Diffusion weighted imaging for detection and assessment of response to treatment of cancer in the body

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Disclaimers

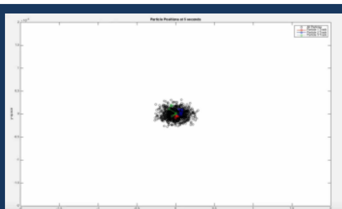
- Research support from and intellectual property licensing to GE Healthcare and Siemens Healthineers

Outline

- Some basics on diffusion
- Some technical consideration for diffusion-weighted imaging (DWI) and quantitation
  - Acquisition
  - Analysis
- Some clinical applications of DWI in the body

What is diffusion?

- In MRI, diffusion refers to the Brownian motion of water molecules
  - self-propelled by thermal energy
  - First discovered and named after the botanist Robert Brown who observed the life-like but random movement of pollen grains in water (1827)
  - The Fick's laws provide a phenomenological description of diffusion in terms of particle movement from high to low concentrations without bulk motion (1855)
  - Modern framework is attributed to Einstein (1905)



Random walks

http://youtube.com

- The mean displacement of diffusion is 0
- The mean squared displacement is given by Einstein Equation:

$$\langle r^2 \rangle = 6D\Delta t$$

for diffusion in a homogeneous medium with no boundaries

D is the diffusion coefficient, which is dependent on temperature, viscosity, and other properties of the medium and has a unit of mm^2/s (in contrast to velocity, in unit of mm/s)

Diffusion in tissues

- For pure water at a body temperature of 37 °C, $D \approx 30 \times 10^{-3}$ mm^2/s:

$$\sqrt{\langle \delta r^2 \rangle} \approx 30 \times 10^{-3} mm$$

for a time interval of 50 ms (typical echo time for diffusion imaging).

- Fortuitously, this distance is the size of multiple cells:
  - "restricted" intracellular diffusion when H2O crosses cell membranes and intracellular organelles
  - "impeded" extracellular diffusion when H2O encounters the tortuosity of extracellular matrix

Propagator function

- aka conditional probability or van Hove correlation function:

$$P(r, r_o, t)$$

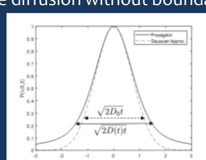
the probability of finding a particular particle at location r after a time interval t when it is first at location r_o?

- Mathematically derivable from the Fick's Law
- Has a simple Fourier relationship with the MR signal in q-space (therefore directly measurable in so called q-space imaging

Gaussionality

- In the simplest case of free diffusion without boundaries:

$$P(r, r_o, t) = \frac{1}{\sqrt{4\pi D t}} e^{-(r-r_o)^2/4Dt}$$



Jespersen, ISMRM 2018

  - The propagator is a Gaussian function
  - D is the width of the propagator

- In general, the propagator is not a Gaussian, and the simple diffusion coefficient is not a constant but time-dependent!

- Deviation from Gaussianality: stretched exponential, kurtosis...

Diffusion-weighted imaging (DWI)

Moving spins accumulate phase in the presence of magnetic gradient:

$$\varphi(t) = -\gamma \int_0^t \overrightarrow{G(t')} \cdot \overrightarrow{r(t')} dt'$$

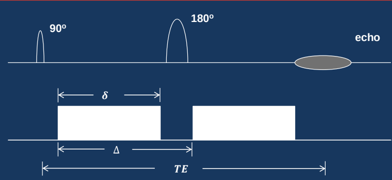
- *For a large ensemble of spins with random trajectories, the net phase is zero.*
- *However, there will be a spread of phase, which results in signal intensity reduction (Bloch-Torey Equation):*

$$S(t) = S_0 e^{-D \int_0^t \overrightarrow{k(t')} \cdot \overrightarrow{k(t')} dt'}$$

in which:

$$\overrightarrow{k(t')} = \gamma \int_0^t \overrightarrow{G(t')}\, dt'$$

Stejskal-Tanner pulsed field gradient (PFG)



$$S(t) = S_0 e^{-bD}$$

$$b = \int_0^{TE} \overrightarrow{k(t')} \cdot \overrightarrow{k(t')} dt' = (\gamma G \delta)^2 \left[\Delta - \frac{\delta}{3}\right]$$

b-value is a scan parameter, and D is the property of the tissue

Diffusion measurement

Quantitation of diffusion (simplest case):

$$D = -\frac{1}{(b_2 - b_1)} \ln \left[\frac{S(b_2)}{S(b_1)}\right]$$

Alternatively, a linear fit can be used if measurements at more b-values are available.

Diffusion anisotropy

Diffusion in anisotropic medium may be represented by a 3x3 second order rank tensor:

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

Diffusion weighted imaging can be used to determine the rotationally invariant parameters like mean diffusivity and fractional anisotropy, or even the full diffusion tensor (six independent elements).

