Diffusion Imaging – What Can It Tell Us About Cancer?

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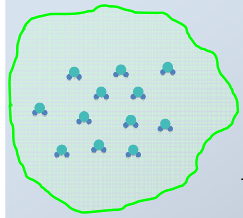
What is "Diffusion" in MRI?



"Diffusion" ≈ self-diffusion of water (1)
+
geometric restrictions (2)

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

Isotropic Diffusion (1)

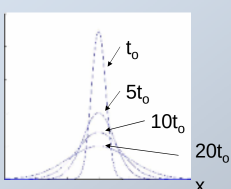
$$\frac{\partial n(\vec{r},t)}{\partial t} = D\nabla^2 n(\vec{r},t)$$

1D solution

$$n(x,t) = \frac{K}{(2Dt)^{1/2}} e^{-x^2/4Dt}$$

What is Diffusion?

$$n(x,t) = \frac{K}{(2Dt)^{1/2}} e^{-x^2/4Dt}$$



Gaussian distribution that expands over time.

Reminder: x = final position - initial position

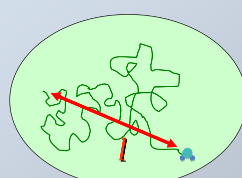
Diffusion Basics

Characteristic Diffusion length:

$$l = \sqrt{2Dt}$$

At 25° C,
D= 2.2 x 10^{-3} mm^2 / second

t=10-20msec; l ~ 5-15 μm



Typical MRI scale lengths: < 30 microns.

Generating Diffusion Weighting

Steiskal-Tanner sequence:

Gradients, g, turned on for a short time, δ:

Moments acquire a large phase, depending on position, $r_i(t)$.

After time Δ, equal-but-opposite gradient is turned on.

Moments lose phase depending on their second position, $r_f(t)$

↑ movement during Δ, δ: ↑ phase dispersion, ↑ signal attention (A)

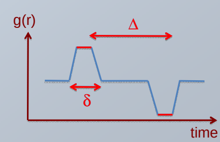
$$\Delta\phi_i = \omega_i \delta \qquad \Delta\phi_f = \omega_f \delta$$

$$\Delta\phi_{tot} = (\omega(t_i) + \omega(t_i + \Delta))\delta$$

$$\omega_i = \gamma B(t_1) = \gamma(B_o + g(\vec{r}_i))$$

$$\omega_f = \gamma B(t_1 + \Delta) = \gamma(B_o - g(\vec{r}_f))$$

$$A_{DW} = \exp\left(\frac{-\langle(\Delta\phi_{tot})^2\rangle}{2}\right)$$



Remember: DW occurs for diffusion ALONG gradient direction.

Generating Diffusion Weighting

Solve for the ***diffusion coefficient*** D in a particular direction:

Traditional Method: acquire a DW image and a non-DW ("b=0") image

$$A_{DW} = S_{DWI} / S_o = \exp(-b\mathrm{D})$$

$$\mathrm{D} = -\frac{1}{b}\ln(S_{DWI} / S_o)$$

"b-value": factor allows for adjustment of imaging contrast

$$b = (\gamma^2 g^2 \delta^2) \cdot t_d$$

$$t_d = (\Delta - \delta/3)$$

"b=0" or "b0" image is often a T2W image → S_{DWI} is a T2W × DW image.

Role of the b-value

What b should we pick?

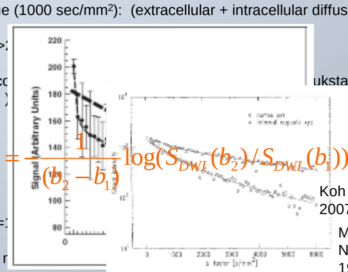
Typical DWI scanning: (b=1000 sec/mm²) + (1 or more b0)

Very low b-value (<100 sec/mm²) : capillary perfusion

Medium b-value (1000 sec/mm²): (extracellular + intracellular diffusion)*

High b-value (>

*(even single-c ... ukstanskii, et al. MRM 2003)



$$\mathrm{D} = \frac{1}{(b_2 - b_1)}\log(S_{DWI}(b_2) / S_{DWI}(b_1))$$

Koh et al. AJR 2007

Mulkern et al. NMR Biomed 1999

Alternative: (b=

Question: Use r

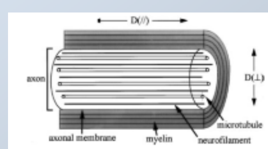
Is Biological Diffusion Gaussian?

