What is DTI, its use in research and clinical practice, and its future potential

Ipek Oguz with thanks to many, many people
Departments of Computer Science and Psychiatry
UNC Neurodevelopmental Disorders Research Center
UNC Neuro Image Research and Analysis Lab
• Interpretation/validation of DTI properties
  – Rat spinal cord studies
• Validation of tractography
• What can DTI be used for? Many different applications…
  – Main part of the talk
• Future of DTI: looks bright…
DTI Properties (again)

Fractional Anisotropy (Tensor shape), 0..1

Mean Diffusion (Tensor volume)

\[ \lambda_1 = \lambda_{||} \]

Axial Diffusion
In WM: Diffusion parallel to axon

\[ \frac{\lambda_2 + \lambda_3}{2} = \lambda_{\perp} \]

Radial Diffusion
In WM: Diffusion orthogonal to axon

WM/GM
CSF
Spinal Cord Degeneration

- 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
Spinal Cord Degeneration

Lesion at Day 3

Day 30

AD

RD

FA

0

1

2.5

0

1

10^{-5} cm^2/s

AD

RD

Injured side

Contralateral side

16H 38H 3D 14D 30D

16H 38H 3D 14D 30D

16H 38H 3D 14D 30D

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

- LFB: Myelin
- SMI: neurofilaments
  - 31: hyper-phosphylated
  - 32: hypo-phosphylated
Spinal Cord Degeneration

• Day 3 (as compared to unlesioned side)
  – DTI: significantly reduced AD and increased RD.
  – IHC: Reduced phosphorylated, increased nonphosphorylated neurofilaments, swollen axons, myelin ovoids, no loss of myelin.

• Day 30 (as compared to day 3)
  – DTI: no reduction in AD but increase in RD
  – IHC: Gradual clearance of myelin, no changes in neurofilament

• Conclusion:
  – DTI, AD/RD sensitive to axon degeneration
  – FA captures all effects, but cannot differentiate
  – Correlation of RD with myelin degeneration
  – Correlation of AD with loss of phosphorylated neurofilaments
Demyelinating Lesions

- Rat model of autoimmune encephalomyelitis/MS
- Injection of cytokines (TNF-α, IFN-γ) or lipopolysaccharides => spinal cord lesions
- DTI & Immunohistochemistry
- FA, AD and RD correlate with axon counts and degenerating axon counts
- FA and T2-w intensity correspond to changes in myelin loss and axon phosphorylation
Validation of Tractography

• Are results of DTI tractography anatomically correct? Yes and No…
• Many studies using synthetic ground truth & MRI phantoms show convincingly positive results
• In/Ex vivo: stimulation mapping, manganese imaging, tracer studies
  – Several performed in primates, Dauguet 2007 (NeuroImage)
Validation of Tractography

- Good agreement for major fiber bundles
- Sensitivities to fiber crossings and small fiber bundles
  - Higher models of diffusion (Qball, DSI)
  - Anatomical knowledge via source and target selection
  - Novel tractography on DTI: multi-tensor or probabilistic tracking
- Overall convincing evidence for DTI tractography
  - Major fiber tracts are valid
  - #fibers highly variable!
  - Size of tracts variable!

![Bar graph showing number of fibers per scan](Scans' Comparison:Fibers (ROI: essai3-th69). Second Method without Interpolation and Second Method with Interpolation)
Intermezzo

OH, PLEASE... THE PHOTOS ARE OBVIOUSLY AIRBRUSHED TO MAKE THEIR BRAINS APPEAR MORE DEVELOPED...
Applications of DTI

• General:
  – Atlases
  – Parcellation of striatum, thalamus
  – Segmentation of MS lesions
• Neoplasm, preoperative planning
• Demyelinating and neurodegenerative diseases
• Normal brain development and aging
• Congenital anomalies and diseases of white matter
• Traumatic brain injury
• Ischemia and stroke
• Epilepsy
• Dementia, schizophrenia, depression, autism
DTI is Translational

Humans
• Large Variability

Mouse, Rat
• Genetic control, small variability

Monkey
• Reduced complexity and variability
DTI Population Atlases

- Definition of standard space
- SNR increase
- Better tractography

Neonate 1 year 2 year Adult

Rhesus (15mo)
Fiber tracts in Atlas

- fornix and uncinate
- genu, splenium, motor
- uncinate
- Neonate (n=270)
- Macaque (n=52)
Brain Evolution

- Arcuate fasciculus, associated with language/expression
  - Temporal lobe projection absent/smaller in non-human primates
- Rilling, 2008 Nature Neuroscience
- Probabilistic tractography
DTI based Segmentation

