense
  - Which direction is “cyan”?
  - Coloring is not unique
- Only for visualization: Do not analyze colors

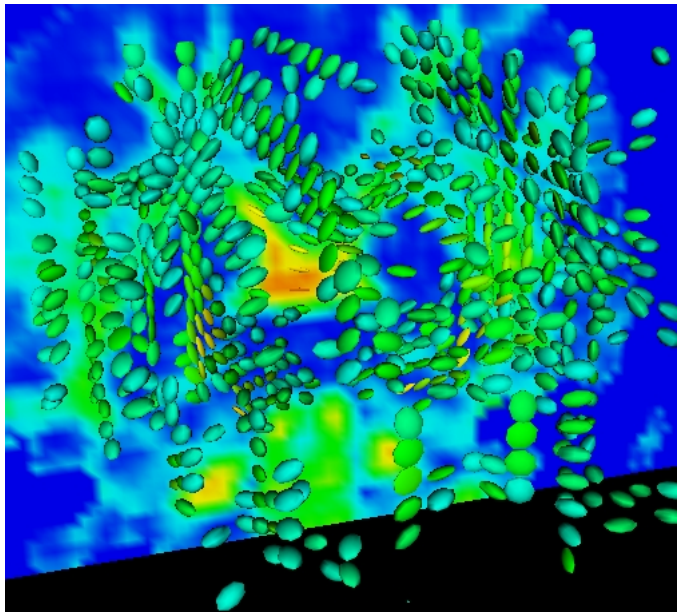




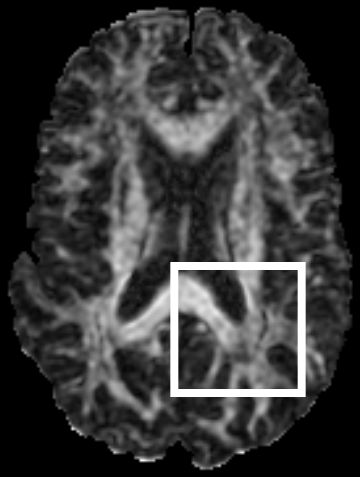
Visualization with Glyphs

- Density and placement based on FA or detected features
- Place ellipsoids on regular grid

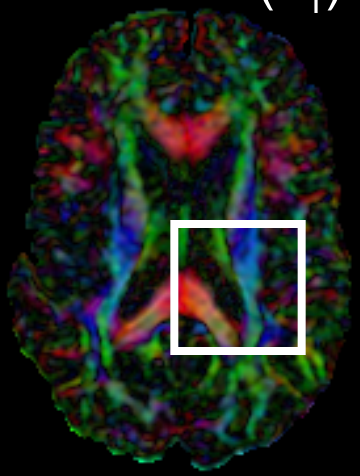


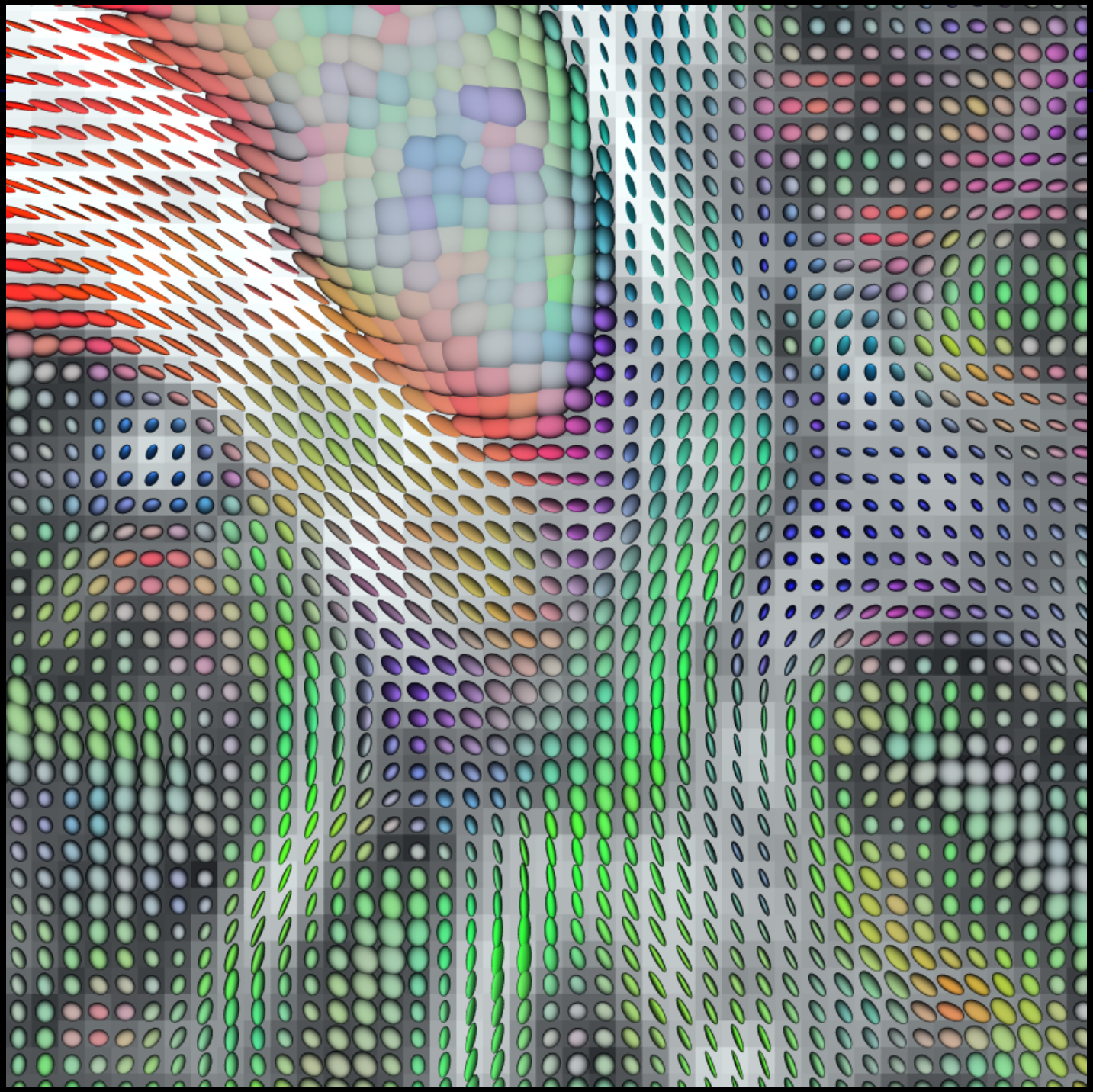


Backdrop: FA

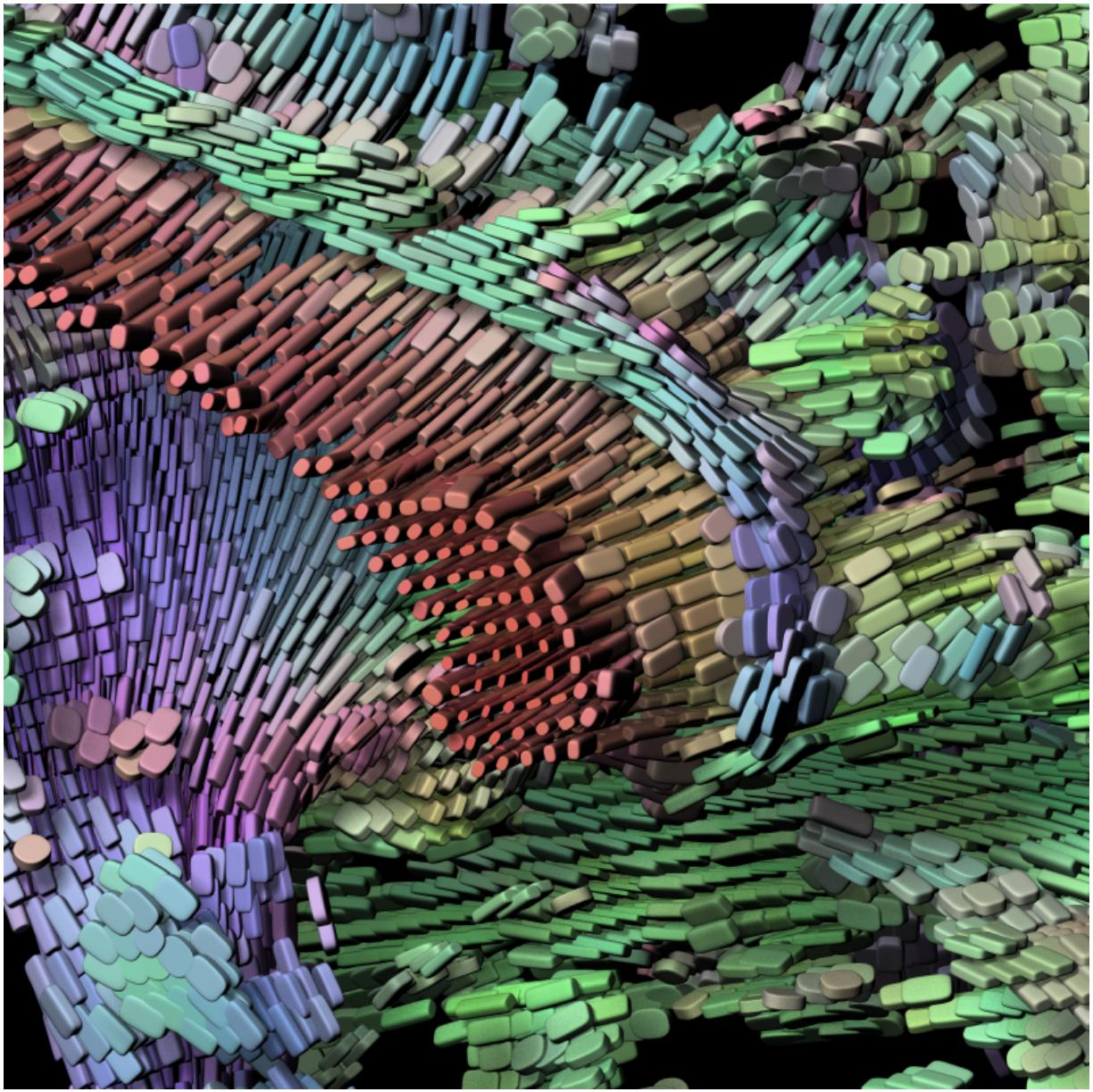


Color: RGB($\mathbf{e}_1$)





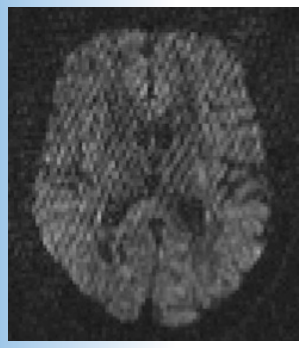
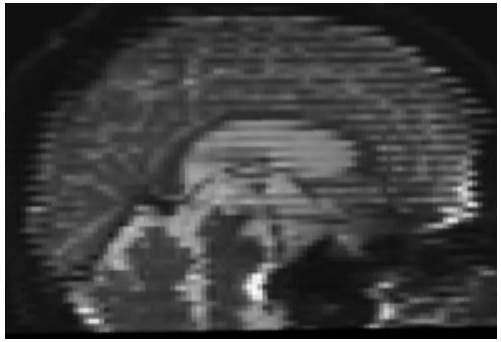
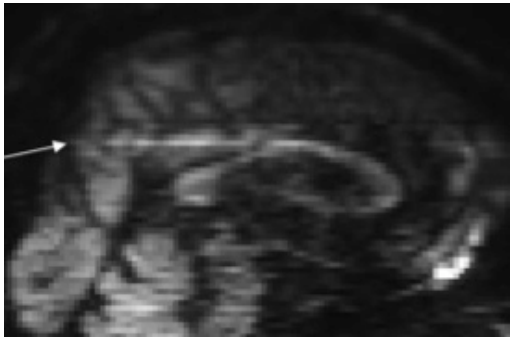
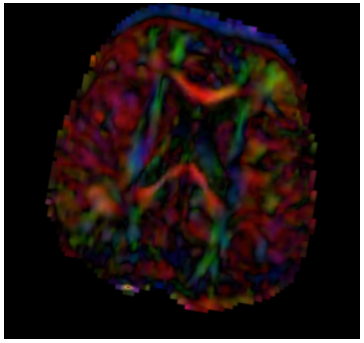
G. Kindlmann



G. Kindlmann

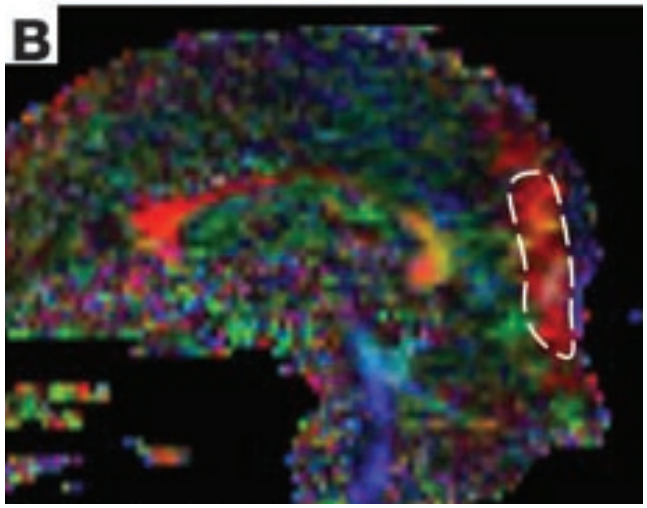
Caution: DWI/DTI QC

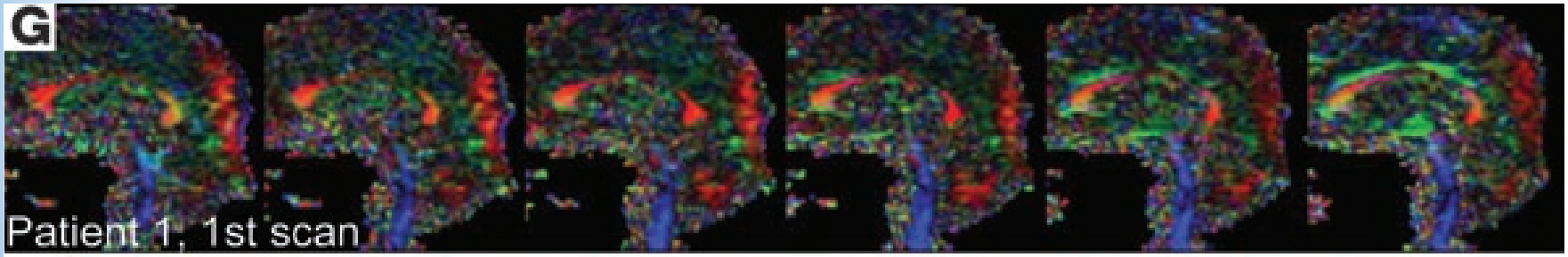
- DTI/DWI noisy, artifact rich => QC needed
  - Often neglected => Bad data
  - Correct motion & eddy currents
  - Reject bad gradients
- How to automatically detect bad gradient?
- How much rejection is still okay?
- Tools: DTIPrep (UNC), Turtoise (NIH)

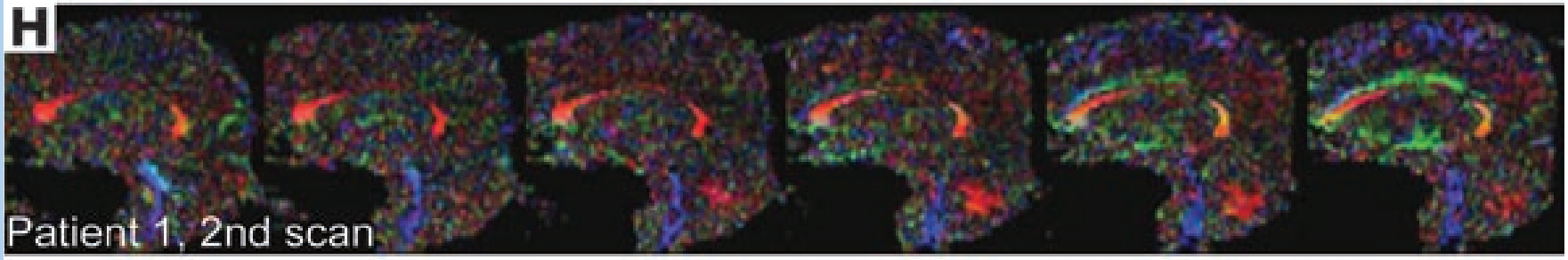





What if bad QC?

- JCI 2006, Voss et al Possible axonal regrowth in late recovery from the minimally conscious state
- DTI artifact
  - No real effect, likely vibration or eddy current
  - Axonal regrowth/reorganization postulated based on low SNR DTI artifacts



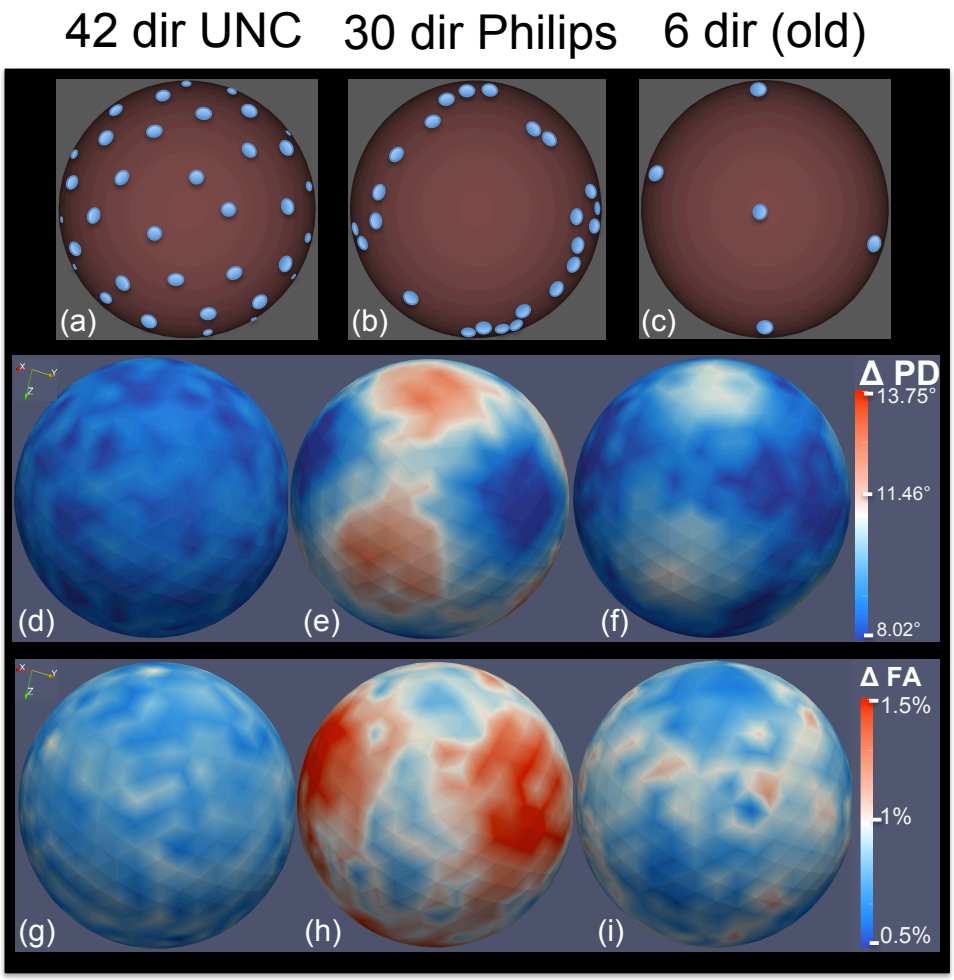




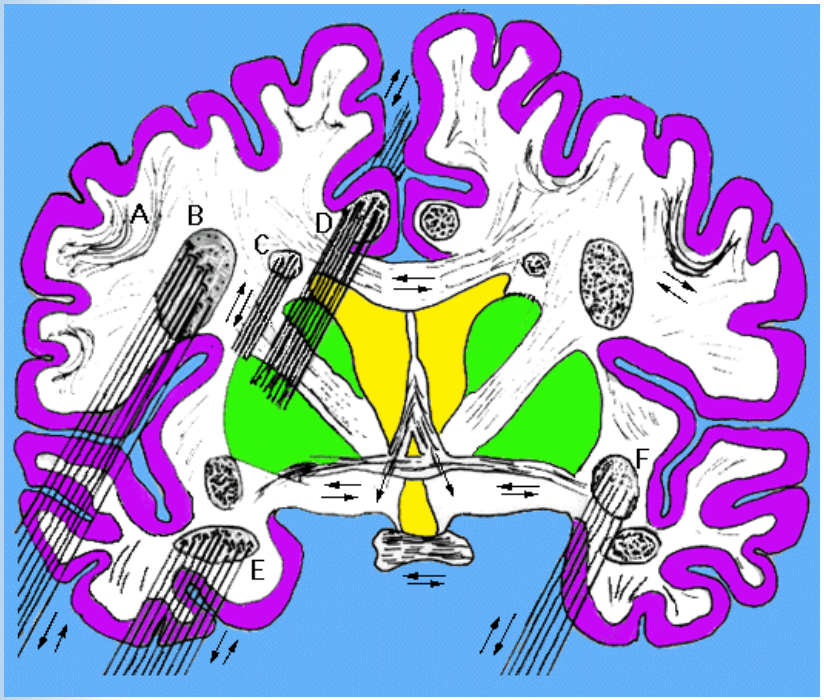
Caution: Good Protocol!