"Diffusion" ≈ self-diffusion of water (1)

+

geometric restrictions (2)

Revisit (2). For the most part, anisotropy of diffusion results from non-gaussian behavior.



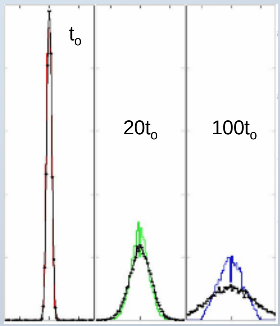
Beaulieu, NMR in Biomed; 2002

Contributing factors:

- cell membrane
- permeability/exchange rate
- intra/extra-cellular diffusion
- myelin*
- inner cell structures

D → "ADC" (apparent diffusion coefficient)

Gaussian vs. Non-Gaussian



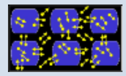
Random-walk simulation

Key:
- color = diffusion within impenetrable compartment
- black =unconstrained diffusion

1) Non-gaussianity depends on diffusion time

2) Multiple compartments + permeability = somewhere in between

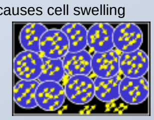
Multi-compartment Aside: Intracellular vs. Extracellular (stroke)

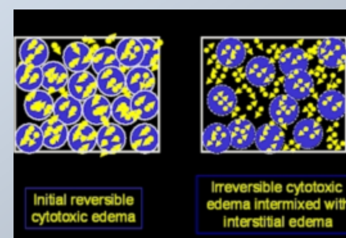


Normal cells

From Radaideh, et al. Neurographics, 2(1), Article 1, 2002.

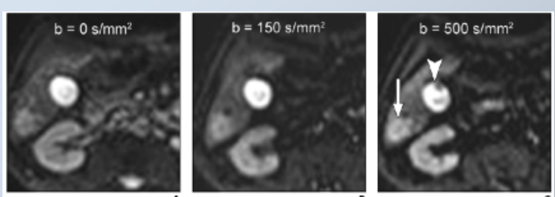
Ischemia disrupts sodium pump—influx of water causes cell swelling

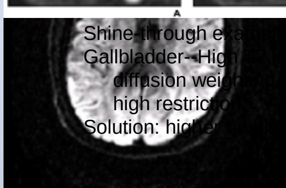




As stroke progresses, inter- and extra-cellular water diffusion properties (and compartmental fraction) changes → DWI changes

MRI Diffusion Imaging Techniques





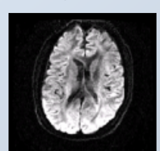
Shine-through example:
Gallbladder--High T2 intensity + small diffusion weighting (b=500) yield apparent high restriction
Solution: higher b-value, or ...

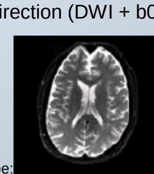
Generally useful, but:
- DWIs suffer from T2 "shine-through"

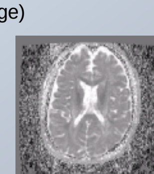
(DWI is diffusion weighted × T2 weighted)

MRI Diffusion Imaging Techniques

1) DWI:
   a) by itself
   b) ADC in one direction (DWI + b0 image)







Slope:

DWI + b0 = ADC

Log(S...(pixel

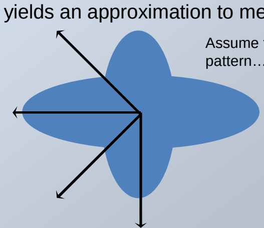
b-value

MRI Diffusion Imaging Techniques

Other ways to measure ADC:

2) b0 + 3 DWIs, acquired at perpendicular directions:
"<ADC>"

This only yields an approximation to mean ADC.



