

NA-MIC National Alliance for Medical Image Computing http://na-mic.org

Diffusion Tensor Processing and Visualization

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Acknowledgments

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National Alliance for Medical Image Computing (NIH U54EB005149)









- 100 billions of neurons
- Complex neuronal networks

DT-MRI Tractography. S.Pujol. Harvard-MIT Health Sciences and Technology HST.583









- 100 billions of neurons
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- White matter ~45% of the brain

DT-MRI Tractography. S.Pujol. Harvard-MIT Health Sciences and Technology HST.583









- 100 billions of neurons
- Complex neuronal networks
- White matter ~45% of the brain
- Myelinated nerve fibers (~ 10 µm axon diameter)

DT-MRI Tractography. S.Pujol. Harvard-MIT Health Sciences and Technology HST.583







White Matter Exploration



Jules Joseph Dejerine (*Anatomie des centres nerveux* (Paris, 1890-1901): Atlas of Neuroanatomy based on myelin stained preparation

> DT-MRI Tractography. S.Pujol. Harvard-MIT Health Sciences and Technology HST.583











White matter tracts appear homogeneous on T1, T2 or Flair images DT-MRI Tractography. S.Pujol. Harvard-MIT Health Sciences and Technology HST.583





Diffusion Tensor Imaging (DT MRI) reveals White Matter Structure





Courtesy of Susumu Mori, JHU





Diffusion in Biological Tissue

- Motion of water through tissue
- Sometimes faster in some directions than others



• Anisotropy: diffusion rate depends on direction anisotropic







• Diffusion of water molecules



From Beaulieu[02]



- Reflects the underlying structure of the tissues
 - Faster diffusion along fibers than perpendicular to them
 - Water diffusion anisotropy used to track fibers, estimate white matter integrity
- Tensor model [Basser]

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Determine the whole tensor to estimate diffusion anisotropy





The Physics of Diffusion

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









Solutions of the Diffusion Equation

- 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)









The universe of matrices

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Physical Interpretation

The diffusion tensor <u>D</u> in the voxel (I,J,K) can be visualized as an ellipsoid, with the eigenvectors indicating the directions of the principal axes, and the square root of the eigenvalues defining the ellipsoidal radii.



DT-MRI Tractography. S.Pujol. Harvard-MIT Health Sciences and Technology HST.583







Bilinear forms and quadratics



 $(D_{11})x^2 + (2D_{21})xy + (2D_{31})xz + (D_{22})y^2 + (2D_{23})yz + (D_33)z^2 = k$ Quadratic equation – implicit equation for ellipse (ellipsoid in 3D)

Eigen Decomposition



- Lambda shape information, independent of orientation
- R orientation, independent of shape
- Lambda's > 0

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Tensors From Diffusion-Weighted Images

- <u>Big</u> assumption
 - At the scale of DW-MRI measurements
 - Diffusion of water in tissue is approximated by Gaussian
 - Solution to heat equation with constant diffusion tensor
- Stejskal-Tanner equation
 - Relationship between the DW images and D









Stejskal-Tanner equation

- Relationship between the DW images and D



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





Tensors From Diffusion-Weighted Images

Solving S-T for D

S-T Equation

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2D

Take log of both sides



- Linear system for elements of D
- Six gradient directions (3 in 2D) uniquely specify D
- More gradient directions overconstrain D
 - Solve least-squares
 - » (constrain lambda>0)







Shape Measures on Tensors

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



Different shapes







Measuring the "Size" of a Tensor

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

Sometimes used. Also called: "Root sum of squares" "Diffusion norm" "Frobenius norm" Generally used. Also called: "Mean diffusivity" <MD> "Trace"







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





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

Properties:

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

FA (not quite)







FA as an Indicator for White Matter

- Visualization ignore tissue that is not WM
- Registration Align WM bundles
- Tractography terminate tracts as they exit WM
- Analysis
 - Axon density/degeneration
 - Myelin
- Big question
 - What physiological/anatomical property does FA measure?









Tensor size (MD) and shape (FA)

• Mean diffusivity (MD)



Cerebrospinal

fluid

High

• Fractional anisotropy (FA)

$$FA = \frac{1}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$
Final Sector is the second se



White

matter





A. Alexander







- Color mapping
- Glyphs





Coloring by Principal Diffusion Direction









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











Visualization with Glyphs

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







Backdrop: FA






































Color: $RGB(e_1)$





Color: $RGB(e_1)$





















- Free diffusion (ventricles) shown as spheres.
- Intersecting tracts can't be properly modeled by a single tensor: Simplified disks in rank-1 tensors.
- Large tracts can be locally modeled by single tensors.