- Different sequences
  - Custom to built-in
- Simulation analysis
  - Same SNR ~ 10
- ΔFA: Average error in FA (SimFA = 0.4)
- ΔPD: Average error in local orientation
- Non-uniform Philips sequence worst

  ~50% higher orientation & ~75% higher FA error

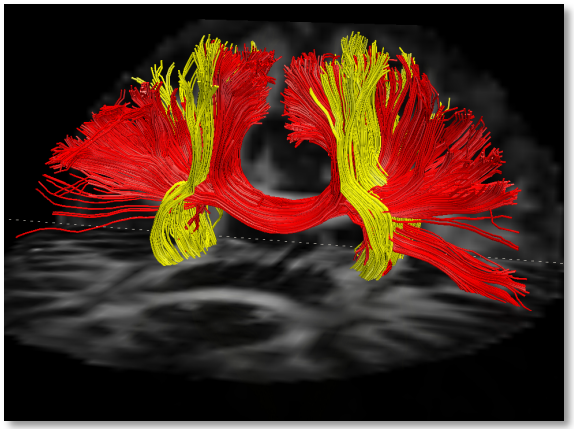


Dream: Connectivity?



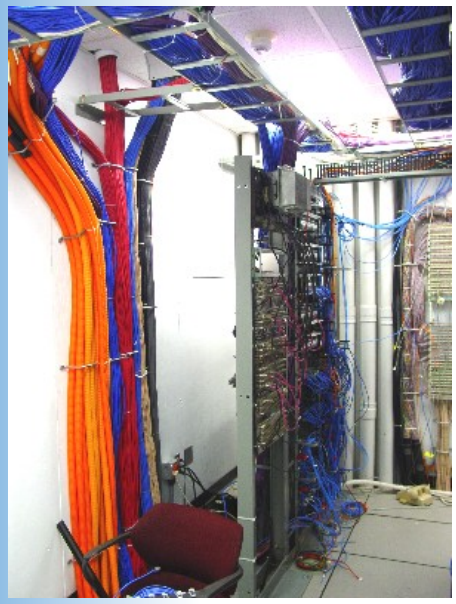
Forebrain Fiber Bundles: General idea of where various fiber bundles are and regions they interconnnect or project to.

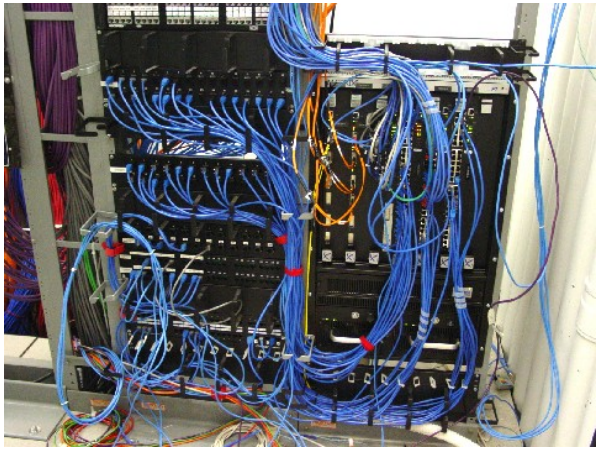
Source: Duke NeuroAnatomy Web Resources (Ch. Hulette)



Tractography: Coronal view
Dell'Acqua et al. NeuroImage '10

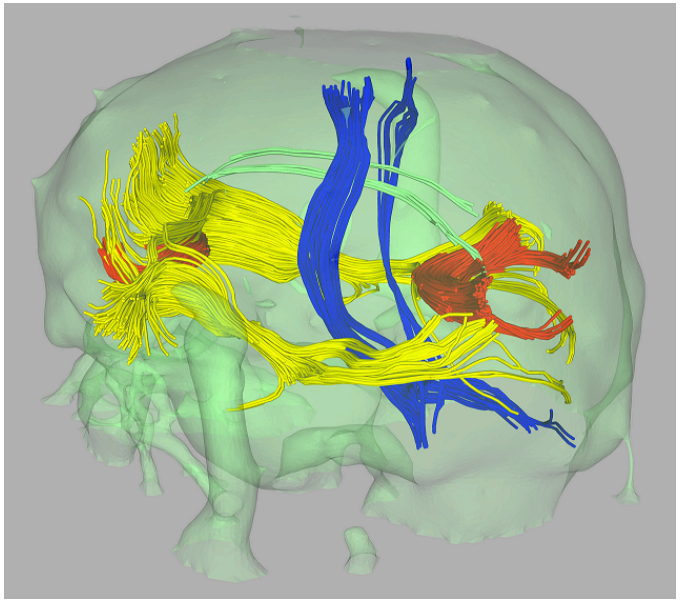
Networking and Brain Connectivity



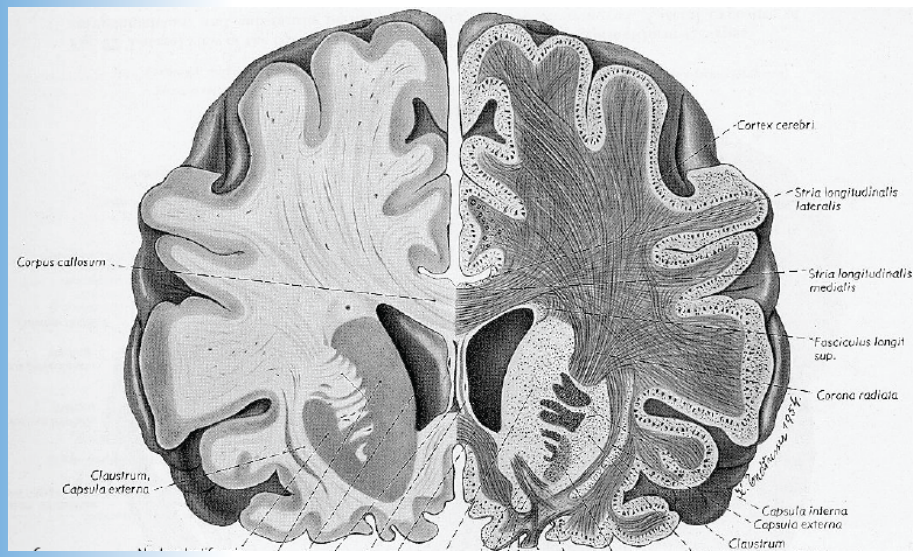


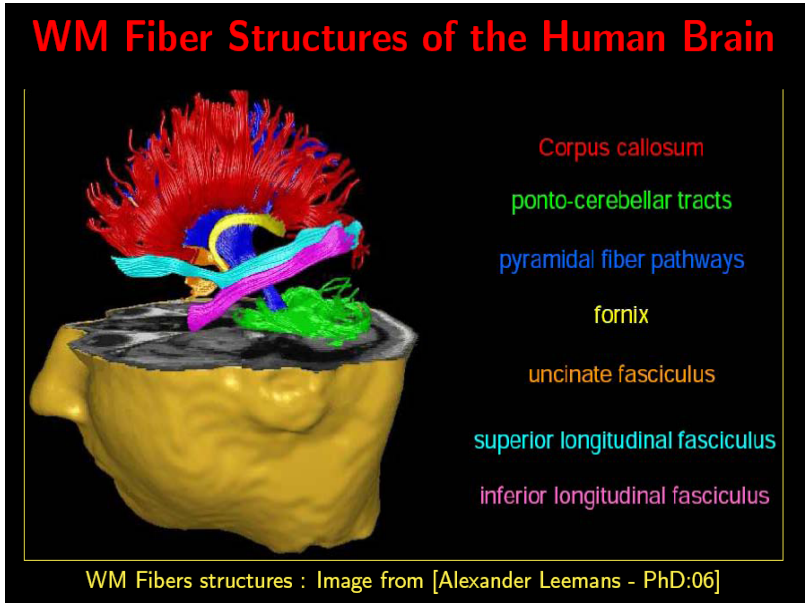
UNC Computer Science: Network wire cabinets

Major Fiber Tracts extracted from DT MRI



White Matter Tracts





- In tractography fibers are traced, with the aim to visualize white matter tracts.
- The word “tractography” is not related to “tracking”, but to “tract”.
- White matter tract, white matter fasciculus

Courtesy Carl-Fredrik Westin

Fiber Bundles via Tractography

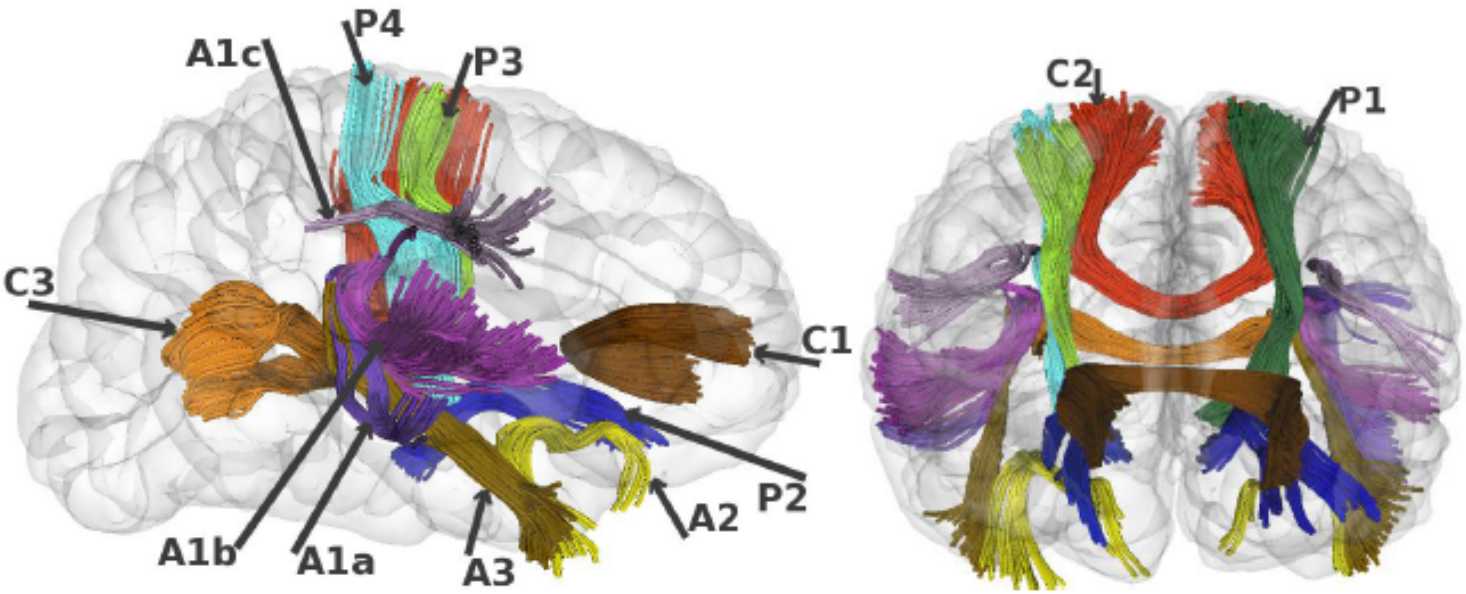
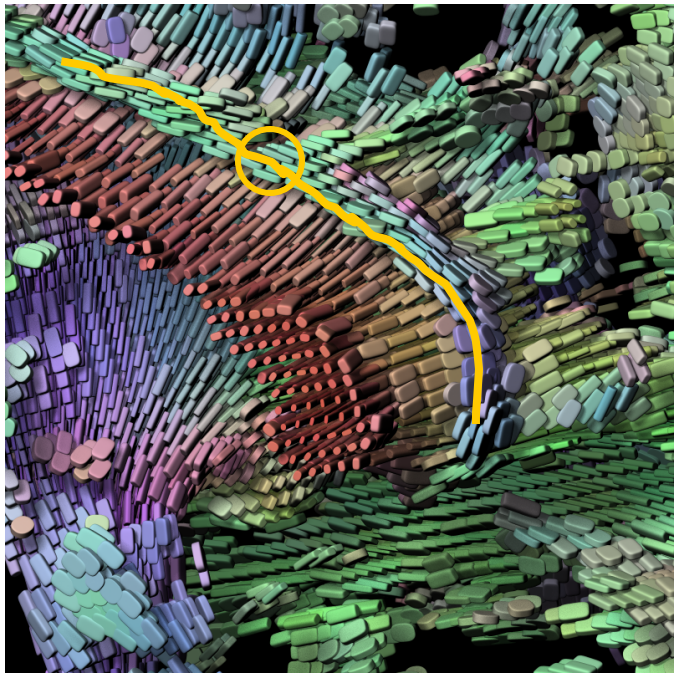


Figure 2. 3D visualization of 21 fiber tracts in sagittal and coronal views. C1, genu corpus callosum (CC); C2, body CC; C3, splenium CC. A1a, arcuate-inferior-temporal tract; A1b, arcuate-superior-temporal tract; A1c, arcuate-superior tract; A2, uncinate fasciculus; A3, inferior longitudinal fasciculus (ILF); P1, posterior limb internal capsule (PLIC); P2, anterior limb internal capsule (ALIC); P3, motor tract; P4 sensory tract.

Geng, Gilmore, Gerig, Styner, et al., 2012

From Tensors to Connectivity?

- Study diffusivity in 3D tensor field
- Propagate principal diffusion direction originating at user-selected seed point
- Display paths as streamlines
- Measurement of FA and MD along path

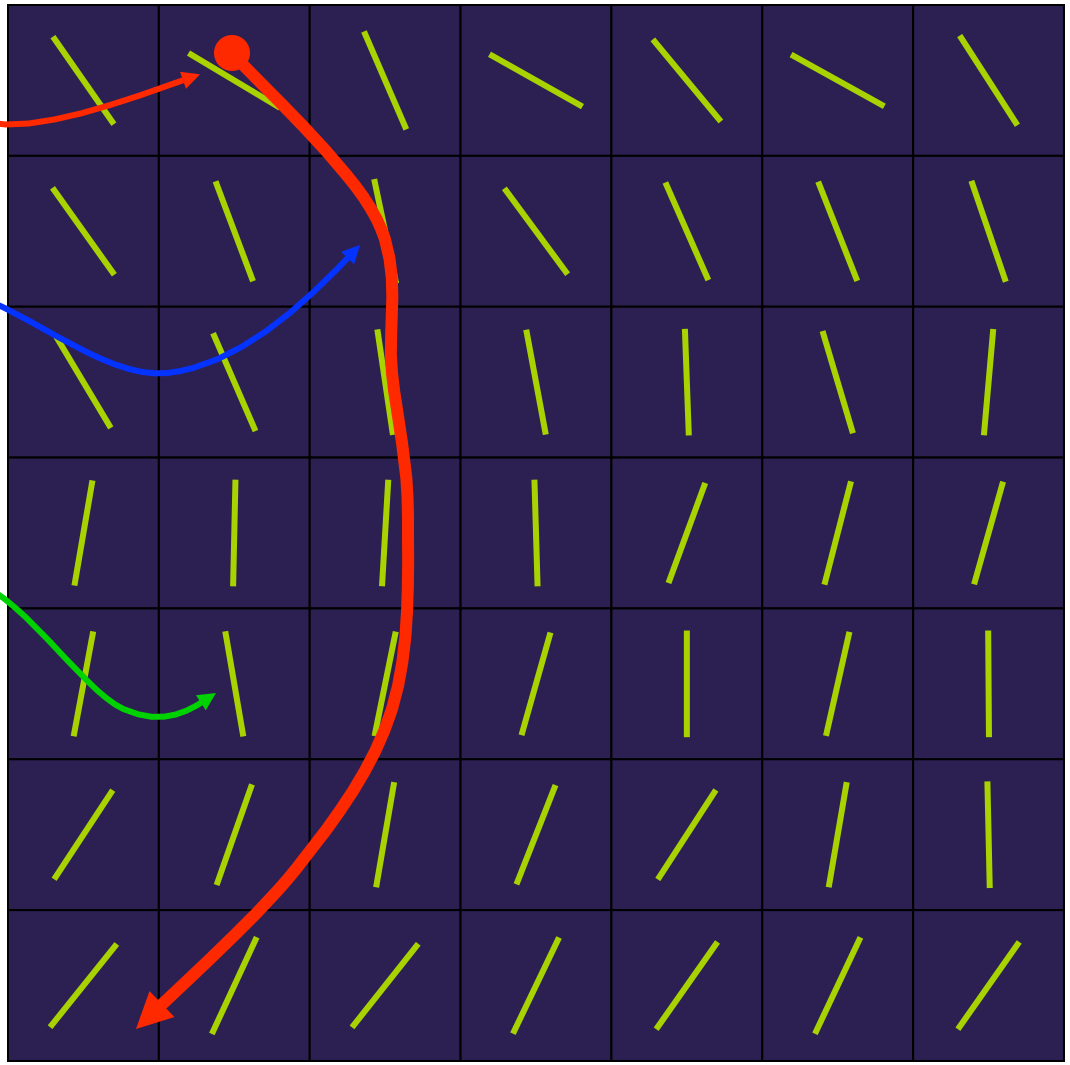


DTI Tractography

Seed point(s)

Move marker in discrete steps and find next direction

Direction of principle eigen value



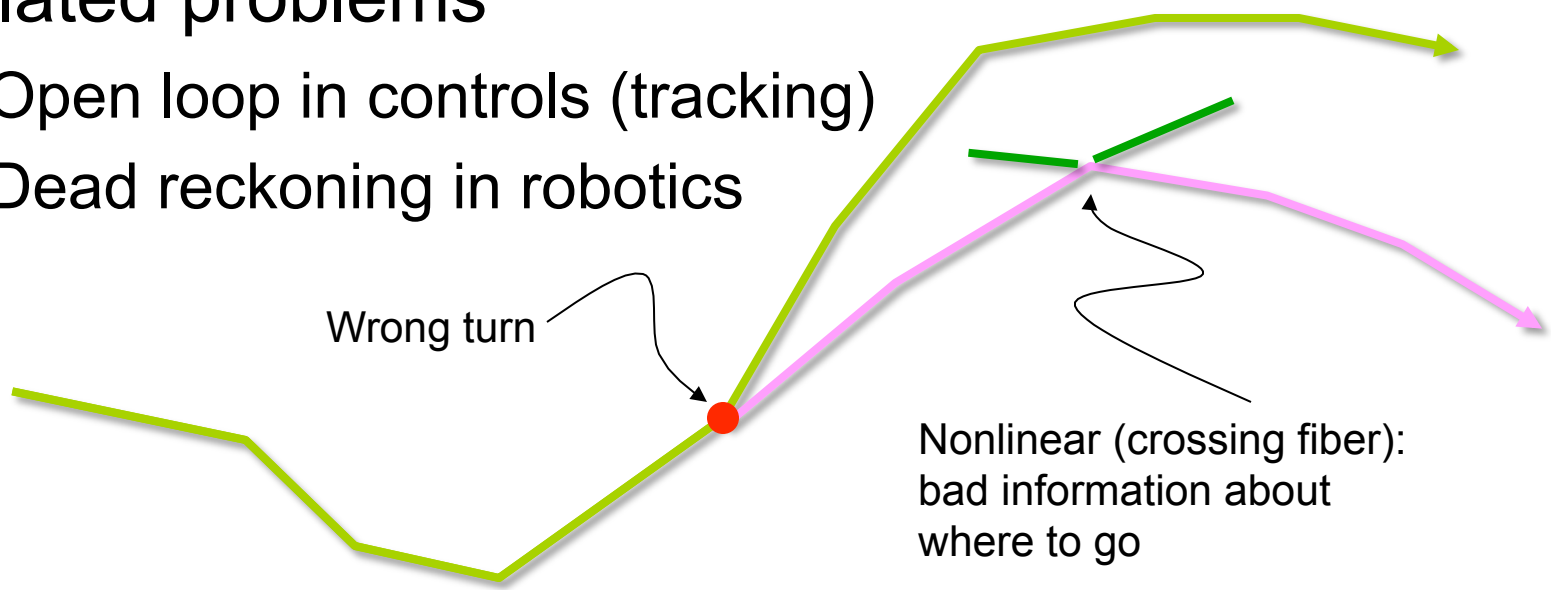
Going Beyond Voxels: Tractography

- Method for visualization/analysis
- Integrate vector field of principle directions
- Requires
  - Seed point(s)
  - Stopping criteria
    - FA too low
    - Directions not aligned (curvature too high)
    - Neighborhood coherence
    - Leave region of interest/volume
- Many methods have been published during the past decade (Basser, Mori, Westin, Vermuri, Kindlmann, Lenglet, etc.)