Assume this non-gaussian diffusion pattern…

<ADC> #1

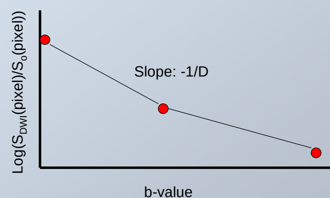
<ADC> #2

MRI Diffusion Imaging Techniques

Other ways to measure ADC:

2) b0 + 3 DWIs, acquired at perpendicular directions:
"<ADC>"

This only yields an approximation to mean ADC.



3) DWI directions + multiple b-values: compartmental detail

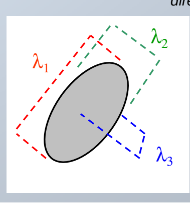
MRI Diffusion Imaging Techniques

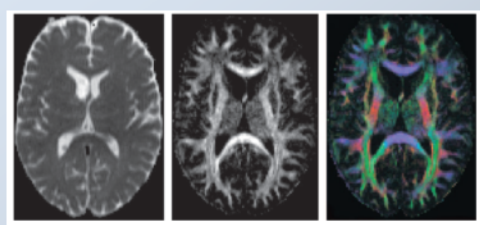
4) DTI: examine the amount of diffusion along various axes
From six or more measurements (+b0), determine tensor in each image voxel:

→ three eigenvalues of diffusion magnitude (e-values: λ_i)
→ three eigenvectors of diffusion direction (e-vectors: ε_i)

Also, fractional anisotropy (FA).

Nominally distribute gradient directions over sphere.





FA image (map + color-code)

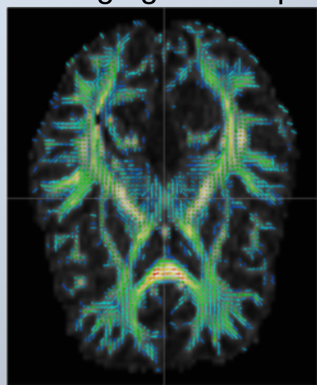
So, DTI gives you diffusion magnitude information, anisotropy, and directional information.

From Hagmann, et al.
Radiographics, 2006; 26: S205-233

MRI Diffusion Imaging Techniques

Principle Eigenvector Map – primary direction of diffusion

(DaSilva, et al. 2003, Neurosurg. Focus, 15: 1-4).



17

Applications of Imaging to Cancer

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

Treatment Planning Tool – ischemia, necrotic core

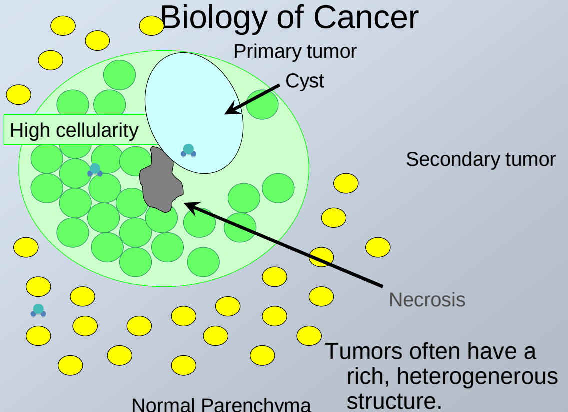
Treatment Monitoring – changes in ADC value during treatment

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

In general, ADC map offers the most direct DW-based tool to work with.