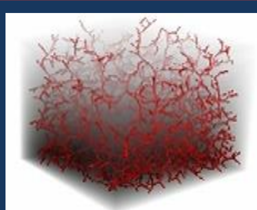
Apparent diffusion coefficient (ADC)

Because of its complexity compared to homogeneous media, diffusion in biological tissues is represented by ADC, instead of diffusion coefficient (D).

Further, in vivo measurement of ADC is affected by:

- *Perfusion*
- *Noise*

Perfusion



http://iopscience.iop.org/article/10.1088/0031-9155/57/19/6103

- Perfusion refers to blood flow in microcapillaries that are embedded in tissue
  - Has linear velocity
  - Microcappillaries can be assumed to be distributed with random orientation on a voxel scale

Perfusion or IVIM

- *Signal contribution can be modelled as pseudodiffusion or intravoxel incoherent motion (IVIM) in the bi-exponential model:*

$$S(b) = (1 - f)e^{-b\,D} + f\,e^{-b\,D^*}$$

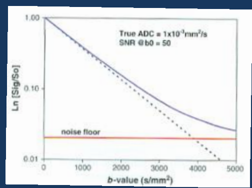
f is the perfusion fraction and D^* is the peudodiffusion constant

Le Bihan, D., et al. (1988). "Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging." Radiology **168**(2): 497-505.

Keep in mind that in the presence of perfusion:

- *tissue diffusion may be overestimated without IVIM*
- *Perfusion usually affects signals at only low b-values (≤100-200 x 10³s/mm²)*

SNR

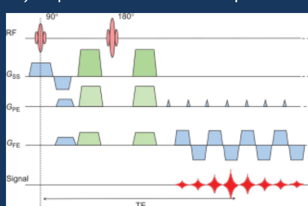


Chenevert, Diffusion Weighted MRI – Applications in the Body

- Noise floor raises the signal at high b-values → lower ADC
- Calculated ADC is dependent on <u>baseline SNR, selected b-values and true ADC</u> (which is unknown and different for different tissues) → protocol optimization

DWI acquisition

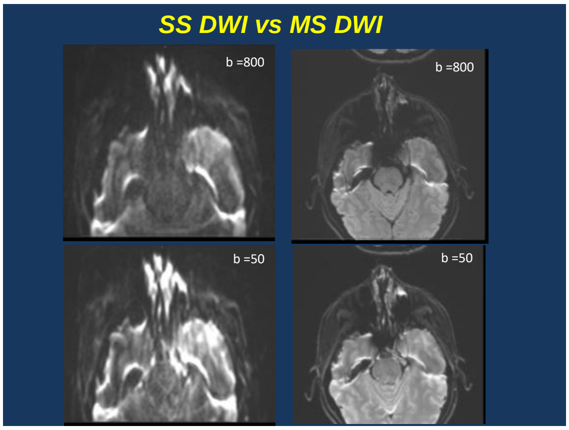
- most commonly performed with the single shot echo planar imaging (ssEPI) sequence because of its speed

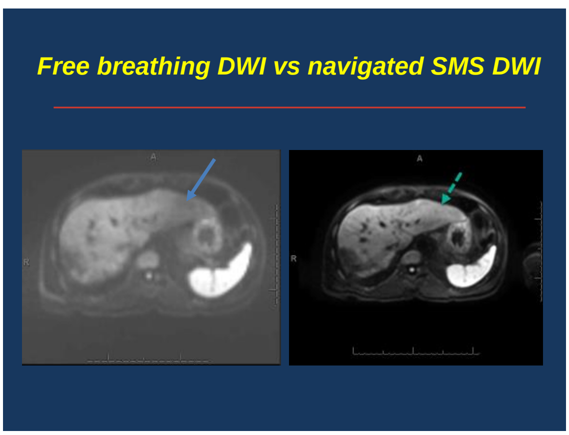


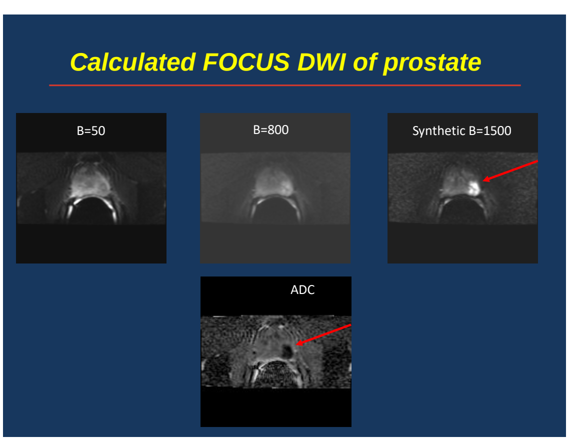
- ssEPI is prone to image distortion and ghosting
  - sensitive to Bo inhomogeneity or chemical shift
  - sensitive to eddy currents