The Problem with Tractography

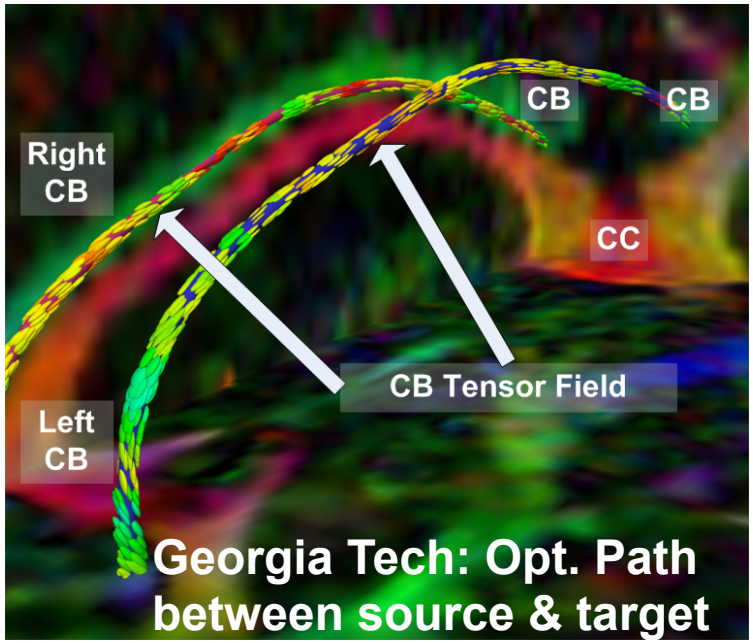
How Can It Work?

- Integrals of uncertain quantities are prone to error => error accumulation
  - Problem aggravates by nonlinearities
- Related problems
  - Open loop in controls (tracking)
  - Dead reckoning in robotics

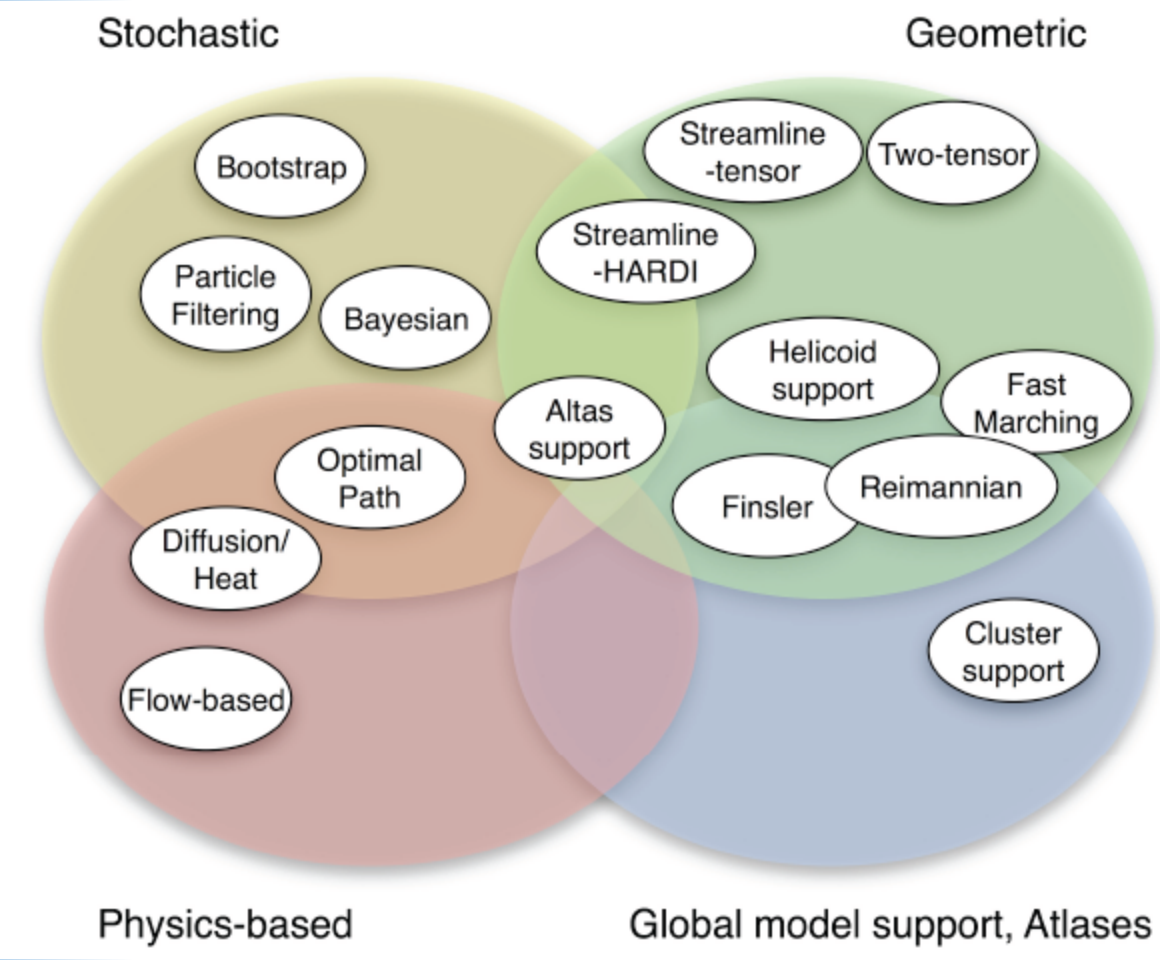


Alternative methods for tractography

- Tracking in tensor field
- Probabilistic tractography
- Optimal path analysis
- Fiber tract by volumetric diffusion
- Higher order representation based tractography

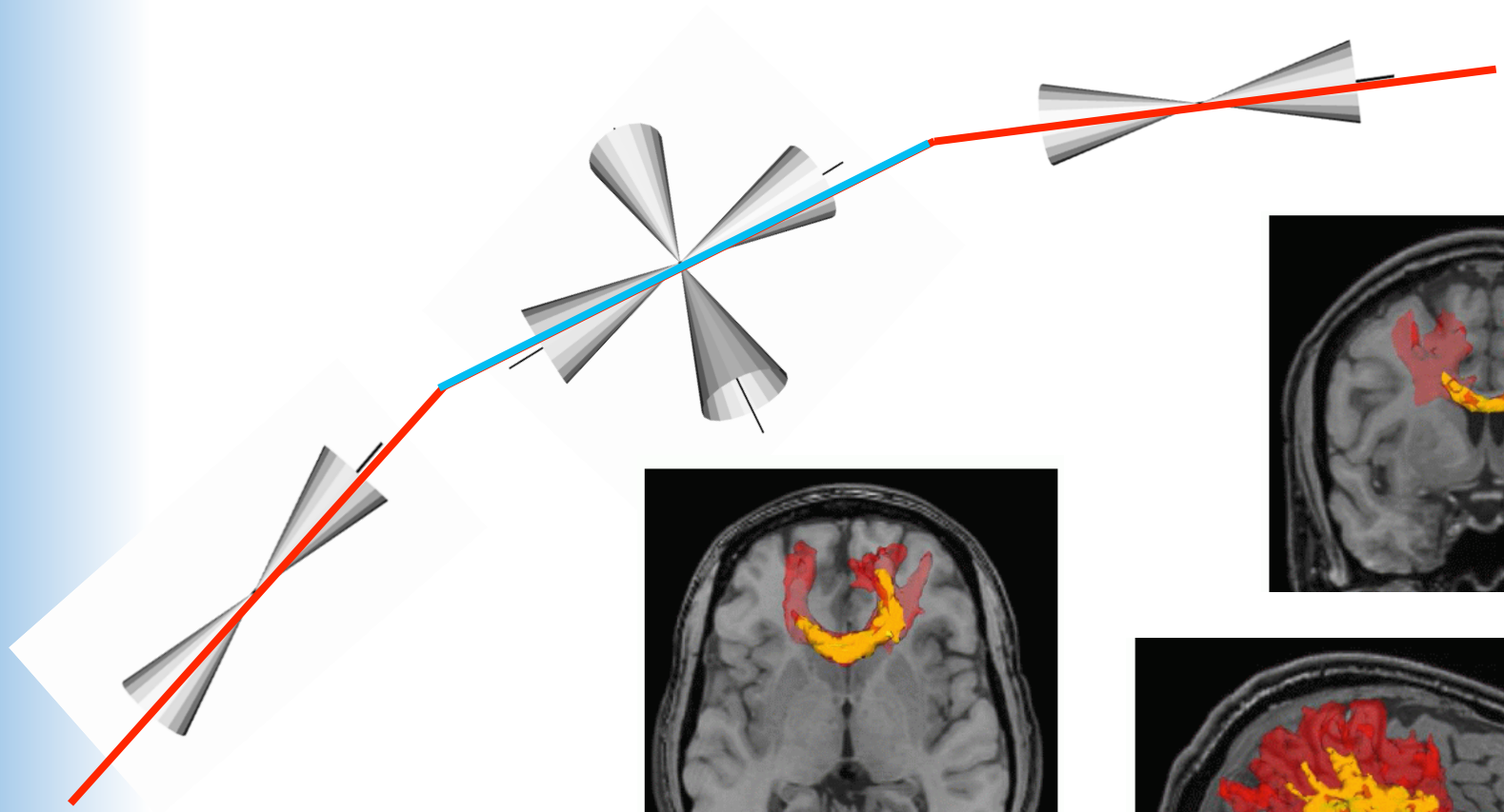


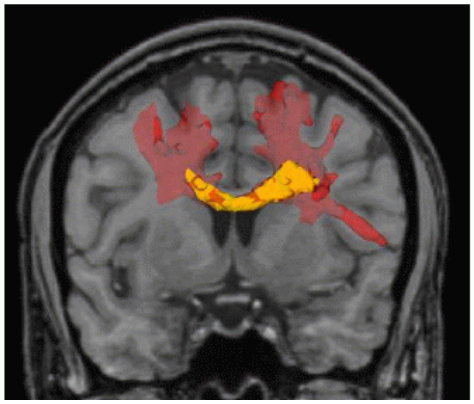
Diffusion MRI Tractography

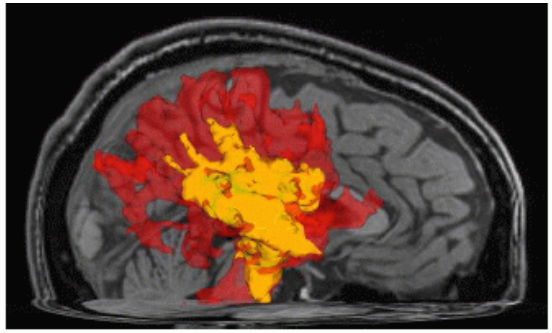


Courtesy Carl-Fredrik Westin

Tractography Incorporating Uncertainty



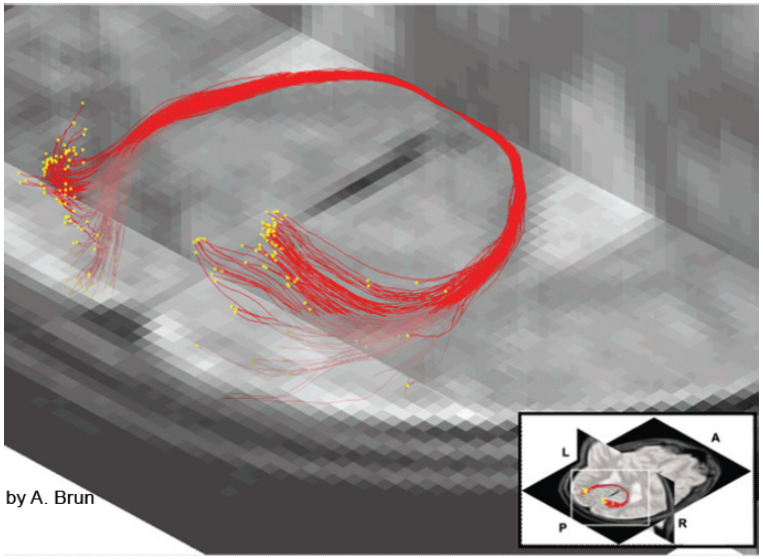




Courtesy of Bruce Pike, MNI

Stochastic Tractography

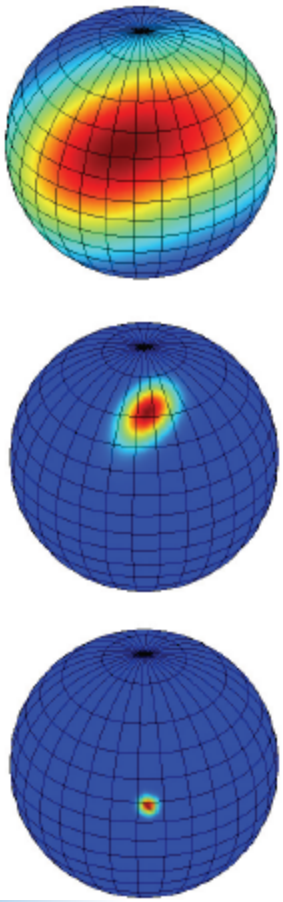
- Lazar, Alexander, **White Matter Tractography using Random Vector (RAVE) Perturbation, ISMRM 2002**
- D. Tuch, Diffusion MRI of complex tissue structure, Ph.D. dissertation, Harvard-MIT, 2002
- Brun, Westin, **Regularized Stochastic White Matter Tractography Using Diffusion Tensor MRI:** Monte Carlo, Sequential Importance Sampling and Resampling. MICCAI 2002.
- Zhang, Hancock, Goodlett and Gerig, **Probabilistic White Matter Fiber Tracking using Particle Filtering and von Mises-Fisher Sampling**, Med Image Anal. 2009 Feb;13(1)
- FSL: Behrens, Berg, Jbabdi, Rushworth, Woolrich, “Probabilistic diffusion tractography with multiple fibre orientations: What can we gain?,” NeuroImage, vol. 34, no. 1 2007.



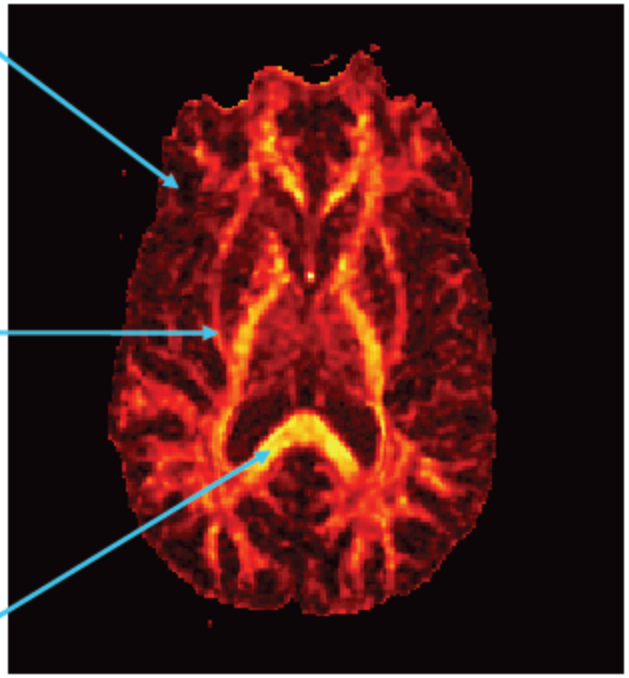
Courtesy Carl-Fredrik Westin

Stochastic Tractography

Friman, Westin MICCAI 2005, TMI 2006



Fractional anisotropy



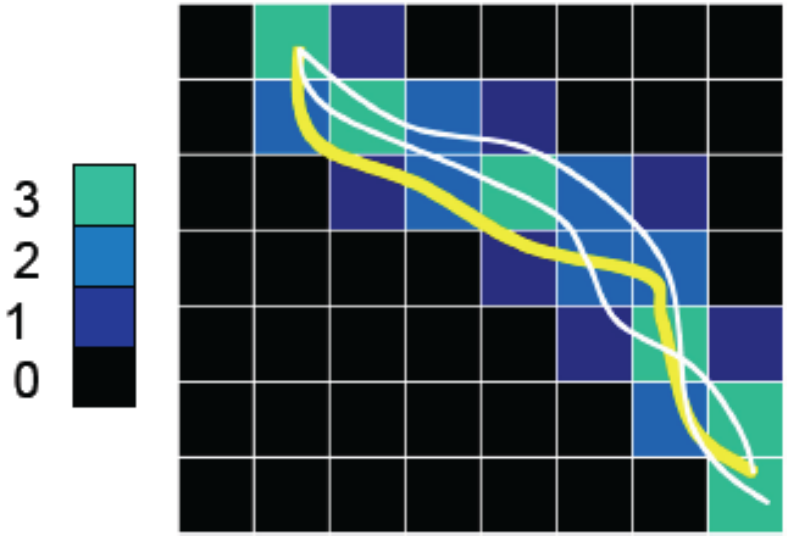
A probability density function of the fiber orientation in each point.

Start point

In every step, draw a step direction from the pdf of the underlying fiber orientation.

Probability of Connection

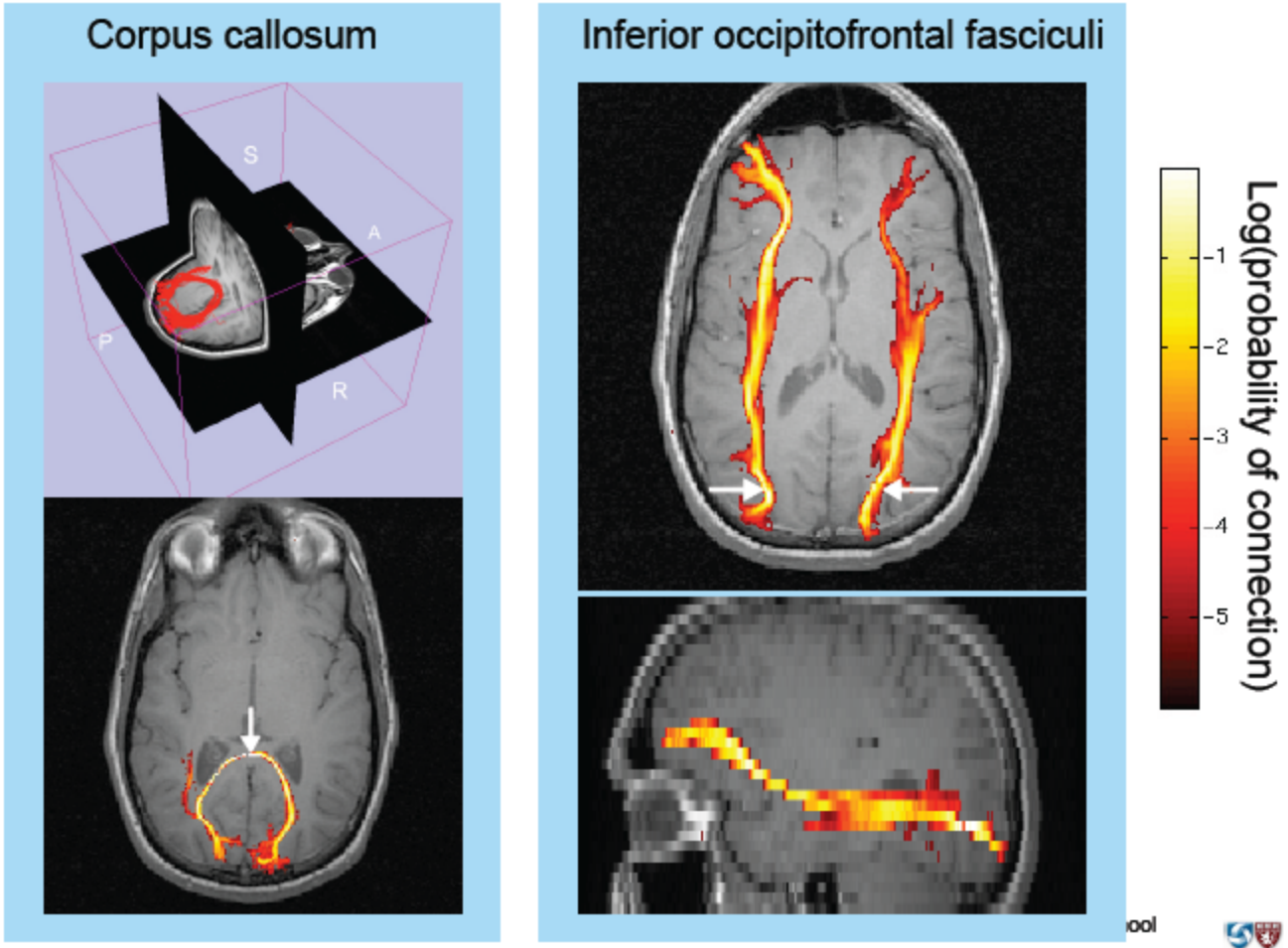
Given a large number of fibers, the probability of a connection between two voxels can be estimated



Probability density function: 1) Add the contribution from all paths, and 2) normalize the total sum of all voxels