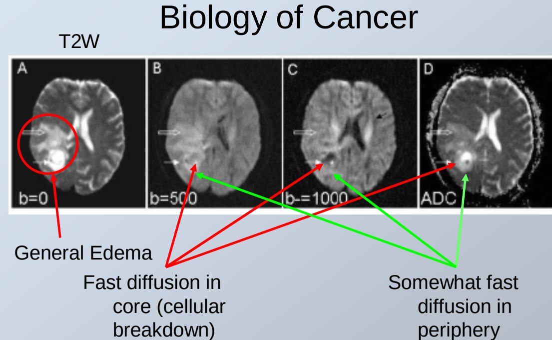
Other uses as well (FA, tracking)

Biology of Cancer



Tumors often have a rich, heterogeneous structure.

Biology of Cancer



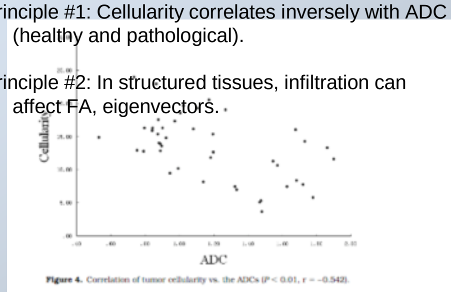
…and so, diffusion behavior can be rich in tumor region.

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.



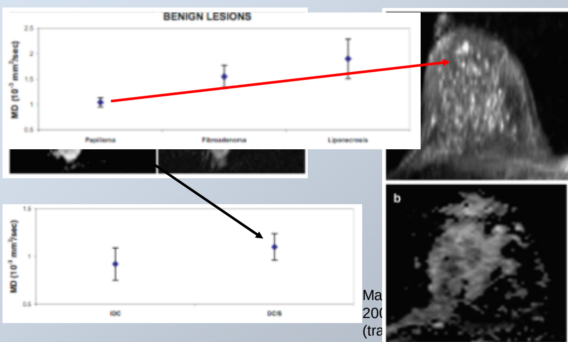
Guo, et al. JMRI, 2002 (cancerous breast lesions)

Organs for Which Diffusion Imaging is Currently Applied

Brain **
Breast
Prostate
Liver
Bone
Pretty much everywhere that motion doesn't hinder

Let's now look at some applications (some basic, some more advanced).

Breast Imaging (Qualitative/Quantitative)



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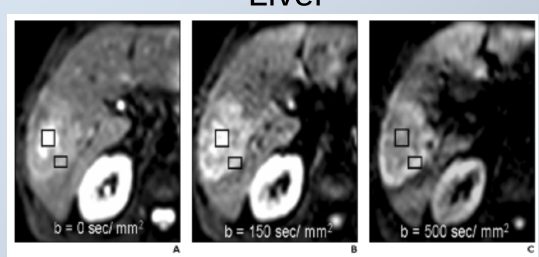
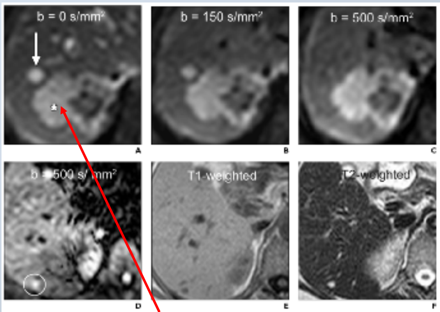
Liver



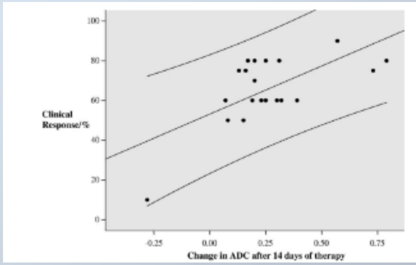
55-yr old male with Liver Metastatis. Necrosis (decrease as b increases) and cellular rim (increase as b increases) are shown in boxes.
Koh & Collins, AJR, 2007

Liver



48-yr old male with Liver Metastatis (high cellularity). Note cyst on b0 image. Hemangioma also shown (circle), but is also bright on T2W.
Koh & Collins, AJR, 2007

