Diffusion Imaging in the Brain

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Are we really looking at diffusion, clinically?

Biological “Diffusion” ≈ self-diffusion of water (1) + geometric restrictions (2) + “random, slow flow” (3)

\[
\frac{\partial n(\mathbf{r}, t)}{\partial t} = \vec{\nabla} \cdot (D(\mathbf{r}) \vec{\nabla} n(\mathbf{r}, t))
\]

Inhomogeneous material, or anisotropic diffusion.

Isotropic Diffusion (1)

\[
\frac{\partial n(\mathbf{r}, t)}{\partial t} = D \nabla^2 n(\mathbf{r}, t)
\]

1D solution

\[
n(x, t) = \frac{K}{(2Dt)^{1/2}} e^{-x^2/4Dt}
\]
Are we really looking at diffusion, clinically?

Biological "Diffusion" ≈ self-diffusion of water (1)  
+ geometric restrictions (2)  
+ "random, slow flow" (3)

For the most part, non-gaussian behavior affects both mean diffusivity and diffusive anisotropy.

Contributing factors:
- cell membrane
- permeability/exchange rate
- intra/extra-cellular diffusion
- myelin*
- inner cell structures
- necrosis

Also: relaxation in different compartments → contrast vs. composition

Beaulieu, NMR in Biomed; 2002
1. Non-gaussian qualities depend on diffusion time.

From LiBihan, 2014, EMBO Molecular Medicine
1) Non-gaussian qualities depend on diffusion time.

2) Multiple compartments + permeability = reality?
1) Non-gaussian qualities depend on diffusion time.  
2) Multiple compartments + permeability = reality?
Diffusion Basics

Characteristic Diffusion length (1D):
\[ l = \sqrt{2Dt} \]

At 25°C, 
\[ D = 2.2 \times 10^{-3} \text{ mm}^2 / \text{second} \] (free water)

Time between pulses: 
\[ t = 10-20 \text{ msec} \] (maybe +)

\[ \rightarrow l \sim 5-15 \mu m \]

(not much exchange between compartments, but much contact with membranes).

Typical MRI scale lengths: < 30 μm.
So, what’s normal and what’s not?

Qualitative: “What does diffusion in healthy tissue look like?”
   Fast/slow
   Characteristics: anisotropy, non-gaussian, variation with b.
   “How does diffusion change with particular pathology?”
   Expectations from understanding of tissue and models/theory.
   Comparison with contralateral/healthy regions.
   “How does that change with disease progression?”

Quantitative: “What values of diffusion metrics are associated with pathology?”
   “What values match with viable tissue before intervention?”
   “Grading of pathology with quantifiable values?”
Stroke
Anatomy of an Ischemic Stroke

As stroke progresses, inter- and extra-cellular water diffusion properties (and compartmental fraction) changes → DWI changes

Normal cells

Ischemia disrupts sodium pump—influx of water causes cell swelling (decreased “diffusion”, restricted & hindered diffusion↑)

Cytotoxic edema → vasogenic (cell death) (increased diffusion)

From Radaideh, et al. Neurographics, 2002

Gonzalez, JMRI, 2012
DWI in a Stroke Protocol

MR images (6000/210/1) in a 67-year-old woman with left hand weakness, left facial droop, and slurred speech.

Clinical standard today: this is where diffusion imaging for stroke stops.


<3 x DWI> “/” b0 → ADC

T2 shine through
Each application of a diffusion gradient, we measure diffusion in ONE direction. Can apply multiple gradients to examine anisotropy.

In structured tissues, restrictions may depend on direction of diffusion. E.g., white matter diffusion is highly anisotropy.

Changes in anisotropy $\Rightarrow$ structural breakdown (or plasticity?)
DTI: examine the amount of diffusion along various axes.

From six or more measurements (+b0), determine tensor in each image voxel:

- three eigenvalues of diffusion magnitude (e-values: $\lambda_i$)
- three eigenvectors of diffusion direction (e-vectors: $\epsilon_i$)

Also, fractional anisotropy (FA).

$$FA = \sqrt{\frac{3(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

Nominally distribute gradient directions over sphere.
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→ three eigenvalues of diffusion magnitude (e-values: \( \lambda_i \))
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Also, fractional anisotropy (FA).

Other WM metrics: axial, radial diffusivity

\[ \lambda_{\text{radial}} = \text{mean}(\lambda_2, \lambda_3) \]

Nominally distribute gradient directions over sphere.
DTI Review

DTI gives you diffusion magnitude information, anisotropy, and directional information.
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Jellison, et al., AJNR, 2004
What is the motor function outcome in stroke rehabilitation?

Monitor DTI metrics longitudinally in the internal capsule (median & 20-month post).

Song et al. Fron. Human Neurosci. 2015

Measure DTI metrics for each hemisphere (posterior limb of IC).

Ratios of metrics (ips. to contr.) at baseline best correlation for future motor improvement.
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DKI Review

DKI: quantifying the non-gaussian components of diffusion.

→ How much hindrance is going on?
Final lesion size post-intervention

Dark ADC $\rightarrow$ lower diffusion

Bright mean kurtosis $\rightarrow$ more hindered diffusion.

Yin et al. Radiology 2018
Slow perfusion in random directions ~ fast diffusion.