DTI based clustering of thalamus

Striatal subdivision
Via cortical connectivity
Draganski, 08 J Neuroscience

Ziyan and Westin, MICCAI 08

Tuch 2003
DTI: Cerebral Neoplasms

Edematous

Destroyed

Courtesy of AL Alexander
Pilocytic Astrocytoma

Preop

T2W
ADC
FA
FA × ε₁

Postop

T2W
ADC
FA
FA × ε₁

Courtesy of AL Alexander
Cerebral Palsy

Courtesy of Susumu Mori
Multiple Sclerosis
Fetal Alcohol Syndrome

Control

Acute EtOH – GD7

3D MRI reconstruction

DTI & Histology

Fiber Tracking

Thickened, dysplastic fimbria

Absent fornix columns
WM Anisotropy Changes with Age

Courtesy K. Lim, Univ. Minn.
Corpus Callosum Tracts: Study of Early Development

Neonate (2 wks)  Infant (1 year)  Adult

Corpus callosum: Commissural bundles, color coding of FA (0=blue, 1=red)
Early postnatal development of white matter on neonates

Analysis of white matter in healthy controls (N=47)

Myelination and axon elimination:
- FA center >> peripheral
- FA splenium > genu
- MD splenium & genu > intcaps
- T1w splenium & genu < intcaps

Gilmore 2007 AJNR
1-2 year old: CC Tracts

Goodlett 2009 NeuroImage
Left Motor Tract

(a) Left cortico-spinal

(b) FA curves

(c) Norm curves

(d) Right cortico-spinal

(e) FA curves

(f) Norm curves
Monkey Brain Studies

- Harlow Primate Lab @ UWisc / Yerkes @ Emory
- Studies: Intrauterine exposure (Flu, LPS), abuse
- Understanding brain development & environment
- Regression with age

Figures courtesy of Yundi Shi
DTI Comparison Y1 – Y5

300 days  900 days  1500 days

FA

0.263  0.329  0.395  0.461  0.527

AD (×10^{-3} mm^2/s)

0.865  0.975  1.085  1.195  1.305

WM

MD (×10^{-3} mm^2/s)

0.644  0.672  0.700  0.728  0.756

RD (×10^{-3} mm^2/s)

0.487  0.521  0.555  0.589  0.623

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DTI Comparison Y1-Y5

300 days | 900 days | 1500 days
---|---|---
FA

GM

AD \(\times 10^{-3}\) mm\(^2\)/s

RD \(\times 10^{-3}\) mm\(^2\)/s

<table>
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<tr>
<th>300 days</th>
<th>900 days</th>
<th>1500 days</th>
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<tr>
<td>0.147</td>
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<tr>
<td>0.630</td>
<td>0.651</td>
<td>0.672</td>
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</table>
Tract development

300 days | 900 days | 1500 days

FA

AD

MD

RD

1.4 x 10^{-3} mm^2/s
1.22
1.03
0.85
0.94 x 10^{-3} mm^2/s
0.63
0.31
0.00
Fiber change statistics

FA | MD | AD | RD -lg(P value)
---|----|----|----------------
3.6 | 2.8 | 2.0 | 1.3
4.0 | 3.2 | 2.4 | 1.6
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
Krabbe: Treatment

- Therapy (Maria Escolar, UNC), Therapy @ Duke
  - 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%)

- New Krabbe’s screening with enzyme test
  - New York started August 2006
  - Parents often wait

- DTI: Assessing damage at birth via DTI
  - Illustration of damage to parents? Diagnosis?
  - Prediction of developmental outcome for motor abilities

- Here: Prelim data of project
Motor Related Fiber tracts

- Left and right hemispheric Cortico-spinal tracts

Courtesy of Jim Fallon
Controls - Left Internal Capsule Tracts

Krabbe’s - Left Internal Capsule Tracts

FA = 0

FA = 1

Worst motor development
FA Statistics along Fibers

Statistics over 6 Krabbe, 53 Healthy neonate babies
FA Stats Center Region

- Center region selection => Mean FA computation
- FA ratio = FA divided by expected FA given gestational age at birth, at scan, birth weight, gender
Outcome Correlation

FA Ratio at Baseline
- 0.70
- 0.89
- 0.91
- 0.84

Gross motor

Cognition

Fine Motor

Calendar Age (months)

Developmental Age

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http://na-mic.org
Next: Tract Profile Stats

Controls

Krabbe
Conclusion Krabbe

- Correlation of DTI with outcome after treatment
- Current investigation:
  - Natural history of development with DTI
  - Can DTI predict, when symptoms will arise if untreated?
Future of DTI

• Highly valuable MR based modality
  – Many applications
  – Considerable validation (though more is needed)
• What’s next?
  – Higher order of diffusion representation
  – Improved tractography algorithms
  – Network analyses
  – Need for automatic, blackbox processing
Higher Order Diffusion Representations

- Active field of research since 2003
  - Qball, Tuch
  - DSI, Van Wedeen
- No real clinical tools yet
  - Next evolutionary stage for DTI?
Network Analyses

- Structural network using diffusion spectral imaging
- Combination with functional imaging (resting state, event driven)
- Main issue: stability, clinical application
- Hagmann 2008 PLOS Biology
Blackbox Processing

• DTI property images (FA, MD, AD, RD) clinically useful
• But tractography application lag behind in clinical use
• Current processing is
  – Mostly interactive
  – Significant training in DTI necessary
• Need for automatic blackbox tools
  – No technical training needed
  – Adequate in presence of pathology
  – Includes analysis framework
The last slide

• We love DTI!
• And there are many reasons why, as shown in this talk…
• Thanks!