Courtesy Carl-Fredrik Westin

Probability of Connection

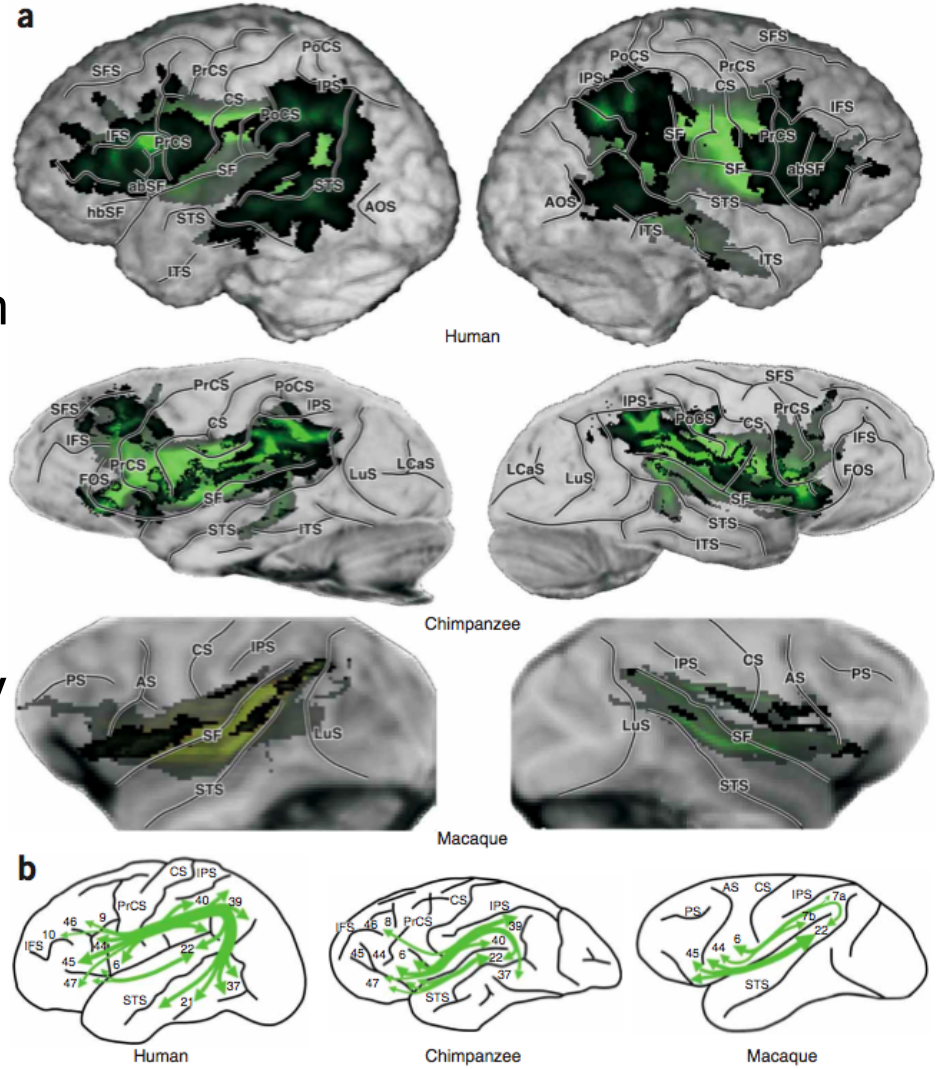


Work with O. Friman

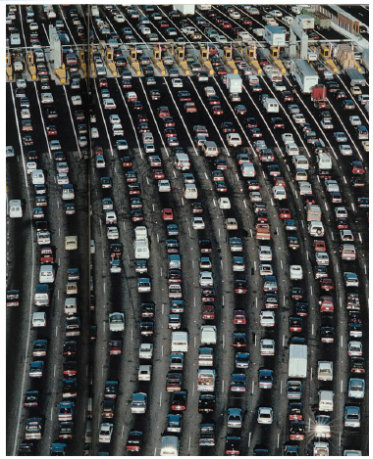
Courtesy Carl-Fredrik Westin

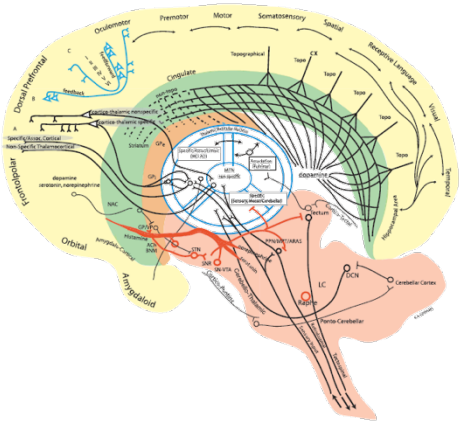
Brain Evolution Probing via Stochastic Tractography

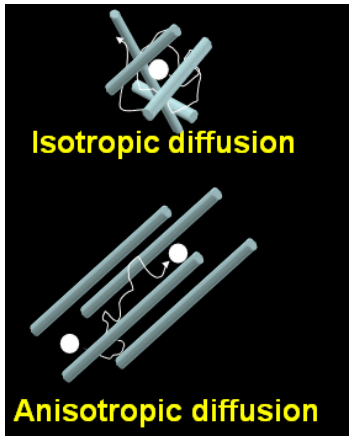
- Arcuate fasciculus, associated with language/expression
  - Temporal lobe projection absent/smaller in non-human primates
- Rilling, 2008 Nature Neuroscience
- Stochastic tractography is used for groups/ populations
- Not stable enough for individual data



Word of Caution



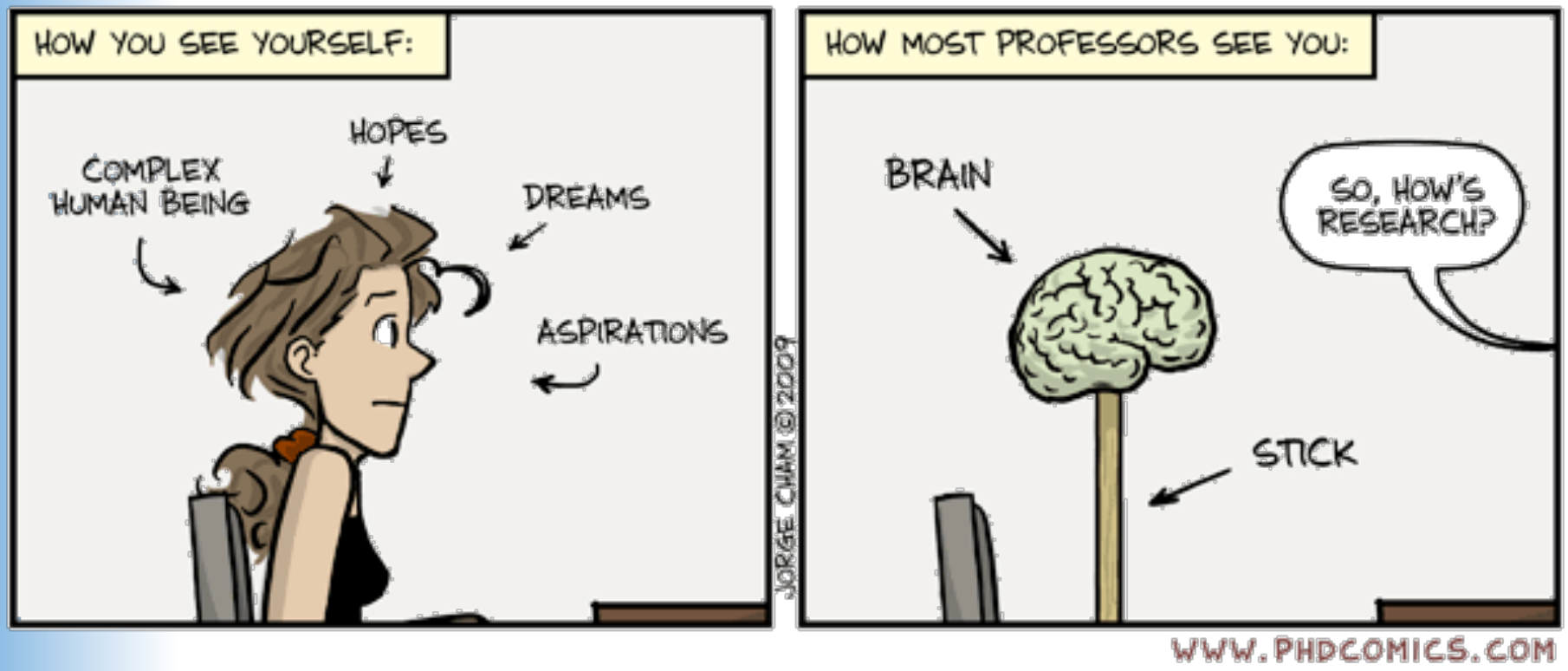




- Curves and streamlines from tractography are NOT AXONS but possible paths in vector/tensor field.
- “Fiber counting”, Fiber scientifically questionable.
- Do not “blindly” use the word “Connectivity” when applying DTI

Break!!

PhDcomics: Brain on a stick



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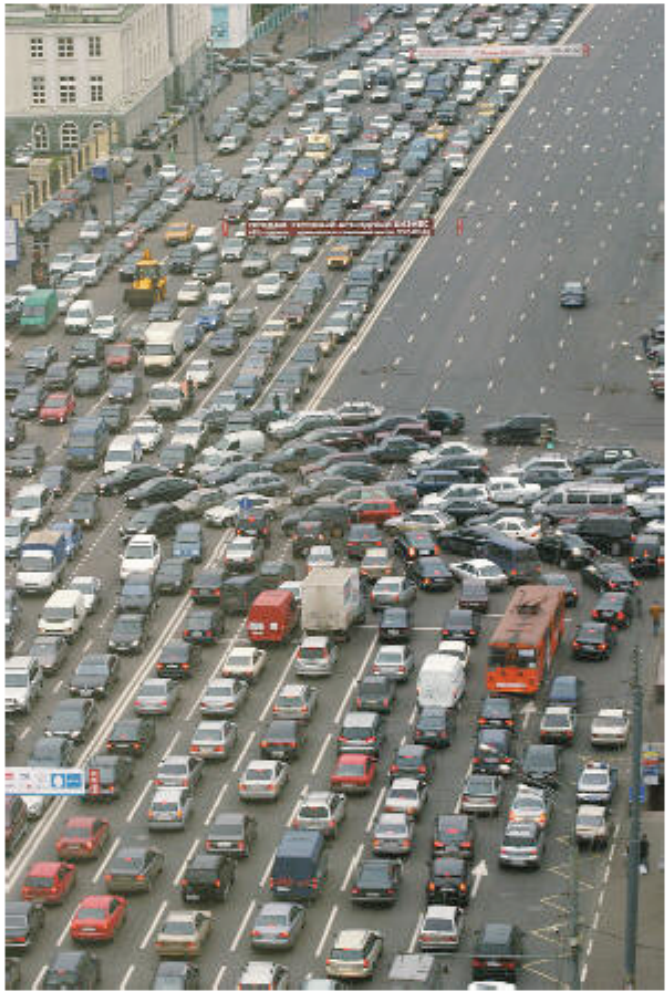
Limitation of Tractograpy: Infer global structure from local estimate

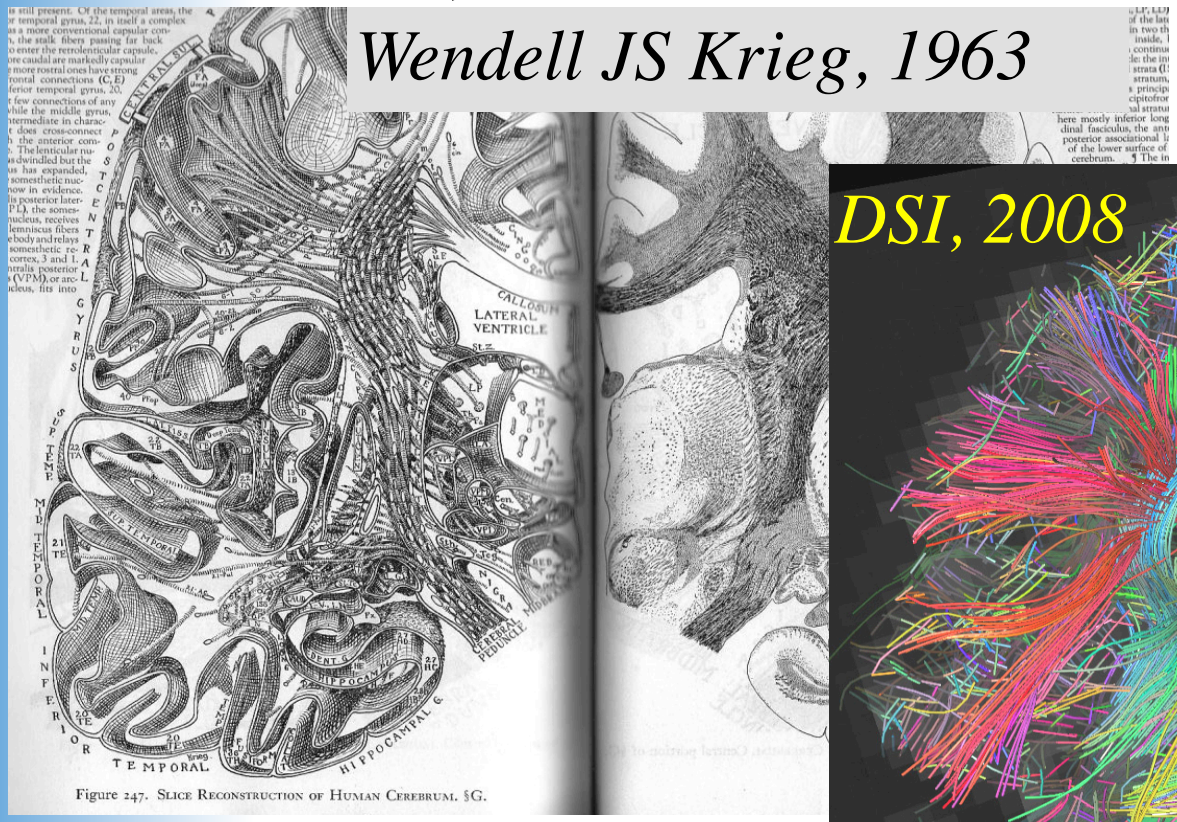


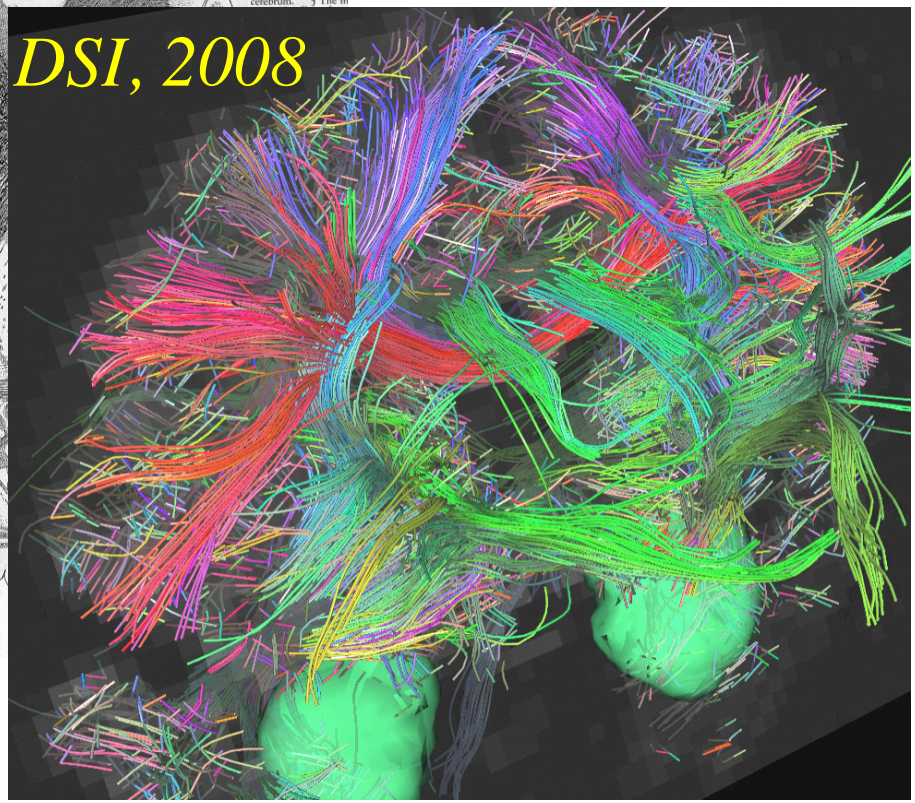
We measure diffusion structure of local elements (2x2x2mm3) and make inference/guess about road network → axonal bundles.

- Voxel size: cubic mm
- Axon diameter: micrometers

Courtesy Carl-Fredrik Westin

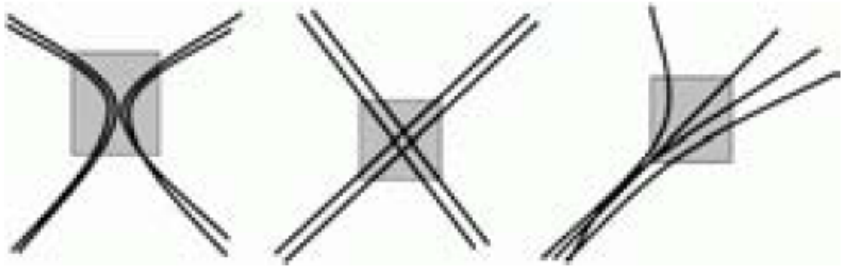
New Techniques: HARDI, DSI, Q-Ball





VJ Wedeen, R Wang, T Benner
MGH-Martinos Center,Harvard Medical School

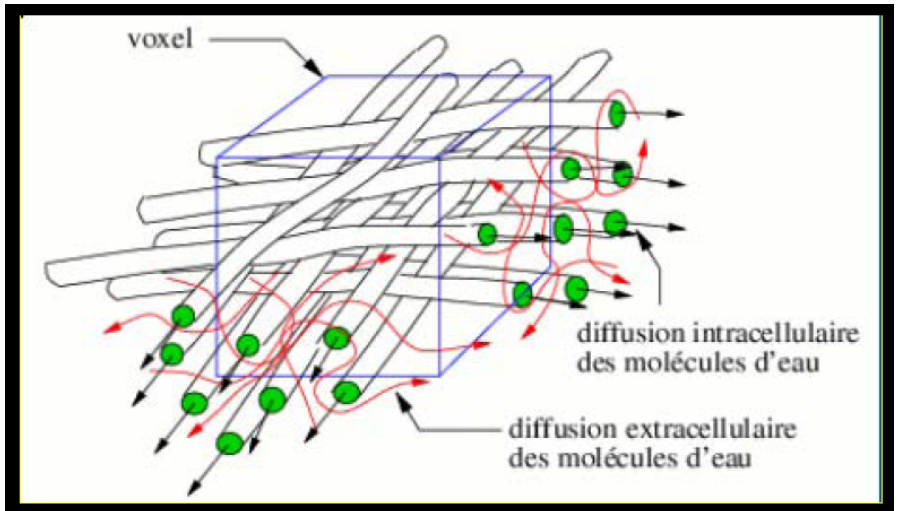
Limitations of the Diffusion Tensor Model



Kissing Crossing Splaying.