IVIM: quantifying the fraction of microcirculation.

→ How is perfusion affected throughout stroke volume?

IVIM and Acute Stroke

Microperfusion in stroke core

IVIM and Acute Stroke

Ahem ... this is a patient that we’re dealing with.

Scanning speed is not irrelevant. pMRI is critical!

E.g., without pMRI:

- **DWI** (3 directions + 1 b0 image (TR~ 16 sec, 30 slices))
  - scantime: ~ 1 min

- **DTI** (32 directions, 1 b-value + 1 b0)
  - scantime: ~ 8 min  

- **DKI** (32 directions, 2 b-values + 1 b0)
  - scantime: ~ 16 min

- **multi-exponential** (DWI scan (3 dir), 16 b-values, NEX increases with b-value to increase SNR → 84 scans)
  - scantime: ~ 21 min

- **High Angular Resolution Diffusion Imaging** scantime: ~ a long time.
Cancer
Primary tumor

Secondary tumor

High cellularity

Necrosis

Normal Parenchyma

Tumors often have a rich, heterogeneous structure, changing over time.
Basics of Visual Diagnosis

Principle #0: Very high ADC = cyst, vasogenic edemic region.

Principle #1: Cellularity correlates inversely with ADC (healthy and pathological).

Principle #2: In structured tissues, infiltration can affect FA, eigenvectors, etc.
Basics of Visual Diagnosis

Figure 4. Correlation of tumor cellularity vs. the ADCs ($P < 0.01$, $r = -0.542$).

Guo, et al. JMRI, 2002 (cancerous breast lesions)
Diffusion behavior can be rich in tumor region.

General Edema

Somewhat fast diffusion in periphery

Hindered diffusion in patches (hypercellularity).

Fast diffusion in core (cellular breakdown)

Apparently healthy WM
Applications of Imaging to Cancer

Diagnosis/Classification Tool – heterogeneity vs. homogeneity, ADC value

Treatment Planning Tool – ischemia, necrotic core

Treatment Monitoring – changes in ADC value during treatment

Potential use as a screening tool** – increased cellularity in DWIs (whole body)

Clinically, ADC map offers the most straightforward DW-based tool to interpret (but, less specific about precise tissue changes).
Bilateral inspection of brain tracts can help to reveal the pathology of tumor and/or integrity of WM in case of surgery.
Ganglioglioma, with tracts preserved but shifted in position.

A: T2W
B: post-contrast T1W
C: FA map
D: Tractogram

Jellison, et al., AJNR, 2004
Preservation in color (direction) but reduction in FA indicates edema.

A: T2W
B: post-contrast T1W
C: FA map
D: color-coded FA

Jellison, et al., AJNR, 2004
FA reduced and direction distorted, implying disruption (infiltrating astrocytoma).

A: T2W
B: post-contrast T1W
C: FA map
D: color-coded FA

Jellison, et al., AJNR, 2004
High-grade astrocytoma, with tracts essentially destroyed.

A: T2W
B: post-contrast T1W
C: FA map, normal patient
D: FA map, patient

Jellison, et al., AJNR, 2004
Principle e-vector in DTI (or ODF for HARDI) generally points along neural fiber axial direction.

Various software routines to link directions together and generate “tracts”.

Mukherjee, et al., 2008, AJNR
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Tracts ≠ neural fibers (but correlation).
Tractography

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Tractography

From CAMINO image processing manual
http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.DTI
DTI tractography to examine infiltration

DTI tractography combined with tumor segmentation for pre-surgical planning.

Tracts were seeded using ROIs running through wrist (green) and shoulder (magenta) motor strip regions near cortex.

(Mukherjee, et al., 2008, AJNR)
Brain Imaging – classification (DTI)

Differentiation of oligodendrogliomas from astrocytomas (more homogeneous) and from mixed oligoastrocytomas (heterogeneous).

All are somewhat heterogeneous, so biopsy may not be as precise for grading of tumor.

OD patients respond more to chemotherapy and have better prognosis.


Normal appearing white matter, and non-enhancing lesion tissues (DTI).

Khayal, et al., NMR Biomed 2009

WM – healthy white matter
OD – oligodendroglioma
OA – oligoastrocytoma
AC – astrocytoma
NEL – non-enhancing region around tumor (T2hyper – T1Gd enhancing region)
Many more applications… possibly...

TBI & DKI

DWI, DTI, and MS

Congenital Malformations

Tractography & Huntington’s Disease

Abhinav, et al. 2014

Goldberg-Zimring, et al., 2005

Wahl, et al. 2010 -- dysplasia
Conclusions

• DW-MRI is a powerful tool for looking at changes in tissue microstructure.

• ADC maps provide good qualitative contrast for distinguishing healthy tissue from non-enhancing pathology (cellularity), but less specific about structure.

• More complicated DW-based techniques may provide substantially more information, but more benchmarking/clinical testing required.
Questions?

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Other Uses (time permitting)
Multi-exponential grading of gliomas

Use of microperfusion to distinguish high and low grade gliomas.

Federau, et al. AJNR 2014
Diffusion and treatment response

Monitoring change in ADC during treatment.

Schmainda, CNS Oncol, 2012

Mostly Glioblastoma multiforme patients...