 $\lambda_1 \approx \lambda_2 \approx \lambda_3$ - Isotropic Prevalent in CSF and gray matter regions of the brain.

 $\lambda_1 {\approx}\, \lambda_2 {>>}\, \lambda_3$ - Oblate

Arise in white matter regions.



Prevalent in white matter regions.

 \underline{e}_3







Shape Characterization: Westin

$$c_{l} = \frac{\lambda_{1} - \lambda_{2}}{\lambda_{1}}$$
$$c_{p} = \frac{\lambda_{2} - \lambda_{3}}{\lambda_{1}}$$
$$c_{s} = \frac{\lambda_{3}}{\lambda_{1}}$$



$$c_l + c_p + c_s = 1$$

Westin et al., MICCAI'99





Limitations of the Diffusion Tensor Model



Courtesy B. Vemuri, MICCAI 2008 workshop







Courtesy of Susumu Mori, JHU

Diffusion ellipsoid





Two Tensor Model (C-F Westin, S Peled, G Kindlmann)



Courtesy Carl-Fredrik Westin, MICCAI 2008 workshop









Provided by L O'Donnell







Results Two-Tensor Tractography

Single tensor model

Two-tensor model



A Qazi, A Radmanesh, L O'Donnell, G Kindlmann, S Peled, S Whalen, C-F Westin, A J Golby. Resolving crossings in the corticospinal tract by two-tensor streamline tractography: method and clinical assessment using fMRI. NeuroImage 2008







Orientation Distribution Function (ODF)
Fiber distribution
ADC profile
Diffusion ODF

Descoteaux/Angelino/Fitzgibbons/Deriche in Magnetic Resonance in Medicine, 2006 and 2007



Courtesy Rachid Deriche, MICCAI 2008 workshop







Higher Order Tensor can capture fiber crossing geometry

- Excised full rat brain
- S₀ + HARDI (32 dir., B-value=1250 s/mm²)
- Data provided by Drs Carney and Mareci



Courtesy Baba Vemuri, MICCAI 2008 workshop

Junction of CC and singulum







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Courtesy Baba Vemuri, MICCAI 2008 workshop







Spatial Transformations of Diffusion Tensors



Warmer colors indicate higher anisotropy

Principal diffusion directions in anisotropic regions of a DT-MR image slice



James Gee, Department of Radiology University of Pennsylvania









James Gee, Department of Radiology University of Pennsylvania

anatomical structure of the

image.









James Gee, Department of Radiology University of Pennsylvania DTs orientations remain consistent with the

anatomy.





Affine Tensor Transformations

(Alexander et al, MICCAI 1999)





•





AVERAGE BRAIN

SINGLE BRAIN



Jones et al, 2002









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



Hulotte, Duke University: Staining to get axonal projections.









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



Source: Duke NeuroAnatomy Web Resources (Ch. Hulette)











UNC Computer Science: Network wire cabinets Major Fiber Tracts extracted from DT MRI











- 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, MICCAI 2008 workshop







From Tensors to Connectivity?

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









Going Beyond Voxels: Tractography

- Method for visualization/analysis
- Integrate vector field associated with grid 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.)















White Matter Fiber Tract Atlases



Fig. 7 Reconstruction of the ILF in the average DT-MRI data set. The long fibres originate from extrastriate areas of the occipital lobe and terminate in lateral temporal cortex and medial temporal cortex in the region of the amygdala and parahippocampal gyrus.



Fig. 2 Virtual *in vivo* dissection of the ILF and visual pathway of the right hemisphere (medial view) in the average brain data set. Splenial fibres connecting medial occipital regions are also shown. See text for explanation.

Catani et al., Occipito-temporal connections in the human brain, Brain 2003





The Problem with Tractography How Can It Work?

- Integrals of uncertain quantities are prone to error
 - Problem can be aggravated by nonlinearities
- Related problems
 - Open loop in controls (tracking)
 - Dead reckoning in robotics

Wrong turn /

Nonlinear: bad information about where to go







Alternative methods for tractography

- Tracking in tensor field
- Keep history along track: e.g. Kalman filtering
- Probabilistic tractography
- Optimal path analysis
- Fiber tract by volumetric diffusion
- ...
- Variety of methods developed by NAMIC developers











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):5-18



Courtesy Carl-Fredrik Westin, MICCAI 2008 workshop





Stochastic Tractography



Courtesy Carl-Fredrik Westin, MICCAI 2008 workshop







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, MICCAI 2008 workshop








3,000 fiber samples initiated in the splenium of Corpus callosum. The coloring indicates the probability along each path to end up is a specific area.