Diffusivity in a fiber crossing

2nd-order tensor approximation

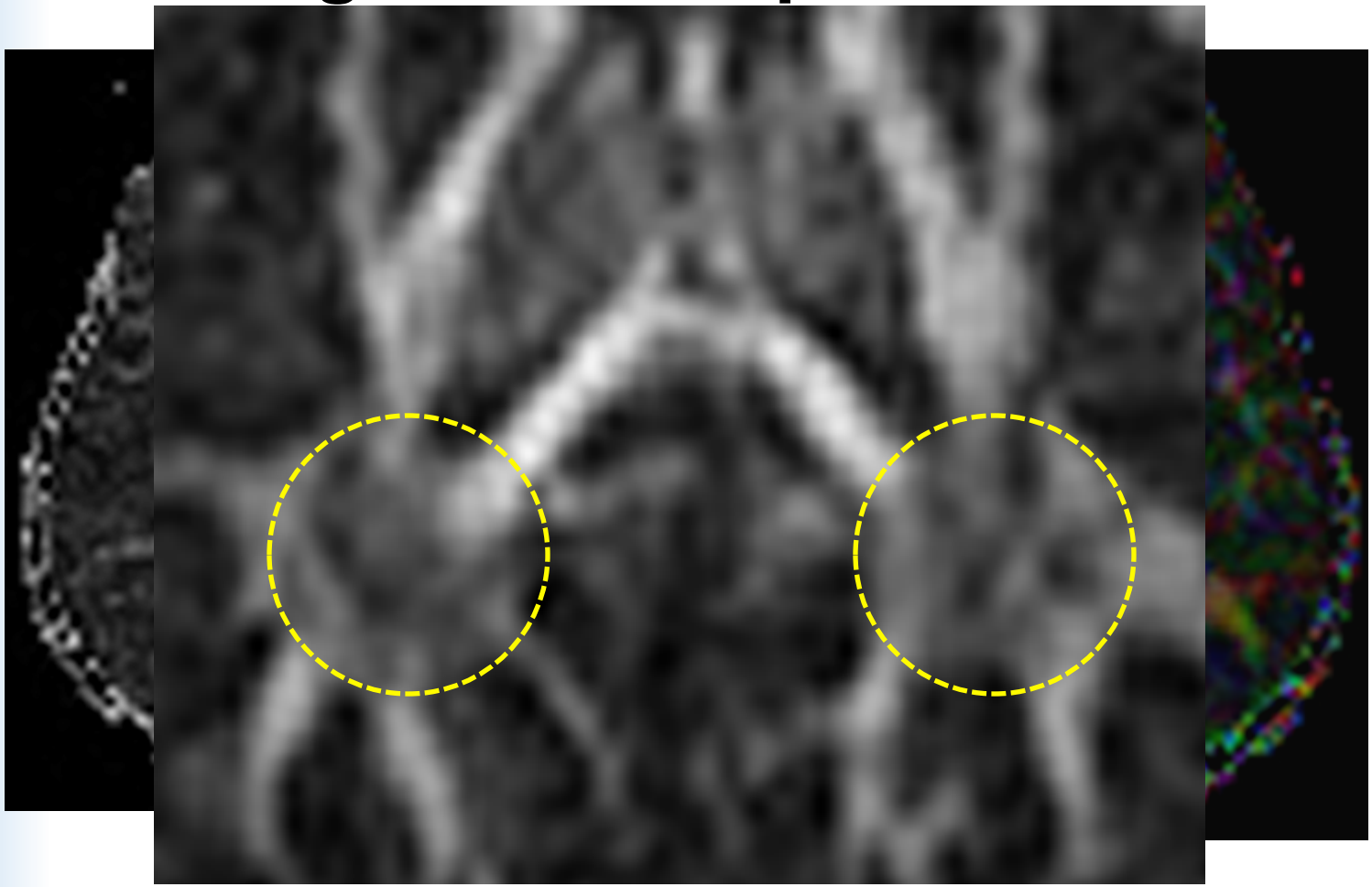


DTI fails when fiber bundles crosses within the same voxel

Non-Gaussian diffusion process - Image from [Poupon-PhD:99]

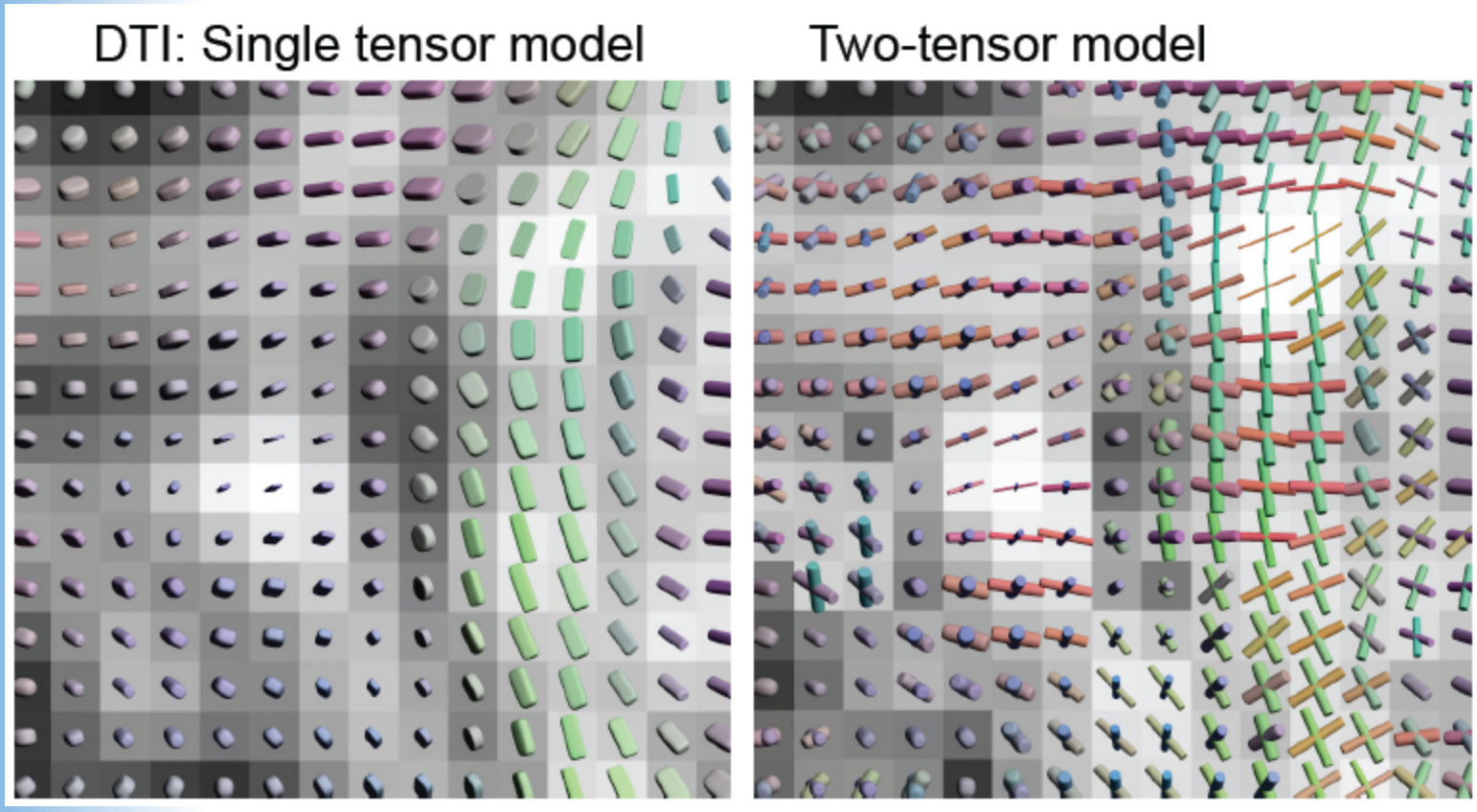
Courtesy B. Vemuri, MICCAI 2008 workshop

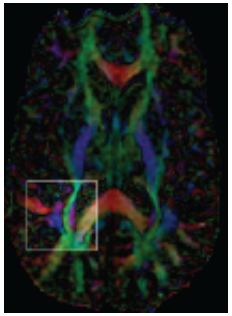
DTI with 12 directions & 2 averages
Crossing Fibers Dropout on FA



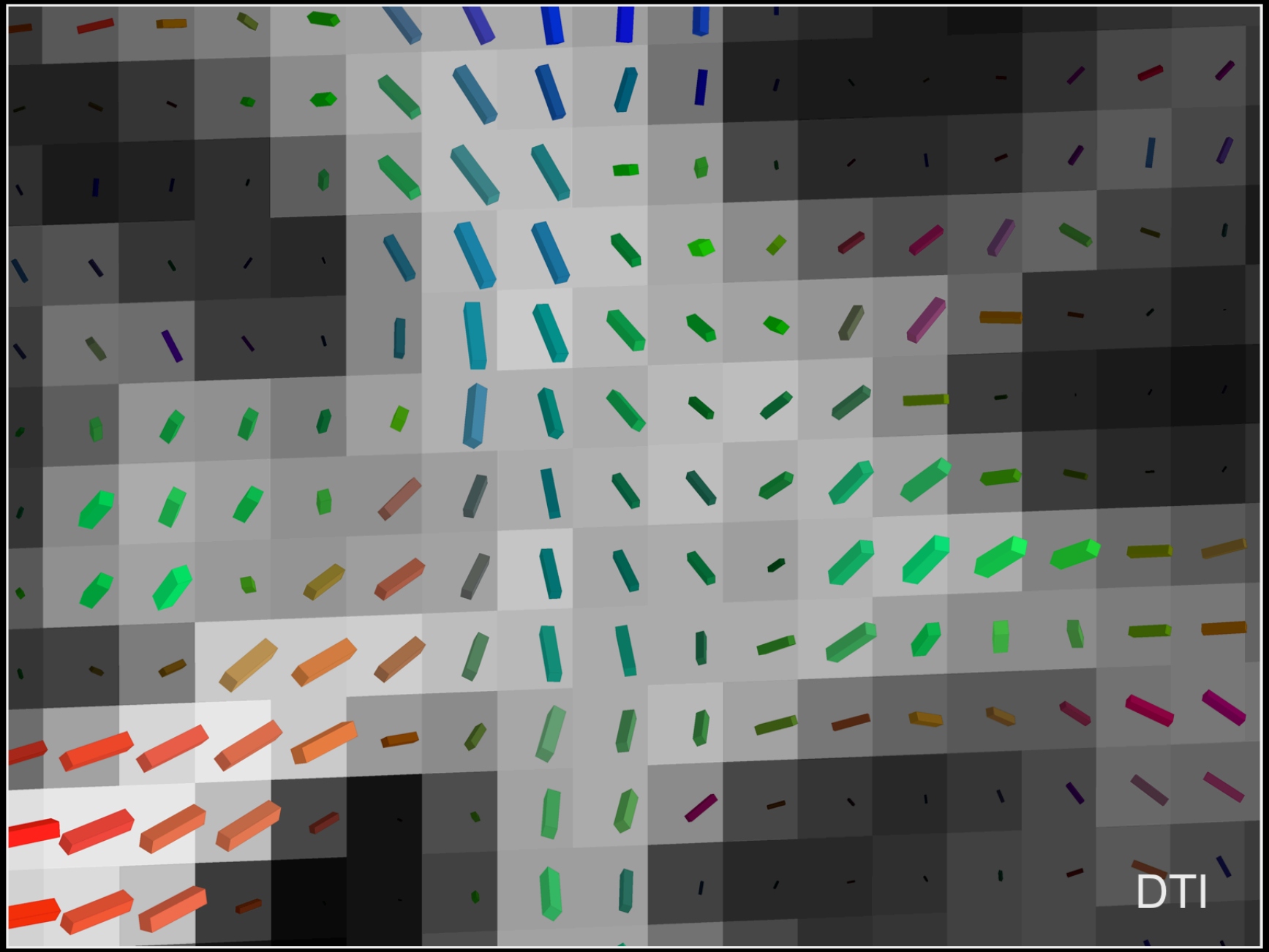
Courtesy R. McKinstry

Two Tensor Model

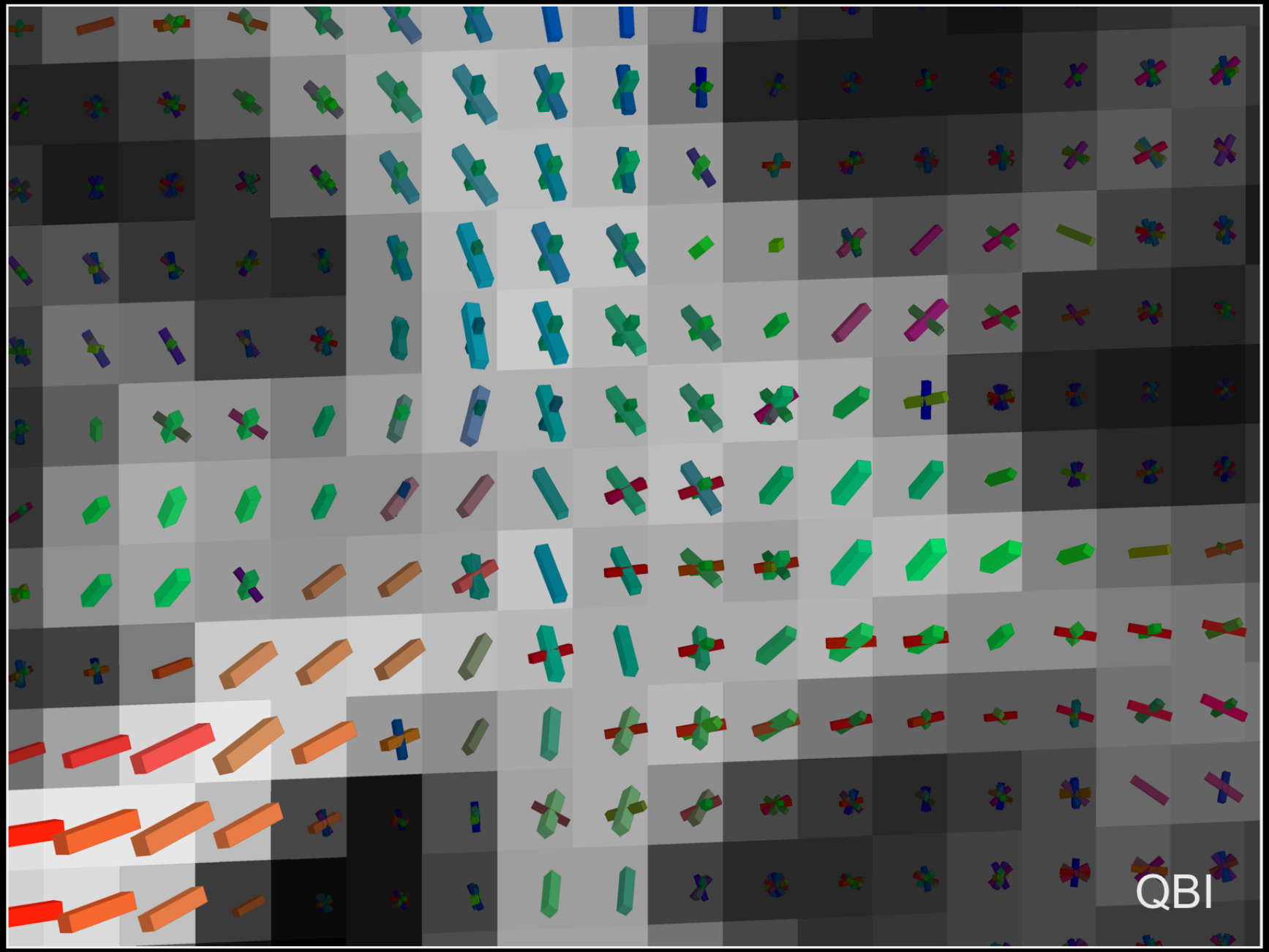




Courtesy Carl-Fredrik Westin, MICCAI 2008 workshop



MGH / DT

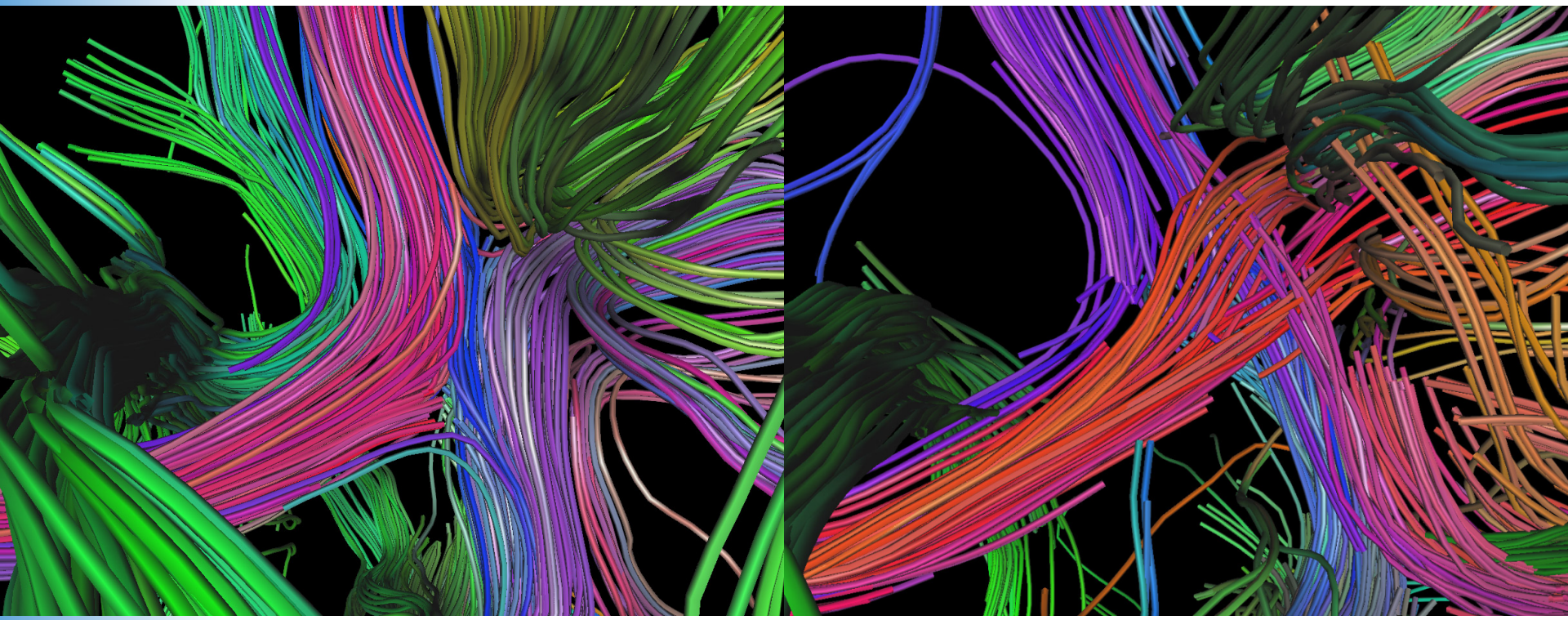


MGH / DT

Centrum Semiovale

corpus callosum (red) & corticospinal tract (blue)

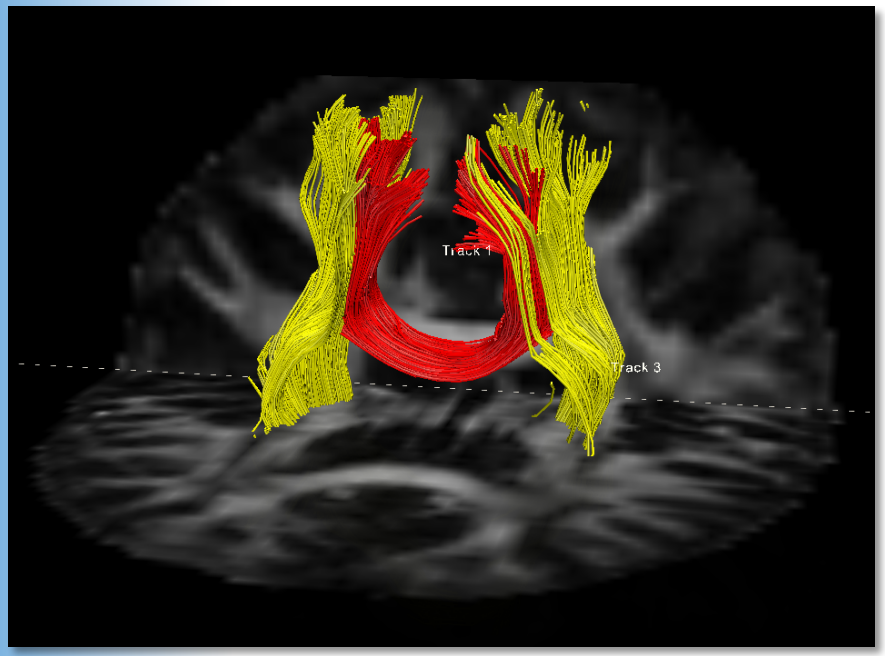
DTI *DSI*



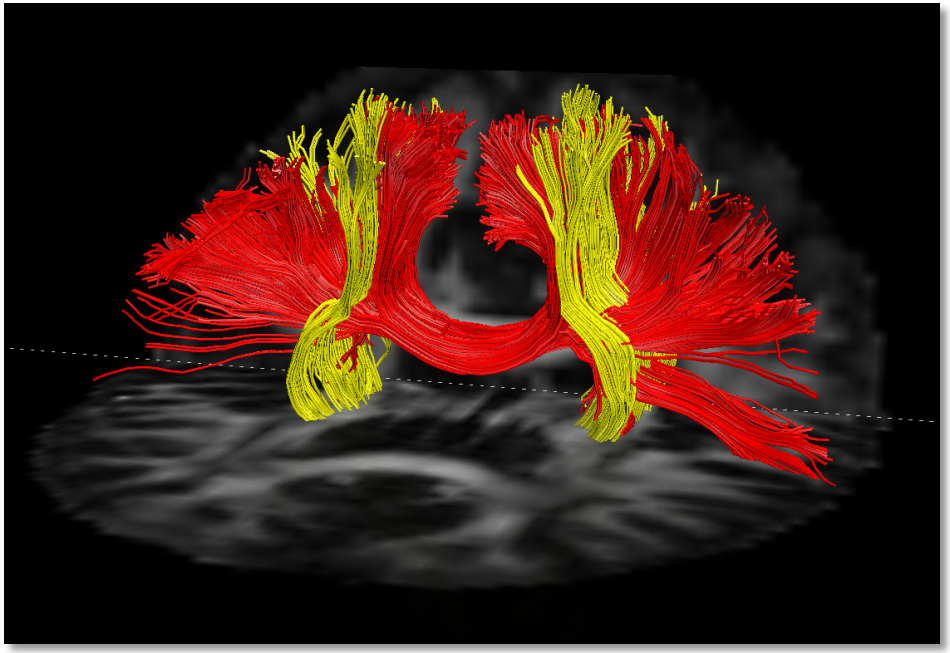
Wedeen / Wang /AGS / MGH - HST

Spherical Deconvolution

DTI Tractography



Spherical Deconvolution Tractography



Close to standard DTI protocols → 60 DW dir, Cardiac Gated, **b=1500** s/mm^2

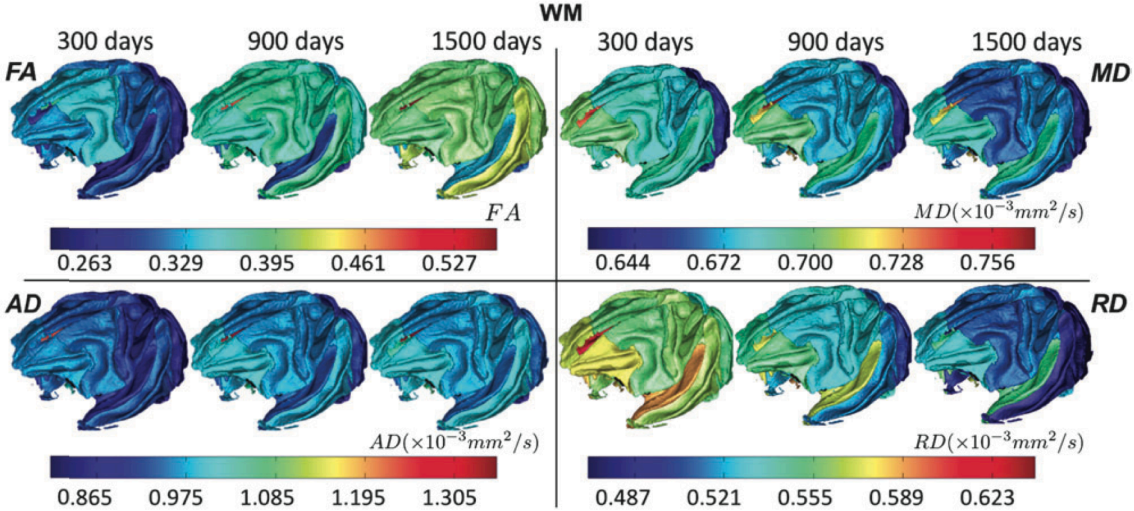
Dell'Acqua et al. NeuroImage 2010

Analysis Frameworks

- 3 major approaches
  1. Regional via structural data or prior atlases
  2. Voxel-wise on whole brain or white matter skeleton
  3. Quantitative tractography: Profiles along fiber-tracts