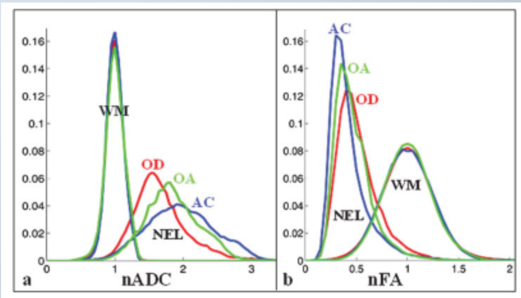
Cervical Cancer (Chemo response)



Cervical cancer size, as measured in MR, shows correlation after 14 days of chemoradiation with clinical response and ADC values.

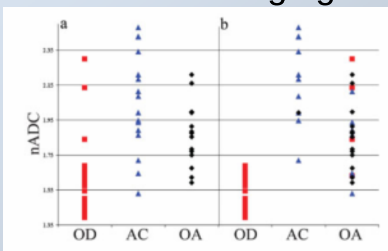
Harry, et al. Gyn. Onc. 2008

Brain Imaging



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

Brain Imaging

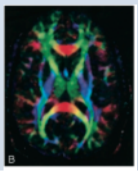


Comparison between nADC and pathology (erroneous classification on left side, corrected on right side).

Khayal, et al. NMR Biomed, 2008

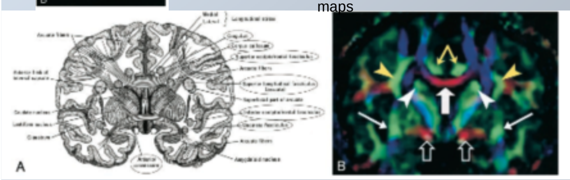
Diffusion Tensor Imaging in Brain

Directionality in DTI can help assess tumor behavior in white matter.

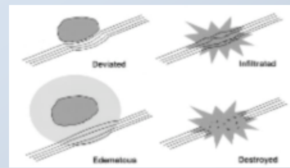


Jellison, et al., AJNR, 2004

Normal color-coded FA maps



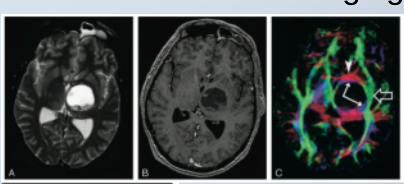
Diffusion Tensor Imaging in Brain



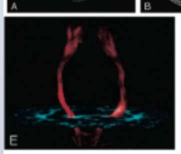
Jellison, et al., AJNR, 2004

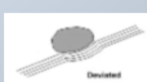
Bilateral inspection of brain tracts can help to reveal the pathology of tumor/integrity of WM in case of surgery.

Diffusion Tensor Imaging in Brain



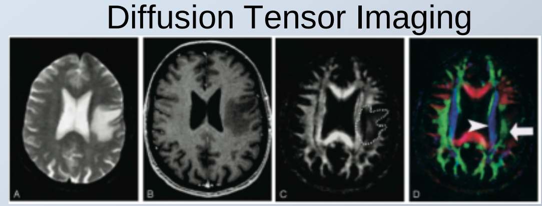
A: T2W
B: post-contrast T1W
C: FA map
D: Tractogram

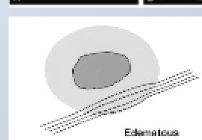




Ganglioglioma, with tracts preserved but shifted in position.

Diffusion Tensor Imaging

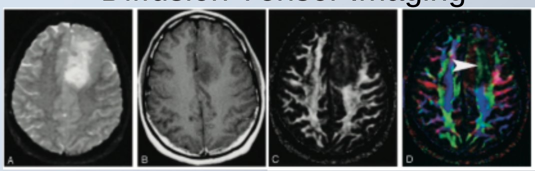


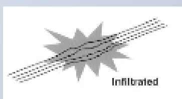


Preservation in color (direction) but reduction in FA indicates edema.

