DIFFUSION MR

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Abstract

SEQUENCE OBJECTIVE

What is diffusion?

Diffusion relates to the unexpected, microscopic motion of water and other small molecules owing to thermal collisions. Diffusion is often defined as Brownian motion, labeled after the Scottish botanist, Robert Brown, who first identified spontaneous oscillations of pollen particles under a microscope in 1827.

For comparison, the rate of diffusion of water molecules at room temperature is 2.2×10^{-5} cm2 / s. That is, on average, the water molecule moves and covers a patch area of 0.000022 cm2 every second as shown in **Fig.1**. Water diffusion relies on the microscopic structural conditions in the tissues, and analysis may offer useful insights into regional morphological and anatomical shifts in disease states.
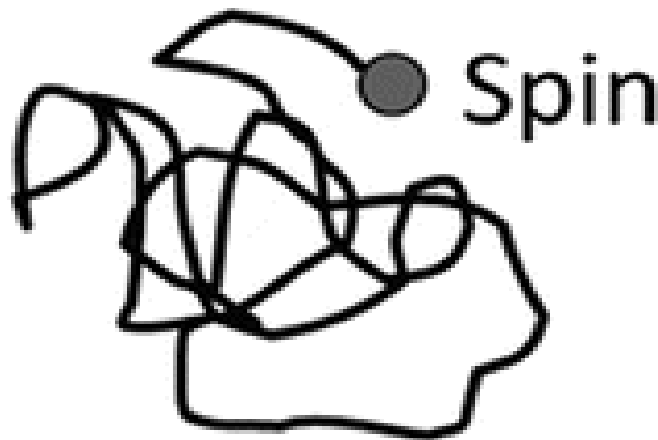
Figure1: water molecule movement

The fastest degree of diffusion happens in free water with no limit. In brain tissue, the borders of cell membranes limit the motion of water to a degree that relies on the mean free path of water molecules. Of starters, in cerebral ventricles, the diffusion of water is fairly unimpeded and the CSF has a strong diffusion coefficient. Gray matter (GM) and white matter (WM) have a weaker diffusion coefficient than CSF owing to their diverse tissue composition.

DWI objective

Water constitutes a significant proportion of body weight as intra-and extra-cellular fluids in the human body. In biological tissues, the movement of water molecules assumes a sequence of tissue composition and properties. In some pathological conditions, such as acute stroke, this pattern of diffusion is disturbed and the quantity of diffusion changes in the injured region. The irregularities may be observed by observing these variations in diffusion. That can be accomplished utilizing a sophisticated magnetic resonance imaging method named Diffusion Weighted MRI (DW-MRI) or DWI, where the movement of water molecules is used to imagine internal physiology. The image contrast in DWI represents the variation in the rate of diffusion across tissues.

The diffusion of water may be observed or calculated using diffusion-weighted imaging (DWI) technology. DWI is sensitized to random molecular motion of water in tissue by applying magnetic field gradients (diffusion gradients) to the RF pulse sequence. In the DWI series, the diffusion weighting is calculated by the "b-value" variable, which would be in the second unit per square millimeter (s / mm2). High "b-value" results in high diffusion weighting, and no diffusion weighting is produced when b= 0.

On a diffusion-weighted picture, the tissue that contains high levels of diffusing water produces a hypo-intense signal. The chart of the apparent coefficient of diffusion (ADC) of the water molecules can be determined from the diffusion-weighted picture. Diffusion-weighted imaging (DWI) has been repetitively improved to probe random microscopic motion of water protons on a per pixel basis. Such DWI methods have developed far beyond the experimental field to routine therapeutic uses in ischemia which are also the field of study in other diseases, including multiple sclerosis, dyslexia, schizophrenia or trauma. Alterations in proton self-diffusion are an early sign of altered cell homeostasis in acute ischemic stroke. Early identification of such changes may have a significant effect on clinical plans and the medical result for stroke patients.