DWI acquisition

- Other pulse sequences:
  - spiral/radial/propeller
  - SSFP/FSE
- Hardware improvements:
  - Stronger, faster, higher-fidelity gradients
  - Multi-channel transmit and receive RF
- Software improvements:
  - parallel imaging
  - Reduced FOV through 2D spatially selective excitation or outer volume signal suppression
  - Multishot imaging with navigators for phase correction
  - Simultaneous multislice (SMS)
  - More robust fat suppression strategies

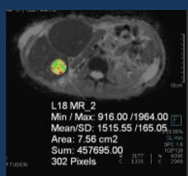

SS DWI vs MS DWI
b =800
b =800
b =50
b =50

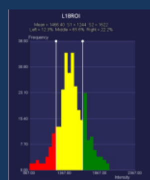

Free breathing DWI vs navigated SMS DWI


Calculated FOCUS DWI of prostate
B=50
B=800
Synthetic B=1500
ADC

DWI – quantitative analysis

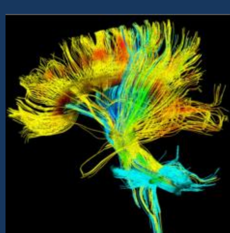
- Model based or data-driven
  - Mono- or bi-exponential
  - Non-Gaussian models
- Measurement can be
  - ROI based
  - Pixel or histogram based
  - Radiomics feature analysis

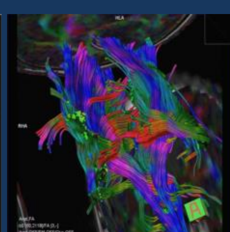




Clinical applications of DWI

- First successful application of DWI is the early detection of stroke
- Another major application of DWI in the brain is white matter fiber tracking





https://usa.healthcare.siemens.com/

Technical challenges of extracranial DWI

- Lower SNR
- Motion (respiratory, cardiac, and involuntary motion)
- Large field inhomogeneity
- Fat contamination

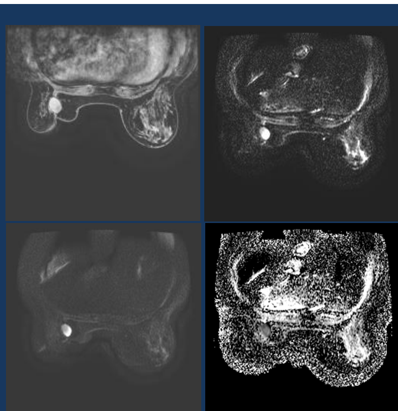
High quality DWI images have been achieved in nearly every anatomical areas due to the technical advances

- Liver/pancreas
- prostate
- breast
- spine
- MSK

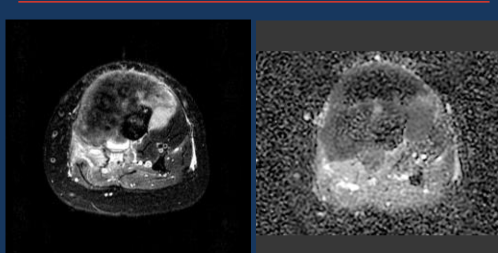
Oncological applications of DWI

- Lesion detection and characterization
  - Improved sensitivity and specificity
- Assessment and prediction of treatment response
  - Changes in diffusion precedes changes in sizes

- The exact biophysical basis is still unclear
  - Malignance or aggressiveness is associated with higher cellularity, tissue disorganization, and increase in extracellular tortuosity → low diffusion
  - Tumors responding to treatment have increased cell death → increased diffusion
    - Diffusion measurement may depend on the timing of imaging during the treatment



DWI of sarcoma



DWI ADC

Myometrial invasion of endometrial cancer

- 51 patients under rFOV DWI in addition to conventional T2W and DCE MRI
- Surgical pathological findings as gold standard
- rFOV DWI gave statistically better accuracy, sensitivity, specificity than T2W combined with DCE

TABLE 2. Ability to Identify r <50% and ≥50%DMI by T2WI plus DCE MRI and rFOV

	Percent				
Reader and modality	Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Reader 1					
T2WI + DCE MRI	84	100	82.2	42.8	100
rFOV	92	100	90	60	100
Reader 2					
T2WI + DCE MRI	96	83.3	97.8	83.3	97.8
rFOV	98	100	97.8	85.7	100

The rFOV sequence had a better accuracy and positive predictive value for DMI for Reader 1 and had a higher sensitivity for Reader 2.