Regional Analysis (I)

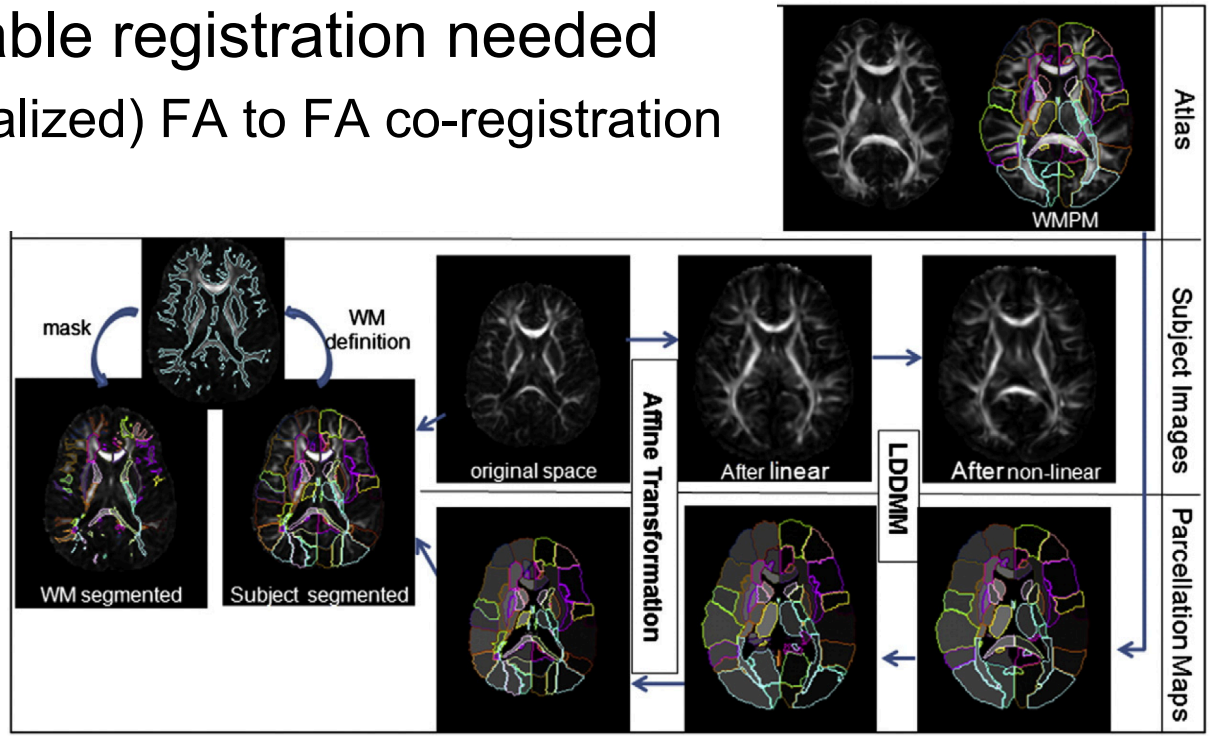
1. Co-registration of structural data
   - Segmented/parcellated structural (T1w/T2w) data
   - Deformable registration needed due to DTI/DWI distortions, usually to Baseline DWI
   - Mean vs Median/Quantile stats
     - Tensor scalars often non-Gaussian



Macaque brain development via DTI, Shi, Styner et al, Cerebral cortex, 2013.

Regional Analysis (II)

1. Co-registration of atlas
   - Atlas with prior regions
   - Probabilistic regions => probabilistic stats
   - Deformable registration needed
     - (normalized) FA to FA co-registration



Faria,Mori, et al, NeuroImage, Nov. 2010.

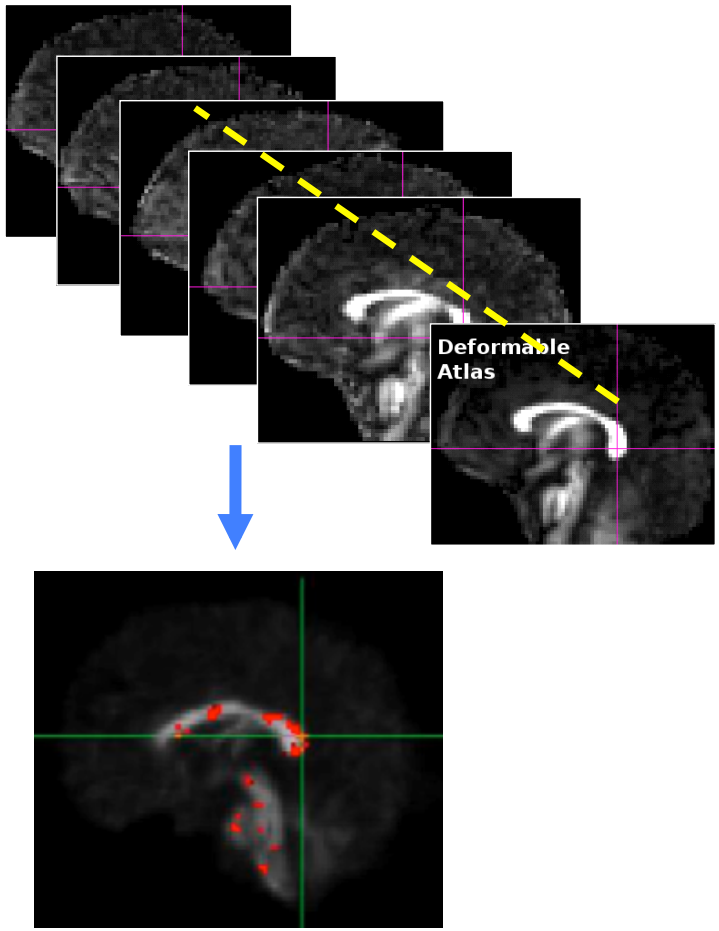
Application to Cerebral Palsy

Regional Analysis

+ “Simple” processing
+ Robust against imperfect registration
- Mixes apples and oranges
  - Different tracts within same region
  - Different fiber situations (crossing vs single)
- Limited localization

Voxel Based Analysis (I)

- Co-registration into study-specific atlas
  - Reference space
- Wild boot strapping stats with FDR
  - Liu, Zhu, Styner ISBI 09
- Test all voxels => great for hypothesis generation
- Needs perfect registration



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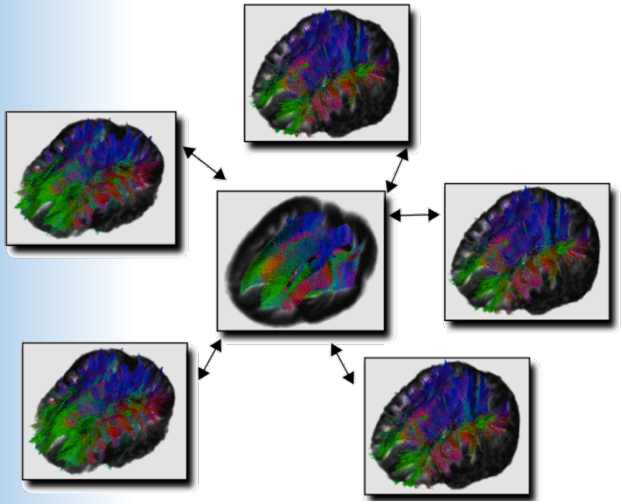
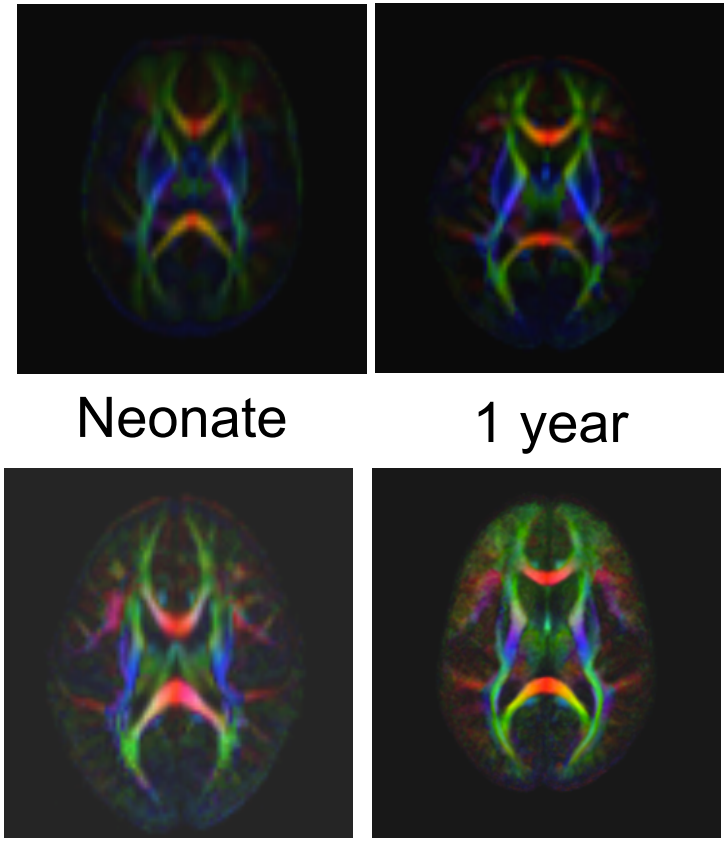
Study Specific Atlases

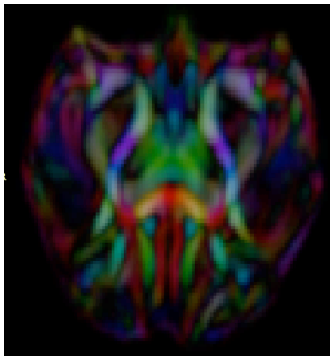
- Reference space
  - Best mapping for a given study
- SNR increase
- Unbiased atlas building (Joshi 2004)





Neonate 1 year

2 year Adult



Rhesus (15mo)

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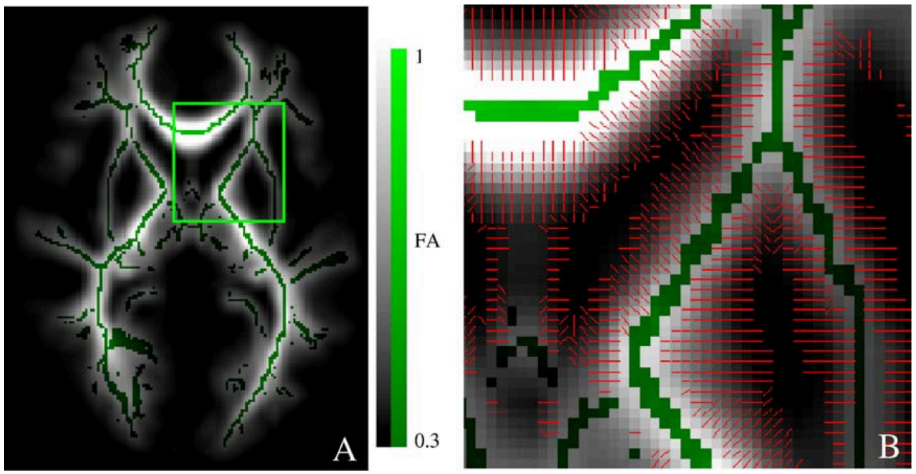
Voxel Based Analysis (II)

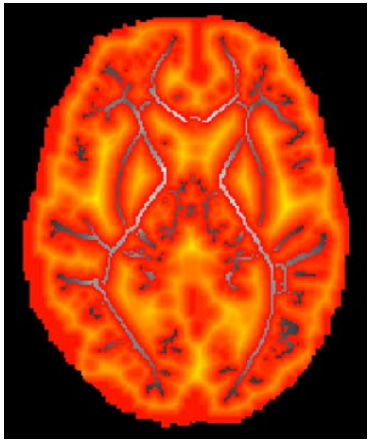
- TBSS: tract based spatial statistics
  - Idea: Analysis on white matter skeleton
  1. Determine WM skeleton
  2. Map max FA values onto skeleton
  3. Voxelwise analysis on skeleton

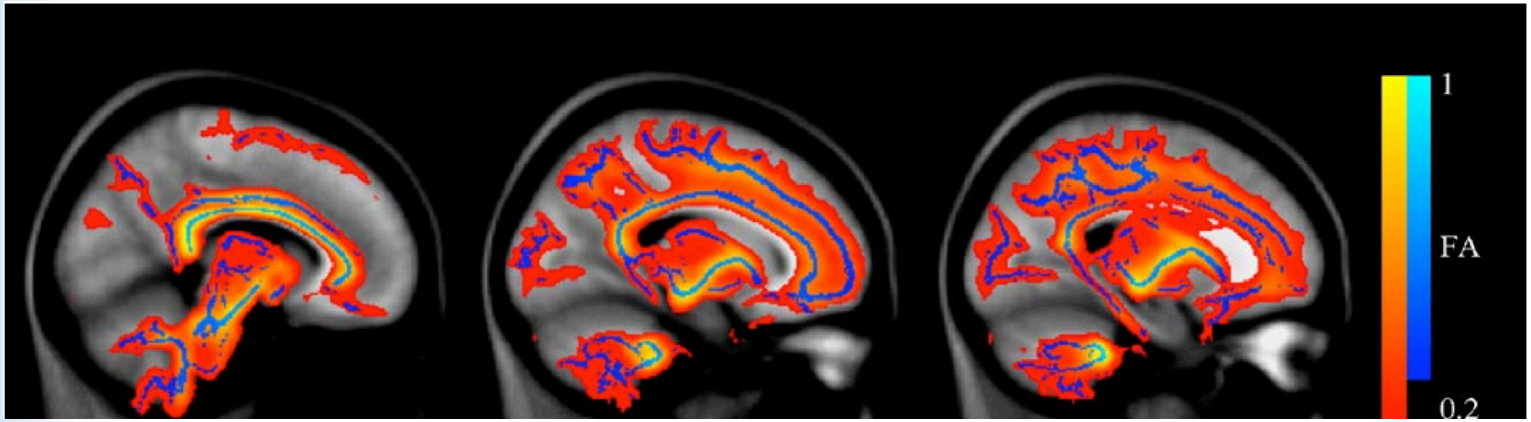
Smith, Behrens et al. *NeuroImage*, vol. 31, no. 4, 2006.



TBSS: Map FA to Skeleton

- Find max FA within nearest voxels perpendicular to skeleton
  - + Works well with imperfect alignment
  - - Max FA is less stable
  - - May mix values from different tracts





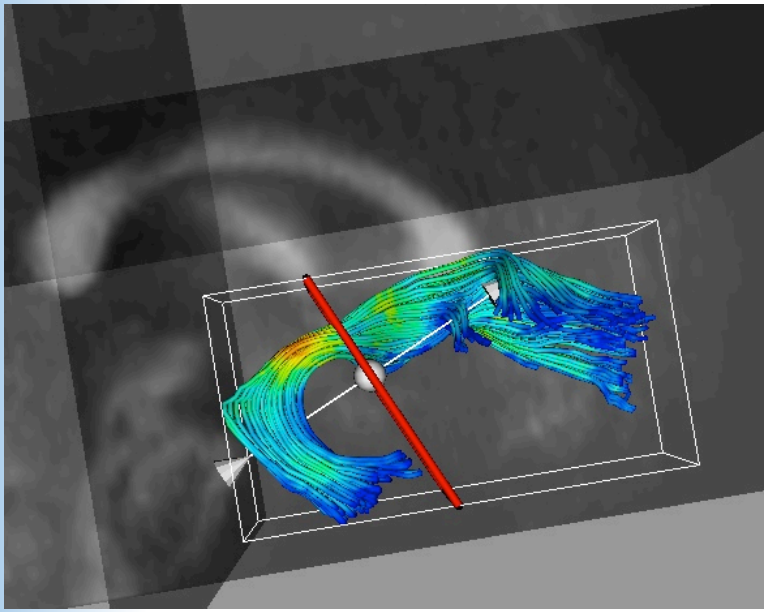
Voxel Based Analysis

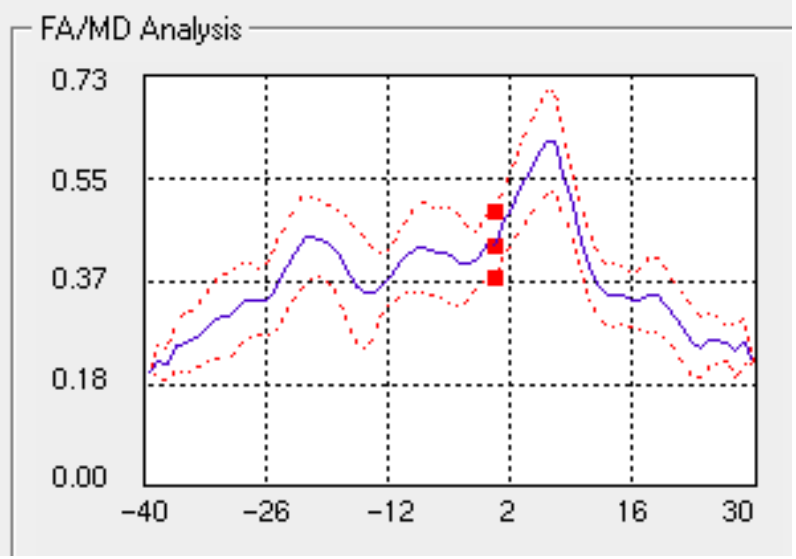
+ Whole brain analysis
+ High degree of localization
- Needs accurate atlas building procedure
- Large number of features vs low sample size – Issues with sensitivity or false-positive errors

- Well suited for hypothesis generation

Quantitative Tractography

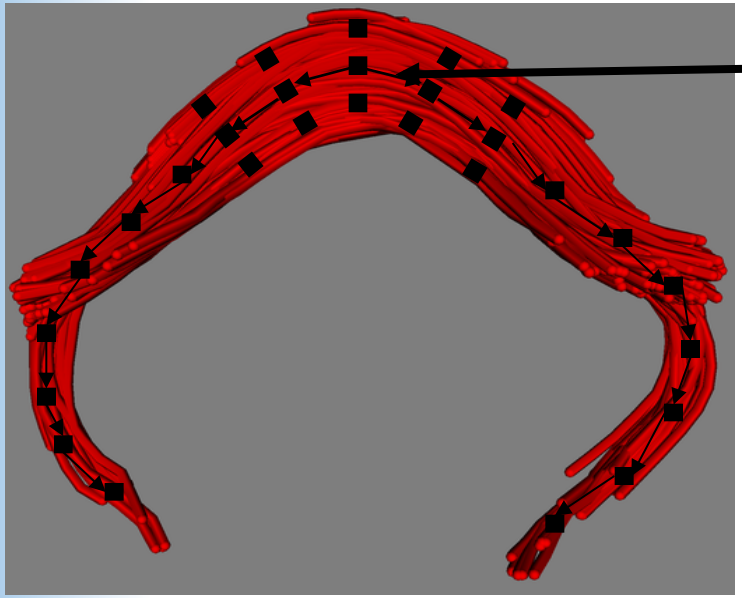
- Use fiber tracts as curvilinear regions
  1. Average within the whole tract
  2. Profiles of tensor scalars along tract



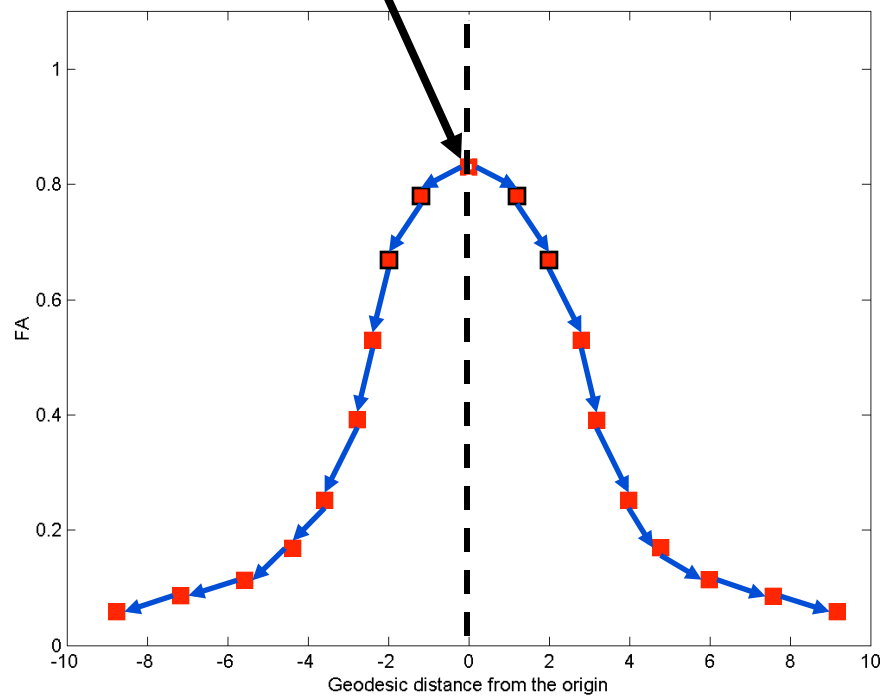


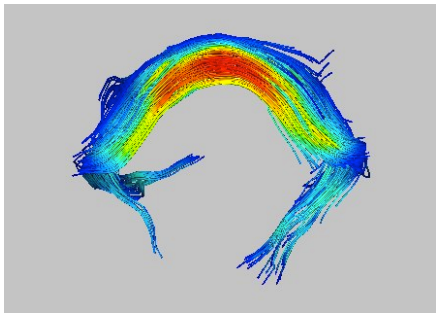
Corouge et al. *Fiber tract-oriented statistics for quantitative diffusion tensor MRI analysis*. Medical Image Analysis 2006.