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

Diffusion Tensor Imaging

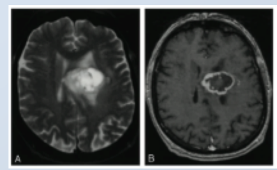


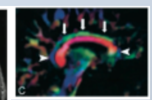


A: T2W
B: post-contrast
T1W
C: FA map
D: color-coded
FA

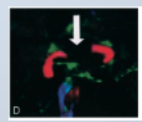
FA reduced and direction distorted, implying disruption (infiltrating astrocytoma)

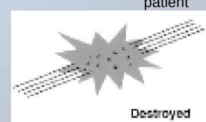
Diffusion Tensor Imaging in Brain





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



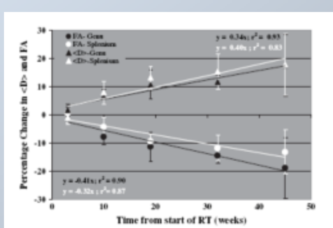


High-grade astrocytoma, with tracts essentially destroyed.

Monitoring Adverse Effects in RT

Nagesh, et al., examined normal-appearing white matter during radiation therapy (J. Rad. Onc., 2008).

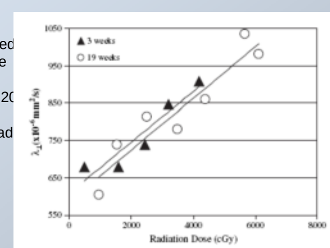
Mostly Glioblastoma multiforme patients…



Monitoring Adverse Effects in RT

Nagesh, et al., examined normal-appearing white matter during radiation therapy (J. Rad. Onc., 20

Dose dependency of rad diffusion



DWIBS (Diffusion Weighted Imaging Body Screening)

How can DWI be applied to body (motion concerns from breathing)?

Re-examine problem…

Motion leads to low signal for INCOHERENT motion within a voxel.

COHERENT motion in a voxel simply leads to a local phase shift.

$$A_{DW} = \exp\left(\frac{-\left\langle (\Delta\phi_{tot})^2 \right\rangle}{2}\right)$$

Relevant for magnitude images only…

DWIBS (Diffusion Weighted Imaging Body Screening)

DWIBS protocol:

Free breathing (benefit of COHERENT phase shift→ good SNR)

Fat suppress (STIR, CHESS, etc…)

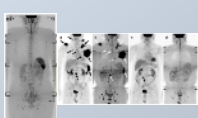
b~500-2000 (background organ signal mandates the strength)

High NEX (~5-10)

Multi-station, knit images together

Scan time: <5-7 minutes per station

DWIBS (Diffusion Weighted Imaging Body Screening)



Healthy 53-yr old female (high intensity: brain, spinal cord, nerves, marrow, spleen, lymph nodes)

44-yr old male w/ diffuse lymphoma (a/b=pre-treatment PET/DWI; c/d=post PET/DWI)

DWI: problems with lymph nodes, better with bladder, GI tract

DWIBS (Diffusion Weighted Imaging Body Screening)

Uses:

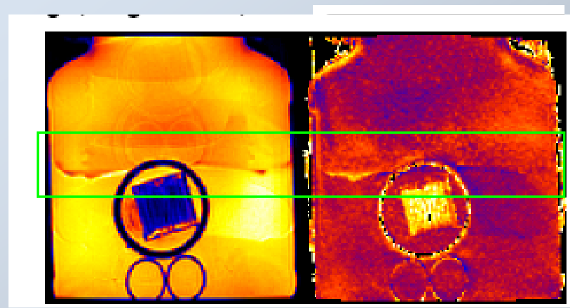
Verification of cancer (adenocarcinoma) (sens/spec = 91%/100%; Ichikawa, et al.)

T2/DWIBS fusion vs. DWIBS vs. T2 for screening abnormal malignancies (ROC area = 0.904 vs. 0.720 vs. 0.822; Tsushima, et al.)