Work with O. Friman

Courtesy Carl-Fredrik Westin, MICCAI 2008 workshop







Probability of Connection









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Quantitative Tractography: NAMIC Tool FiberViewer



- Tractography results in selected fiber bundles of interest.
- Next step for clinical studies is geometrical and quantitative characterization.

Fiber Tract-Oriented Statistics for Quantitative Diffusion Tensor MRI Analysis, Isabelle Corouge, P.Thomas Fletcher, Sarang Joshi, Sylvain Gouttard, Guido Gerig, Medical Image Analysis 10 (2006), 786 - 798



Fiber Tract Modeling and











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Corouge et al. *Fiber tract-oriented statistics for quantitative diffusion tensor MRI analysis*. Medical Image Analysis 2006. FiberViewer software - http://www.ia.unc.edu/dev/

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- Tractography for ROI definition
- Tensor-math. for statistics along tracts





Challenge: Common Coordinate Frame for Population Analysis









Co-registration of image sets (Neonates)



Not registered

Linear registration (affine)







Group statistics of DTI fiber bundles

J.C.				0.86 0.50 0.33 0.17 0.00 -26 -15 -3 8 20 31	0.000
A.P.	No.				
SC				0.81 0.45 0.30 0.15 0.00 -29 -19 -8 2 13 23	0.2
Images	Atlas	Atlas Tract	Mapped Tracts	Sampled Functions	Functional Statistics















Unbiased Diffeomorphic Atlas Construction for Computational Anatomy (Joshi, Davis, Lorenzen)







Symmetric Registration Framework

 $f \circ g = h_2 \circ h_1^{-1} \circ h_1 \circ h_2^{-1} = Id$







Group-wise Atlas Building





A) Choice of template: Analysis is biased by choice of template.

B) Unbiased atlas building:
Minimize total distance
beetween population and
template
(Gee & Avants,
Joshi&Fletcher)







Averaging Anatomies





Motivation:

- Map population into common coordinate space
- Learn about normal variability
- Describe difference from normal
- Use as normative atlas for segmentation

Sarang Joshi, Brad Davis, Matthieu Jomier, Guido Gerig, Unbiased Diffeomorphic Atlas Construction for Computational Anatomy, vol. 23, NeuroImage 2004





DTI: Estimation of coordinate transformations



















Linear registration (affine)

Nonlinear registration (fluid)











 Inear
 nonlinear

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Population Coordinates: DTI Atlas Building



- Balci, Golland, Wells. *Non-rigid Groupwise Registration using B-Spline Deformation Model.* ITK Workshop 2007.
 - Available in sandbox MultiImageRegistration
- Goodlett et al. *Improved correspondence for DTI population studies via unbiased atlas building.* MICCAI 2006, Neuroimage 2009.
 - Tensor processing tools –
 DTIprocess (NeuroLib),
 Teem, Slicer 3





Application: Neurodevelopmental Statistical Atlases



Neonate (N=95)



2 year (N=25)



1 year (N=25)



Adult (N=24)



Collaborative research on studying the early developing brain with John H. Gilmore and Weili Lin, UNC Chapel Hill



National Allianc MICCAI' 08 Workshop Early Dev. Brain Wed





Example: 150 neonate DTI mapped to unbiased atlas



Goodlett, Joshi, Gouttard, Gerig, (MICCAI' 06, MICCAI' 08, NeuroImage ' 09)







Group statistics of DTI fiber bundles

J.C.				0.86 0.50 0.33 0.17 0.00 -26 -15 -3 8 20 31	0.000
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Images	Atlas	Atlas Tract	Mapped Tracts	Sampled Functions	Functional Statistics







Splenium track, 1yr to 2yr infants







Development from 1 to 2 years – Genu Discrimination of Norm



Group Means

Discriminant

Goodlett et al., Neuroimage 2009







Summary: What do we measure?





- DWI measures <u>local</u> diffusivity pattern.
- Local diffusivity pattern is shaped by tissue type, axon structuring, myelination etc.
- Curves and streamlines from tractography are NOT AXONS but possible paths in vector/tensor field.
- "Fiber counting" is scientifically questionable, # is method specific.
- DWI DOESN' T MEASURE AXONS or GLOBAL CONNECTIVITY !









Caution

- Do not "blindly" use the word "Connectivity" when applying DTI
- "Connectivity": Became <u>forbidden C-word</u> in some NIH study sections