BASIC PULSE SEQUENCES FOR DWI

Spin echo- and stimulated echo-based

Merboldt et al. Inserted one diffusion-encoding gradient between the first and the second 90 ° pulse and one after the third 90 ° pulse of the stimulated echo sequence **(Fig.2)** to create diffusion-weighted images. In **Fig.2,** Diffusion-weighting power G_{diff} gradients are performed on the first and third RF pulses. The second RF tips half the spins down down the z-axis. During the mixing time (TM) these spins are only influenced by the somewhat slower T_1-relaxation time. During TM G_{Crush} spoils the

transverse magnetization free, which may interact with the diffusion-weighted signal when the induced echo is created.
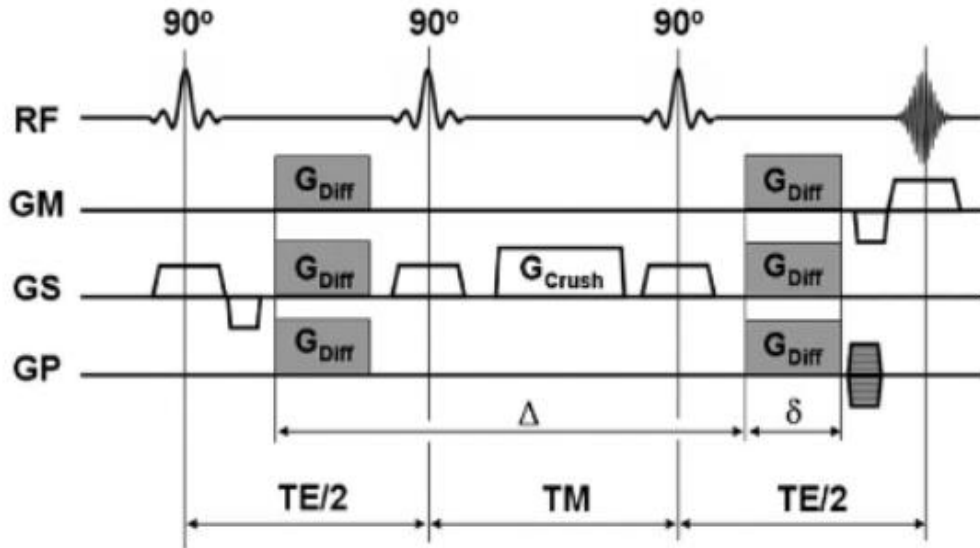

Figure2: Diffusion-weighted stimulated echo sequence

The stimulated echo may be produced by three RF-pulses (note that the RF-pulses must not actually be 90 ° -pulses to create a stimulated echo): the spins are rotated to the transverse plane by the first RF-pulse and lose their phase coherence. The second RF-pulse brings half of the transverse magnetization (i.e. all vector components perpendicular to the phase of the second RF-pulse) from the transverse, z-axis plane. While magnetization is 'stored' along the z-axis (TM), it is only affected by the much slower T1-relaxation process. At the center, after the third RF-pulse, which rotates back into the transverse plane, and after the second precession period (TE/2), a diffusion-weighted induced echo is produced at the time of TE+TM.

Diffusion-weighted induced echo series is of special importance to tissues with brief T2-relaxation periods (e.g. liver) and may often be paired with a number of reading techniques, such as Echo Planar Imaging (EPI) or Spiral Imaging. Diffusion-weighting is primarily determined by the T1-sensitive TM-interval and thus enables one to select brief echo times for a rational diffusion-weighting. It should be kept in mind; however, that the stimulated echoes technically provide only half the signal compared to the spin echoes, with the corresponding signal equation.

$$M_{(TE)STE} = \frac{1}{2}M_0 exp(\frac{-TM}{T_1})exp(\frac{-TE}{T_1})exp(-bD)$$