More validation work required.

What can the Medical Physicist do to help?

Difficulties with Diffusion Imaging

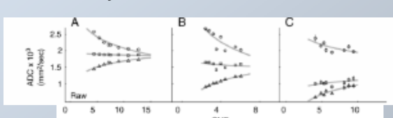


B=0 FA map

Difficulties with Diffusion Imaging

Parallel Imaging: good (improve geometric distortion of EPI) and bad

SNR is now inhomogeneous, so quantitative DW parameters may be affected.



Variation in ADC values radially and axially in capillary phantom (Yanasak, et al. 2008)

Difficulties with Diffusion Imaging

Problems with other sequences:

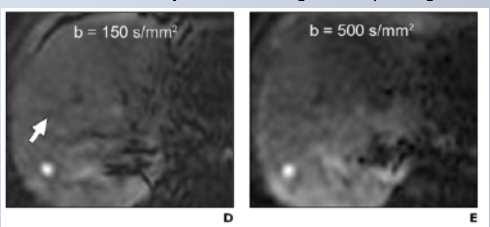
Stimulated echo – Poor SNR

Do SSFP-type sequences really measure diffusivity (considering the steady-state nature of the signal)?

Line-scanning as a motion-immune technique?

Difficulties with Diffusion Imaging

Motion is bad
- Patient/cardiac
- Scanner actually moves from gradient pulsing



Susceptibility/motion artifact present as black lines. (Koh & Collins, 2008).

QA/QC Work Important for Quantitative DW-MRI

Many considerations and questions:

1) What protocol does one use? DWI or DTI?

2) Diffusion has a temperature dependence.

3) Gradients need to be warmed up.

QA/QC Work Important for Quantitative DW-MRI

4) Test object? Water sphere? Homogeneous calibration liquids? Anisotropic structure?

Isotropic Phantoms with Different ADC Fluids
(e.g., Tofts, et al. 2000, Magn. Reson. Med. 43: 368-74)

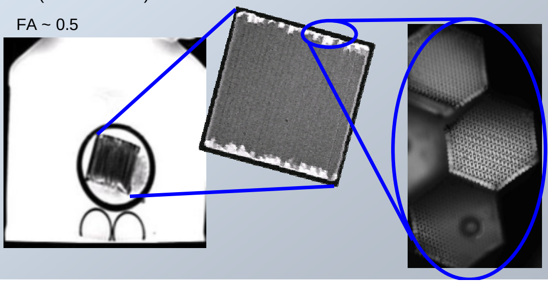
Anisotropic, Capillary/Fiber Phantoms
von dem Hagen, et al. 2002, Magn. Reson. Med. 48: 454-9.
Lin, et al. 2003, NeuroImage 19: 482-95;
Perrin, et al. 2005, Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360: 881-91.
Yanasak, et al. 2006, Magn. Reson. Imag. 24: 1349-61.
Fieremans, et al. 2008, J. Magn. Reson. 190: 189-99.

Anisotropic Phantoms

Cubical container filled with ~1.7L undoped water

1” x 1” x 0.4” compartment containing arrays of glass capillaries (i.d.=22±2 mm)

FA ~ 0.5



Future Developments

DTI + FLAIR

Reliable DTI in difficult tissues: Cardiac, Liver, Spinal Cord

DTI Tractography

A return to days of old…line scanning

Kurtosis/DSI – non-Gaussian diffusion (cell permeability)

Conclusions

• DWI offers a new tool for looking at changes in tissue microstructure.

• There are a plethora of different ways to use diffusion contrast to look at cancer.

• ADC maps provide good qualitative contrast for distinguishing healthy tissue from non-enhancing pathology (cellularity).

• More complicated DW-based techniques may provide substantially more information

• Diffusion MR imaging shows promise in the area of treatment monitoring.

• Quantitative diffusion imaging requires a lot of work, and still requires validation.