Modeling of fiber tracts

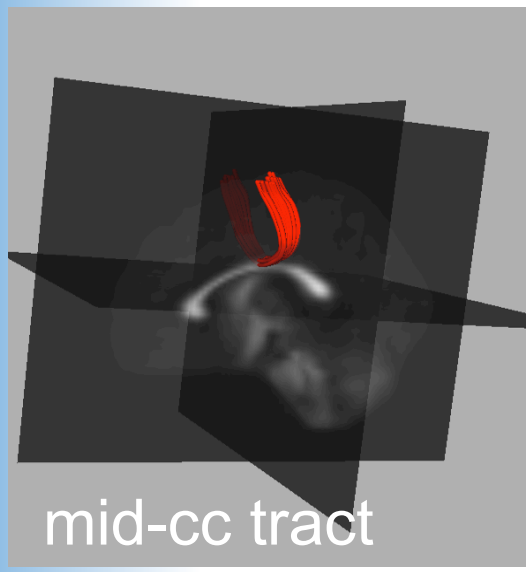


Origin (anatomical landmark)

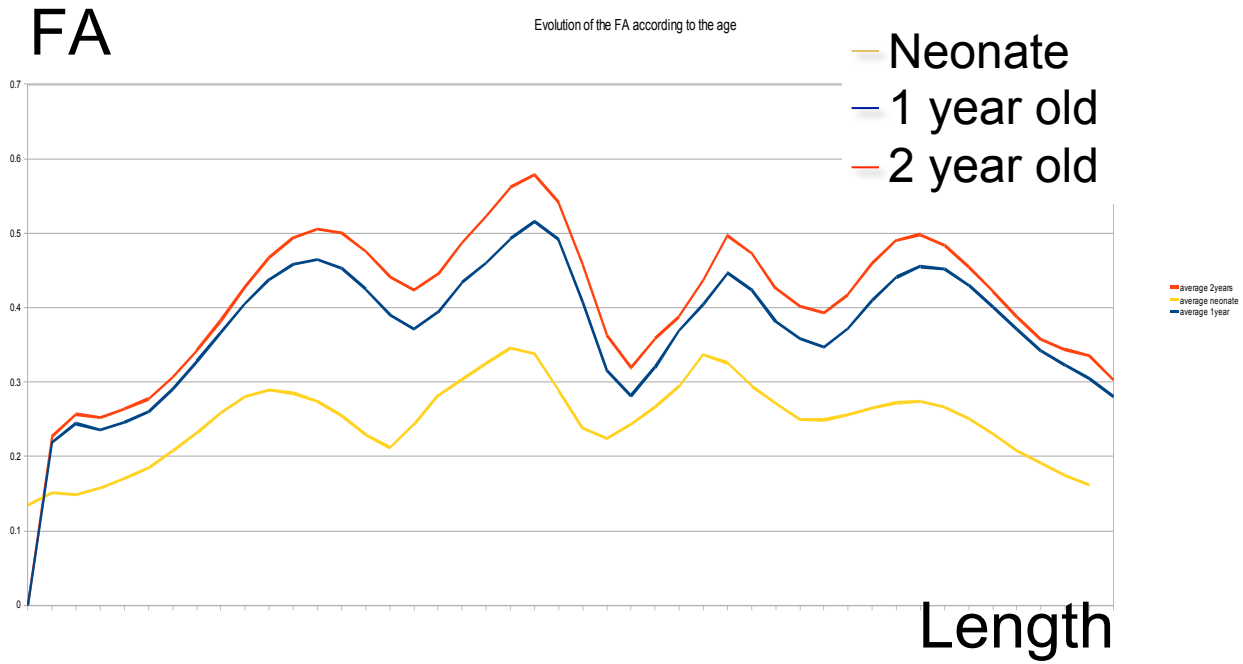




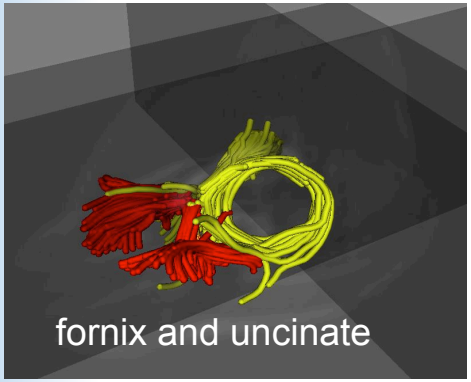
Example: WM Maturation

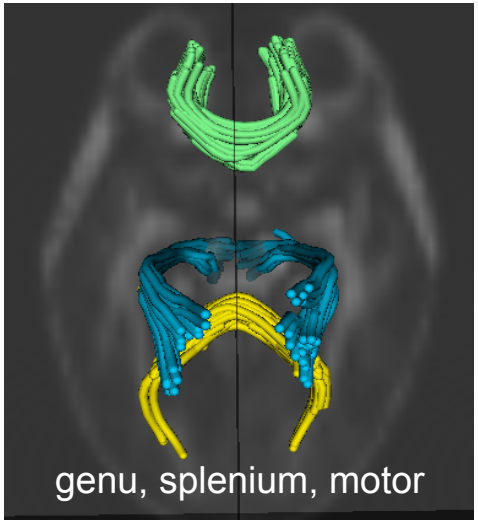


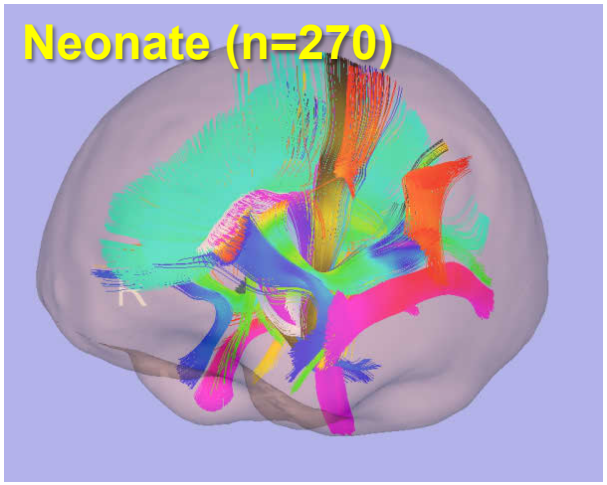
Increased white matter maturation with age

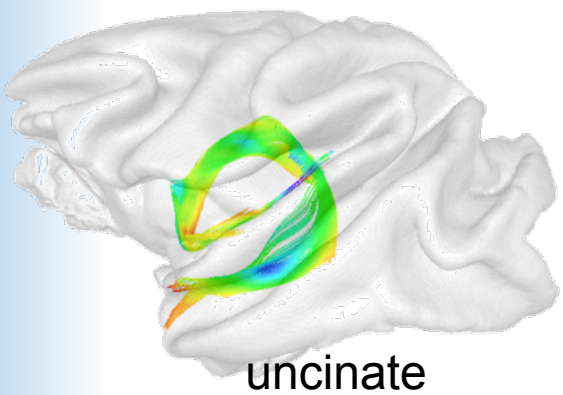


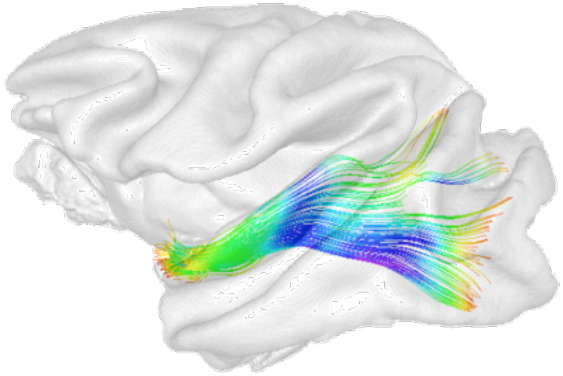
Fiber tracts in Atlas Space

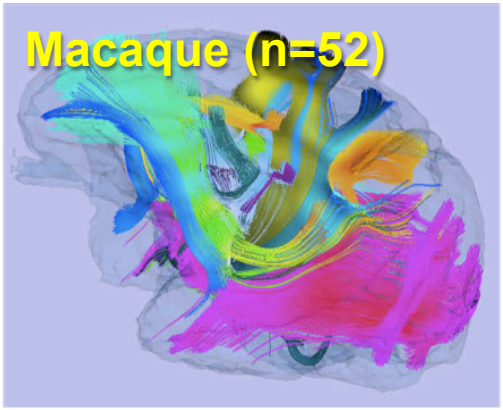












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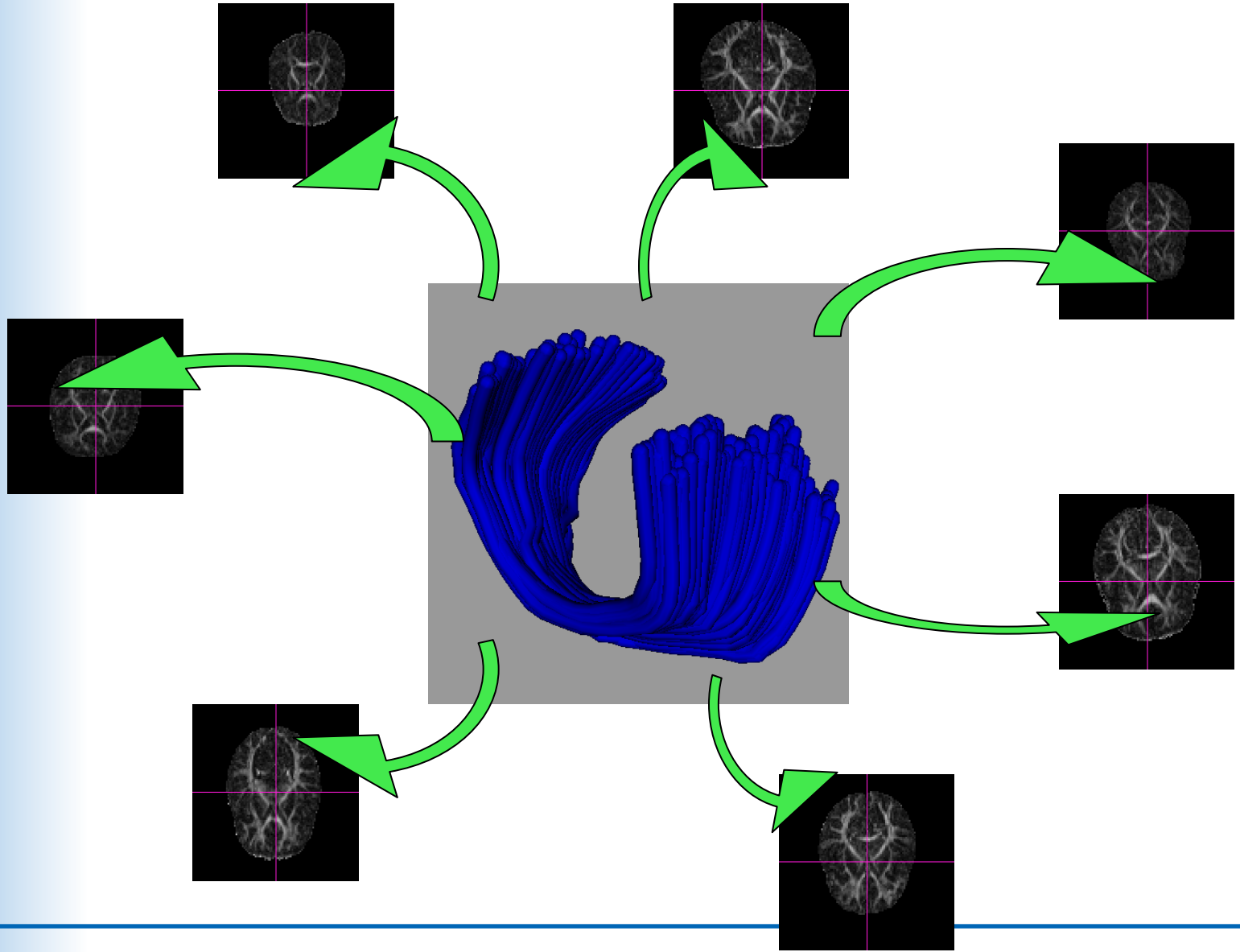
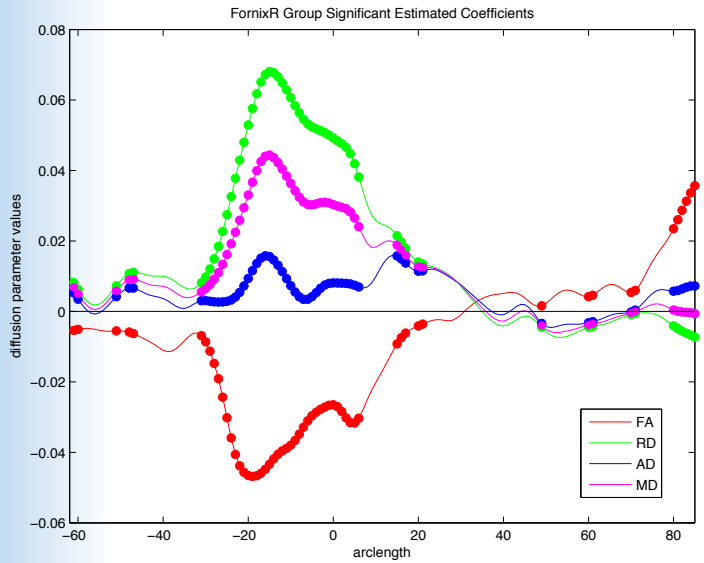
Transfer of Fibers to Cases

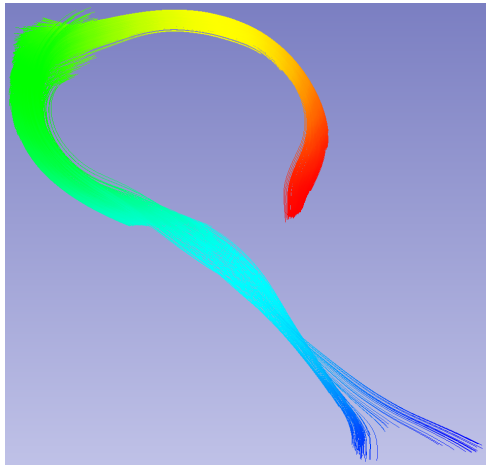


Fiber Profile Analysis

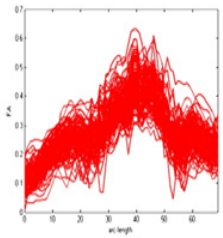
- Profile of average tensor/scalar along tract
- Curvilinear region
- Large number of features along tract
  - Functional analysis of diffusion tensor tract statistics (FADTTS, Zhu NeuroImage 2011)

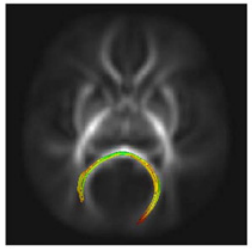


Stats along Fornix tract, group diff (smokers vs non-smokers), controlling for age & gender



FADDTS

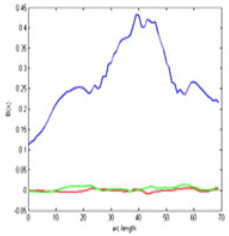




Multivariate varying coefficient model

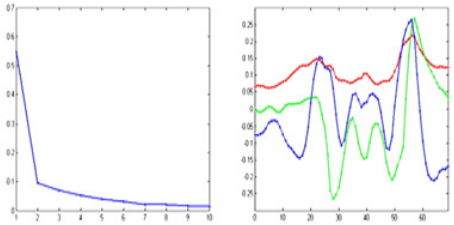
$$y_{i,k}(s) = \mathbf{x}_i^T B_k(s) + \eta_{i,k}(s) + \epsilon_{i,k}(s)$$

Weighted least square estimation



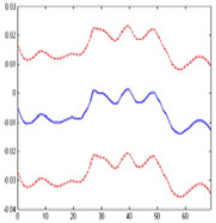
$$B_k(s_j) = B_k(s) + \dot{B}_k(s)(s_j - s)$$

Functional principal component analysis



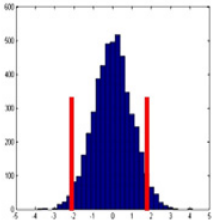
$$\hat{\Sigma}_{\eta,kk}(s,t) = \sum_{l=1} \hat{\lambda}_{k,l}\hat{\psi}_{k,l}(s)\hat{\psi}_{k,l}(t)$$

Confidence bands



$$P(\sup_{s\in[0,L_0]} |G_{kl}(s)| \leq C_{kl}(\alpha)) = 1 - \alpha$$

Resampling methods



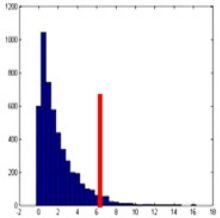
Hypothesis test

$$H_0 : \mathrm{Cvec}(B(s)) = \mathbf{b}_0(s)$$

$$H_1 : \mathrm{Cvec}(B(s)) \neq \mathbf{b}_0(s)$$

$$S_n = n\int_0^{L_0} \mathrm{d}(s)^T[\mathrm{C}(\hat{\Sigma}_\eta(s,s) \otimes \hat{\Omega}_X^{-1})\mathrm{C}^T]^{-1}\mathrm{d}(s)ds$$

Resampling methods



$$p = G^{-1}\sum_{g=1}^{G} 1(S_n^{(g)} \geq S_n)$$

Krabbe Leukodystrophy

- Rare, lethal genetic leukodystrophy
  - Autosomal recessive pattern (not X-linked)
  - Worldwide: 1 in 80,000 births.
  - Isolated communities: 6 per 1,000 births
- Deficiency in galactosylceramidase enzyme
  - **Buildup of undigested fats affects myelin sheath**
  - Imperfect growth and development of myelin
  - Severe degeneration of mental and motor skills
- Lorenzo's Oil featured similar leukodystrophy
- Normal at birth, symptoms usually start 2-6 mts
- Fever, uncontrollable crying, seizures, vomiting, spasticity, paralysis, blind, finally death within 2y
- Juvenile- and adult-onset cases rare

Diffusion Tensor Imaging Detects Abnormalities in the Corticospinal Tracts of Neonates with Infantile Krabbe Disease

Escolar 2009 AJNR

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Krabbe: Treatment

- Therapy (Maria Escolar, U Pittsburgh)
  - Myeloablative chemotherapy followed by stem cell transplantation from umbilical-cord blood
  - Treatment at Birth, no effect at symptomatic stage
  - Treated kids show differences in motor abilities
  - Survival rate depends on survival of therapy (15 of 17 ~ 88%)
- Krabbe's screening with enzyme test
  - New York started August 2006
  - Parents often wait, as no damage assessment at neonate
- DTI: Assessing damage at birth via DTI
  - Illustration of damage to parents? Diagnosis?
  - Prediction of developmental outcome for motor abilities