Bhosale, Ma, et al, J Magn Reson Imaging 2016

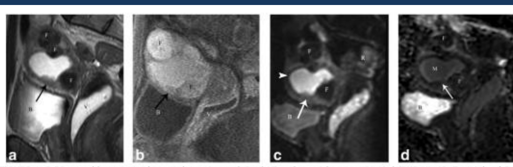
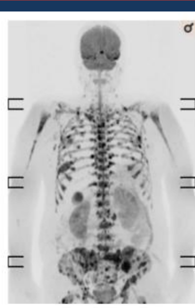


FIGURE 4: A 59-year-old woman with vaginal spotting and Grade II endometrial cancer. Sagittal T_2WI (a), 3D T_1-weighted DCE MRI (b), and FOCUS (c) show fibroids (F) and the tumor (arrow) in the anterior lower uterus, with superficial myometrial invasion, difficult to see on DCE MRI (b) owing to blood products in the endometrial cavity. The tumor is isointense to the myometrium on DCE and is better seen on FOCUS and T_2WI (d). The apparent diffusion coefficient map, with M representing blood products. B: bladder; V: vagina with gel, R: rectum.

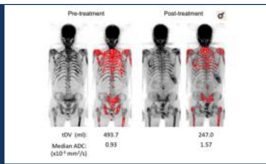
Bhosale, Ma, et al, J Magn Reson Imaging 2016

Whole body DWI

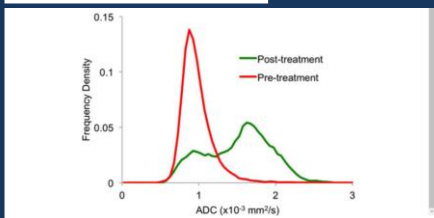


A 60-year-old male with multiple myeloma. Coronal reformatted whole-body DWI image with inverted gray scale contrast for b = 800 s/mm^2 demonstrates diffuse tumor burden in low signal in the bone marrow.

Taoli et al. J Magn Reson Imaging 2016



Taoli et al. J Magn Reson Imaging 2016



A 65-year-old female with metastatic bone disease from breast cancer. Top row: Pre- and posttreatment inverted gray scale maximum intensity projection $b = 900$ s/mm^2 images. Disease segmentation (colored red) allows quantification of total disease volume (tDV) before and after treatment. Note reduction in disease volume after chemotherapy. Bottom image: ADC histograms associated with disease volumes pre- and posttreatment shows more than 50% increase in median ADC values after treatment, in keeping with treatment response.

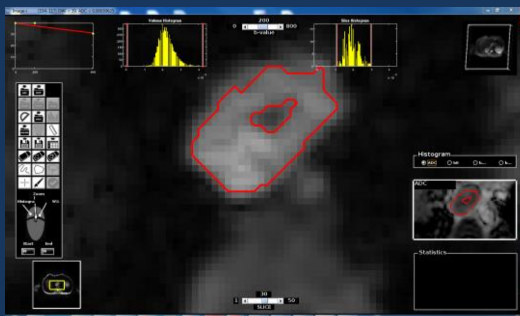
Early marker of response of esophageal cancer to adjuvant chemoradiation

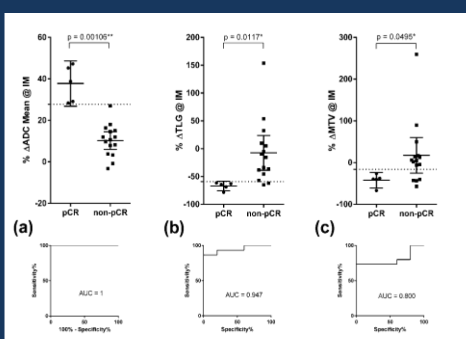
- Esophageal cancer is a leading cause of cancer death worldwide
- The current standard of care is neoadjuvant chemoradiation followed by surgery
- Complete pathological response (pCR) is achieved in ~30% of the patients, for whom surgery presumably may not be needed or can be delayed
- Early prediction of the treatment response is lacking but would have a significant impact on the patient management

Study design

- DWI was performed at baseline, at interim (during 3rd week of CRT), and at followup before surgery
- Quantitative ADC was extracted from the entire tumor volume
- Histopathological results grouped into pCR and non-pCR groups as gold standards
- 20 patients were enrolled the study

In-house built software Image-i





Fang, Musall, et al, Int J Radiation Oncology, Biology, Physics, 2018 (in press)

Summary

- Diffusion provides a fundamentally different contrast mechanism that is sensitive to cellular microenvironment of water molecules
- DWI allows quantitative measurement that is repeatable, standardizable, and requires no exogenous contrast agent
- Technical advancement has enabled diffusion imaging with high quality in many extracranial anatomical regions
- Improved lesion detection, characterization, better assessment of treatment response have been or are being established in many clinical areas

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