SSFP diffusion-weighted imaging

When a train of equidistant RF pulses with flip angle and TR < T2 is added, a state of steady state free precession (SSFP) may develop; because of the very brief TR SSFP imagery, rapid image creation is feasible. In the presence of magnetic field gradients SSFP imaging has long been known for its high flow and diffusion sensitivity **(Fig. 3)** and has therefore received some attention from a number of research groups. In **Fig. 3,** The ECHO part is usually very responsive to diffusion. For this example chain, all gradients are fully balanced and the overall effective gradient is equivalent in each cycle to create a steady state. To minimize the voluminous motion response, bipolar diffusion gradients can be used to decrease the first gradient moment and even (spiral) navigator echoes can be used.
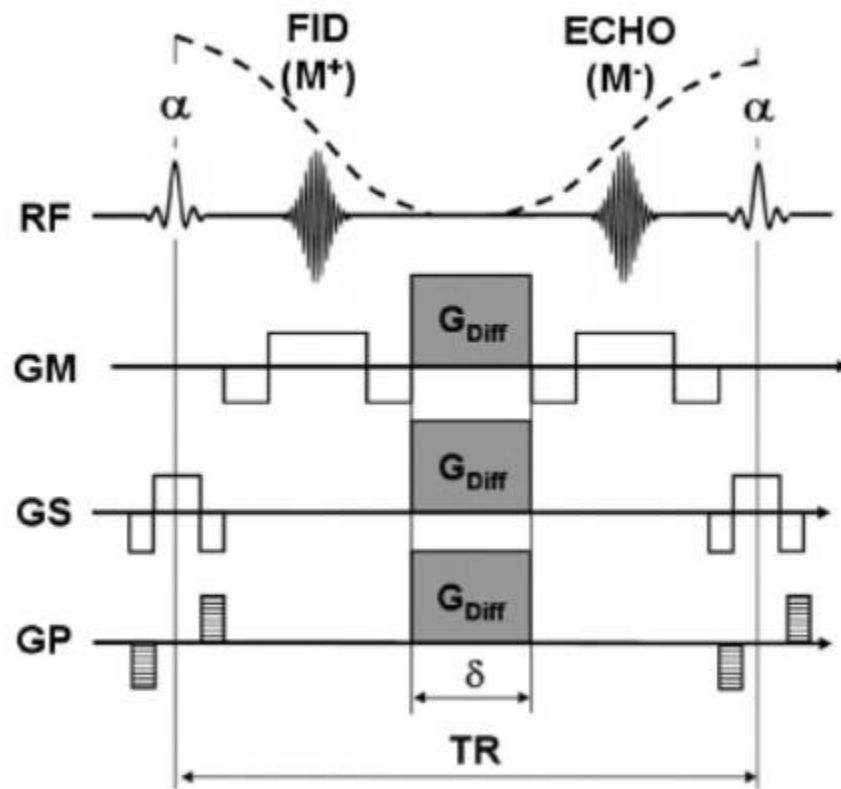
Figure3: One cycle of a diffusion-weighted SSFP sequence

Compared to spin and stimulated echoes, the signal construction in SSFP is, however, a complex mixture between various spin and stimulated echoes, which can be established A multitude of coherent directions, constrained only by the natural T1 and T2 decay periods. This complex signal structure allows the measurement of diffusion very complicated and the diffusion attenuation (b-factor) that differ from tissue to tissue, as the b-factor for this series is often defined by parameters such as relaxation periods and B1-uniformity.

Thus, in comparison to spin echo and induced DWI-based echo, one has to contend not only with 'T2-shine-trough' results, but also with the possibility that b-values are weighted by the underlying stimulation periods and other conflicting variables.