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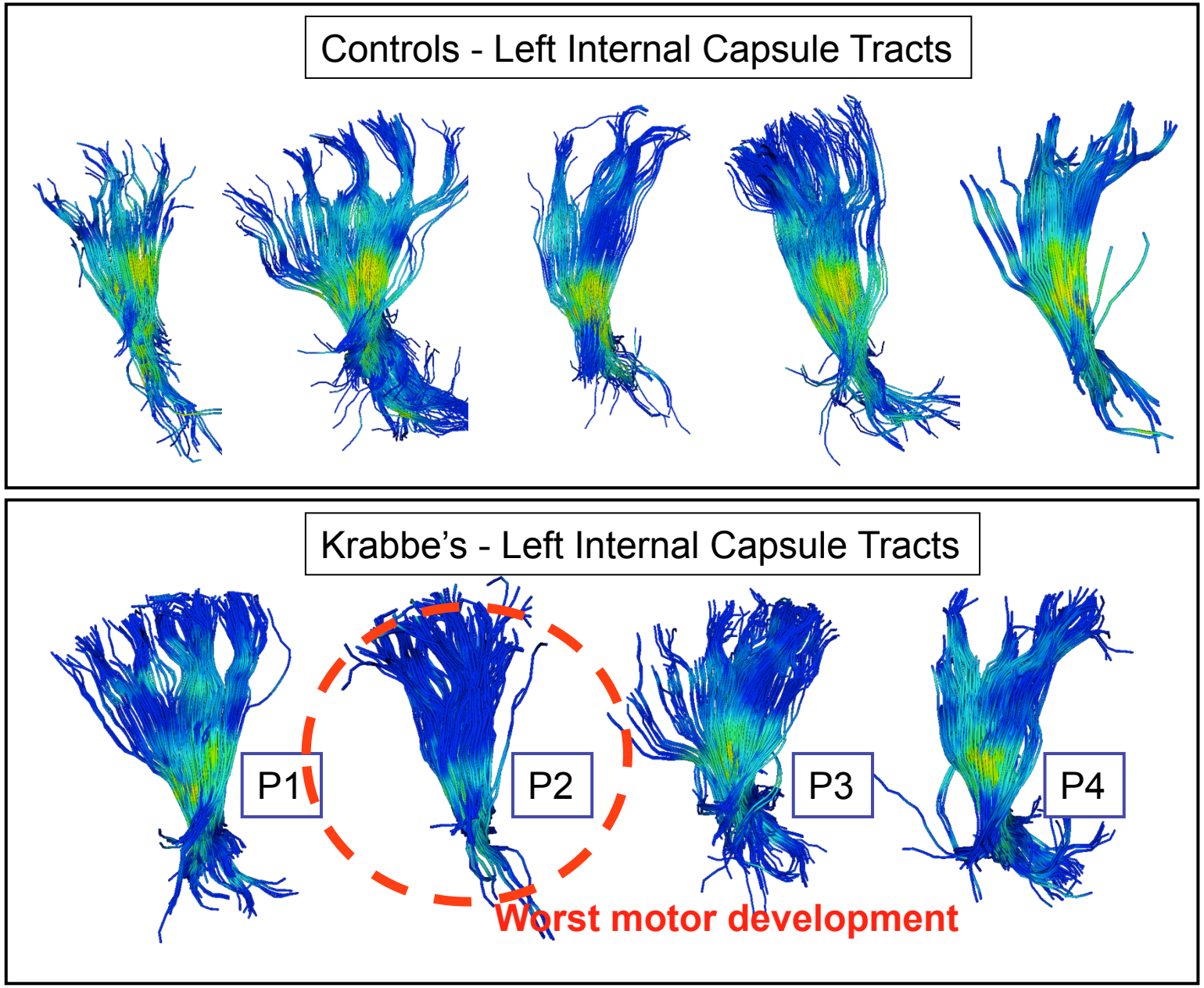
Controls - Left Internal Capsule Tracts
Krabbe's - Left Internal Capsule Tracts
P1
P2
P3
P4
Worst motor development
FA = 0
FA = 1

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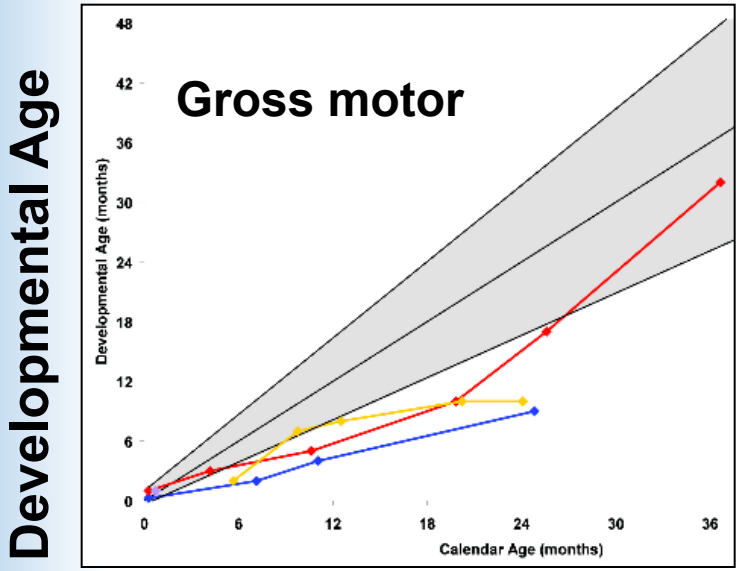
Fiber Region Analysis

FA Ratio at Baseline in central region of CST

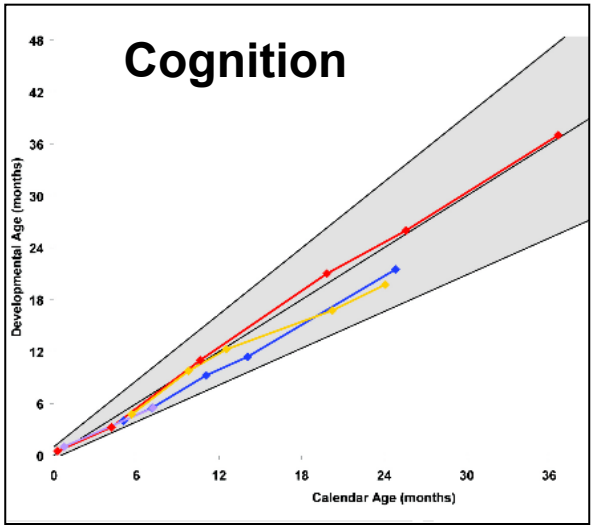
0.70 0.91

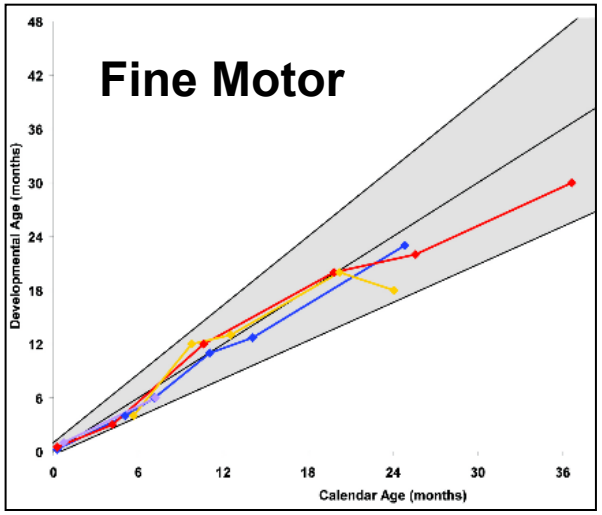
0.89 0.84



Developmental Age

Calendar Age (months)





Escolar, Styner et al JNR 2009

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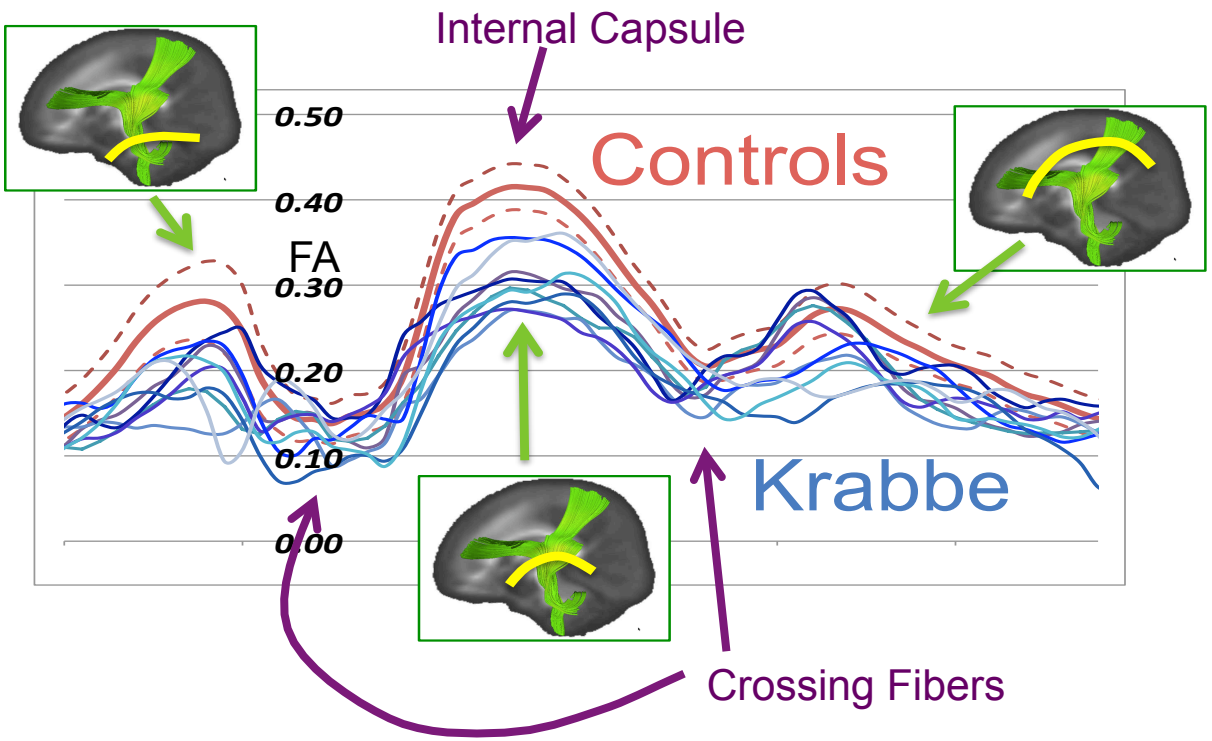
Tract Profile Analysis

In review, unpublished

- Spearman Correlation of Gross Motor and Internal Capsule FA: 0.85 ($p < 0.0001$)
- Group diff results
- Potential marker for WM degeneration in Krabbe



	FA			MD			RD			AD		
	Diff	SE	p	Diff	SE	p	Diff	SE	p	Diff	SE	p
L CSIC	-2.63	0.34	<.001	2.31	0.34	<.001	2.54	0.34	<.001	1.57	0.35	<.001
R CSIC	-2.85	0.34	<.001	2.24	0.35	<.001	2.55	0.35	<.001	1.32	0.35	<.001
L Unc	-2.46	0.35	<.001	1.37	0.34	<.001	1.74	0.34	<.001	0.54	0.34	0.115
R Unc	-2.17	0.35	<.001	1.51	0.34	<.001	1.77	0.34	<.001	0.86	0.34	0.012
Genu	-2.15	0.34	<.001	1.51	0.34	<.001	1.81	0.34	<.001	0.71	0.34	0.036
Splenium	-1.67	0.35	<.001	0.69	0.34	0.041	0.99	0.34	0.004	0.09	0.34	0.798

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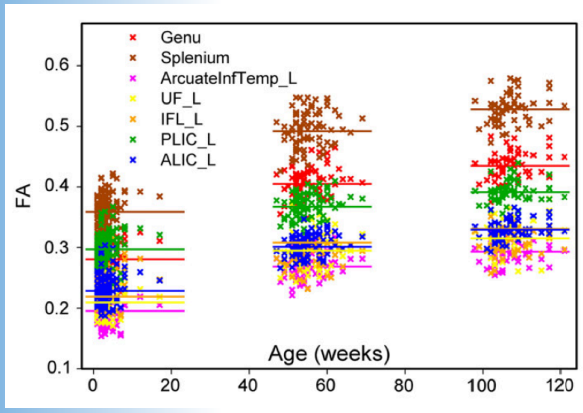
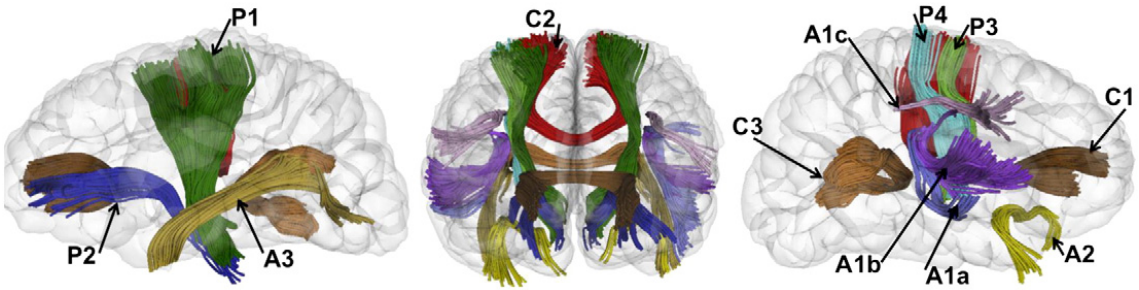
WM maturation 0-2 years

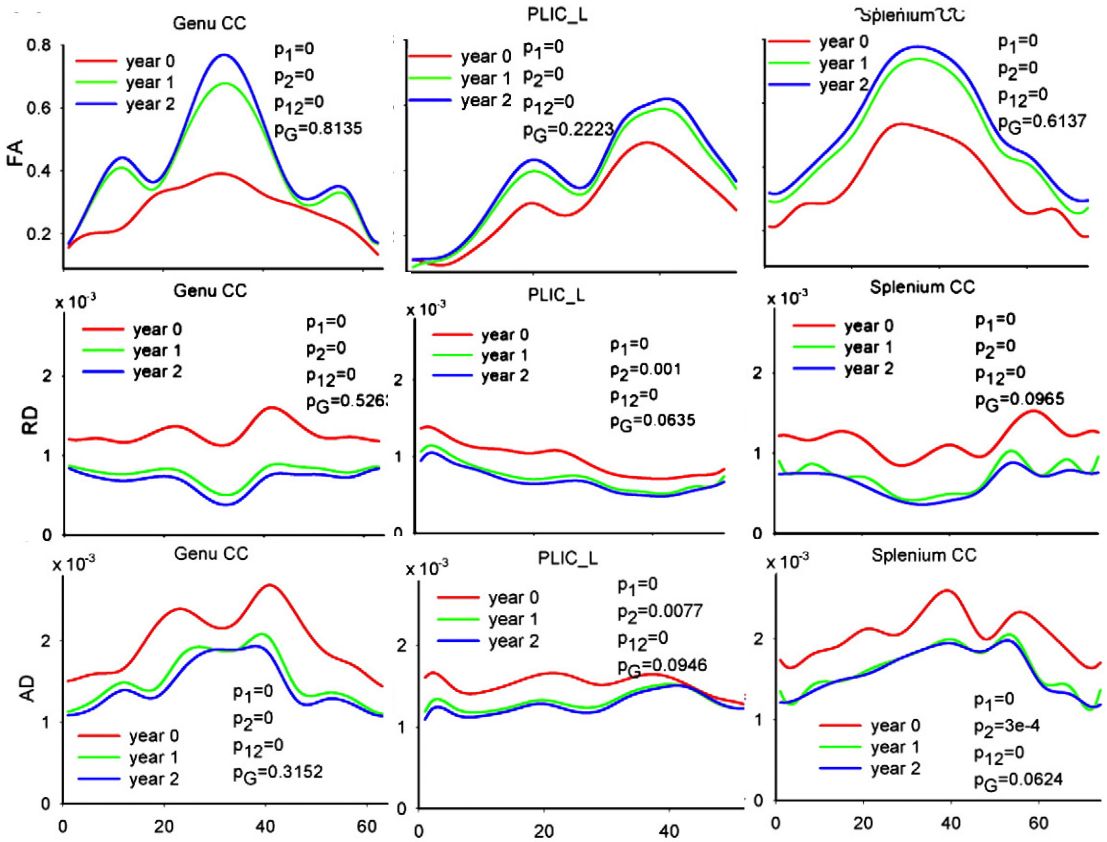
- Geng, Gerig, Styner NeuroImage 2012
- 211 subject (98 male, 113 female)
- Longitudinal modeling
- Single average within tract region
- Along tract profile analysis

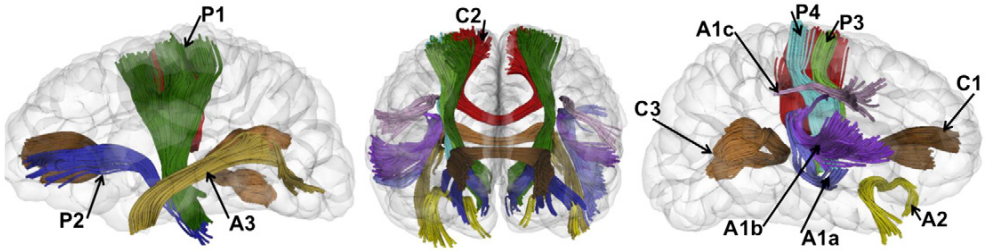




Profile Analysis

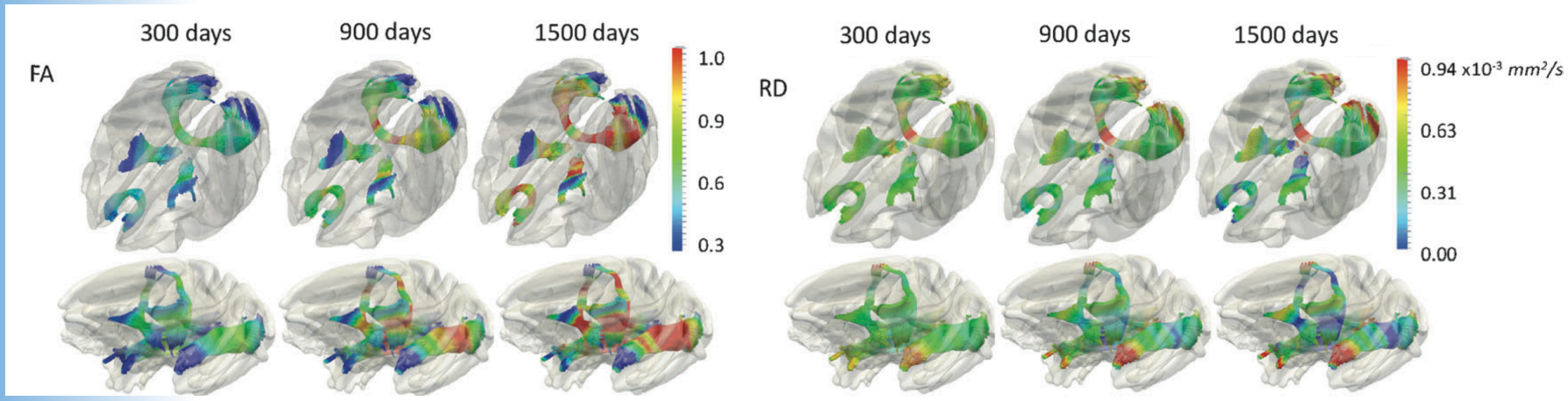
- p_1 = pvalue of 0-1
- p_2 = pvalue of 1-2
- p_{12} = pvalue of 0-1 vs 1-2
- p_G = pvalue of gender effect
- Most change 0-1
- Posterior to anterior wave of development
- RD => mainly myelination
- AD => local organization/ density/fiber spread





Visualization on Tract

- Map stats back on tract for optimal interpretation
- Brain development in macaques 1-5y (~3-15 humans)
- Significant change over this period
- Front to back wave of development, similar pattern to earlier human development



Diffusion tensor imaging-based characterization of brain neurodevelopment in primates,Shi, Styner et al, Cerebral cortex, 2013.

Tract Based Analysis

+ Functional analysis of data
+ High degree of localization
+ Higher sensitivity than voxel-based
- Needs accurate atlas building procedure
- Needs hypothesis for tract selection
- Not fully automatic yet (interactive tractography in atlas space)

Conclusion Analysis

- 3 approaches with different strengths
  - Regional: Easy to do, thus do it…
  - Voxel-based: If you don't know what you are looking for, this is the best
  - Fiber tract: Hypothesis driven, good localization, most time intensive

Conclusion DWI/DTI

- DTI great modality to investigate white matter development & pathology
- DWI's are noisy => do you QC
- DTI fibers are not actual WM fibers
- For good information in fiber crossings => go to higher models than tensor
- 4 major scalars: **FA**, MD, RD, AD highlighting different properties (but not independent from each other)