MRI INSTRUMENTATION

Diffusion-weighted imaging (DWI)

The water diffusion can be detected or measured using the diffusion-weighted imaging (DWI) technology. DWI is sensitized to the water molecular motion in tissue by applying magnetic field gradients (diffusion gradients) in the RF pulse sequence. In a DWI sequence, the diffusion weighting is determined by a parameter called "b-value," which is in the unit of second per square millimeter (s/mm^2). High "b-value" generates high diffusion weighting, and no diffusion weighting is generated when $b = 0$. On a diffusion-weighted image, the tissue that contains high diffusing water generates hypointense signal.

DWI application

The use of DWI on neurological studies has been shown that a wide range of neuropathology causes DWI signal changes. One of the most successful applications is in the stroke study. T_1- and T_2-wt MRI failed to detect the ischemic lesion in acute stroke. Oppositely, the lesion can be detected using DWI. DWI can reveal the immediate temporal changes in ADC that occur upon induction of ischemia. **Fig. 4** shows the DWI and the ADC map of a stroke model using rats. The ischemic region has elevated DWI signal intensity indicating decreased water diffusion in this region. ADC map calculated from the DWI shows decreased ADC in the same region.
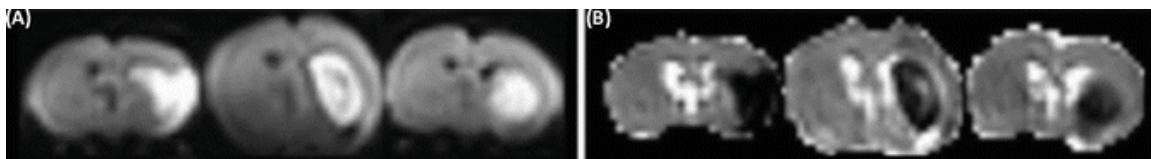
Figure4: DWI and the ADC map of a stroke model using rats

The underlying pathology of the ADC change during ischemia remains unclear. Several theories explain the observation. One of them is the cell swelling theory. This theory assumes that water diffusion is slower inside cells than in the extracellular space. The disruption of blood supply in stroke induces cell swelling (cellular edema). Water molecules then spend more time diffusing in swollen cells, and thus decreasing ADC.

Another theory assumes that the changes in cell membrane permeability may contribute to the ADC reduction. A loss of active intracellular water transport with energy failure may be another cause of the decreased water diffusion.

Diffusion Tensor Imaging (DTI)

DTI is an extension of DWI. Diffusion is a three-dimensional process. In a uniform environment, it is isotropic in all directions and can be represented by a sphere. If water molecule movement is restricted in certain directions, the diffusion becomes anisotropic, represented by an ellipsoid. For example, in fiber-like cell structures, such as white matter tracts, the diffusion is relatively free along the long axis of the fiber tract, but restricted in the other two dimensions. The diffusion in cellular structures is described mathematically by a tensor. A tensor is a 3×3 matrix. The tensor of diffusion is measured using DTI with diffusion gradients in appropriate strength. After a series of mathematical manipulations, the axes of the ellipsoid diffusion and the diffusion magnitudes along the axes can be calculated.
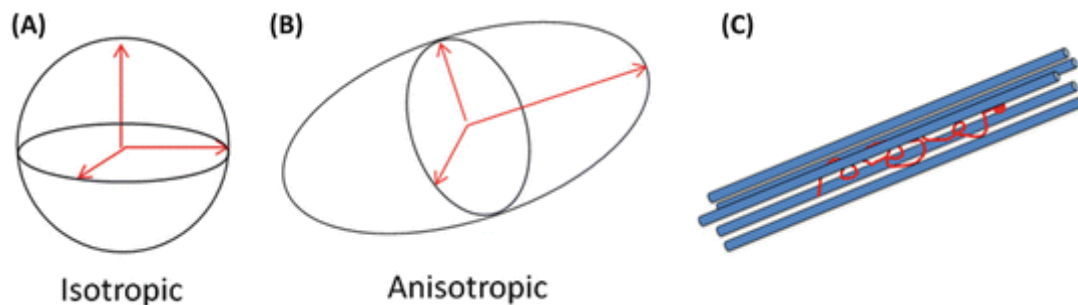

(A) Isotropic **(B)** Anisotropic **(C)**

Figure5: DTI imaging process

DTI application

Apparently the principal axis (the axis with the maximum diffusion magnitude) of the diffusion ellipsoid points to the preferred diffusion direction. It is reasonable to think that for WM, the favorite diffusion direction is along the WM tracts, and thus the principal axis is parallel to fiber tract orientation. Several methods display the principal axis, one of which is the so-called color-encoding technique. In the color-encoding technique, the three components along the directions of the principal axis are encoded with the primary colors (red, x component; green, y component; and blue, z component) and the brightness is scaled by an anisotropy index such as FA. **Fig. 6** explains this method on multiple image slices of a mouse brain where the brightness was scaled by the FA value.
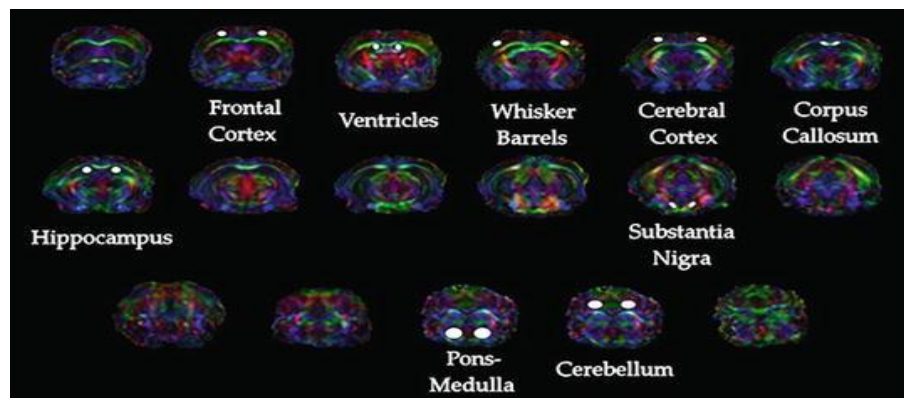
MRI CONTRAST AND DWI

Conventional MRI system changed a lot since it was created through diagnose and investigation of many different kinds of tumors in any organ of the body. Before MRI we were not able to detect any tumor. The process was through very hard method to figure out the body tumors, however with time and all technologies which we already have today we could improve the image of MRI as unfortunately it was not very precise on organs like brain and liver. The difference between DWI and conventional MRI that DWI illustrates the contrasts of the region using the diffusion of water in cells as any region even it was empty it has differences in tissues and microbodies will draw the contrast of the region which will give us a map like.

Using DWI with the conventional MRI

Taking a case like the stroke which arises from ischemia in case like this using MRI without DWI will not be helpful as it will detect the problem after couple of hours and possibly more, but using DWI will detect the problem only in half an hour and maybe less than that. The point is MRI good with tumors and big tissues differences but in a case like stroke we will not figure the problem, however DWI detects the changes in water in tissues so any stroke or different behavior will change the map which is drown by DWI. Unfortunately we can't replace MRI with the DWI totally as it will not be very precise on the levels of tumors it will give a precise map for the region and the hyper and hypo intense signals based on the diffusion, however it will not give anatomical information about the tumor like the MRI sequence.

Using both MRI and DWI together makes the image more complete and precise. Studies show that combining both of them helps in differentiating between benign and malignant tumors which only MRI sequence was not able to differentiate between them correctly before DWI. Another case is prostate cancer. A study by heider et al explains that using both of conventional MRI and DWI together gives a more precise and detailed

imaging. Another benefit of DWI is that it does not require any hardware system; therefore it is very easy to use it on a MRI device to get the best result. **Fig. 7** shows a T2WI (conventional MRI) images and DWI images of a prostate cancer patient. Figure B is DWI and C, D are corresponding ADC maps in gray and color scale.
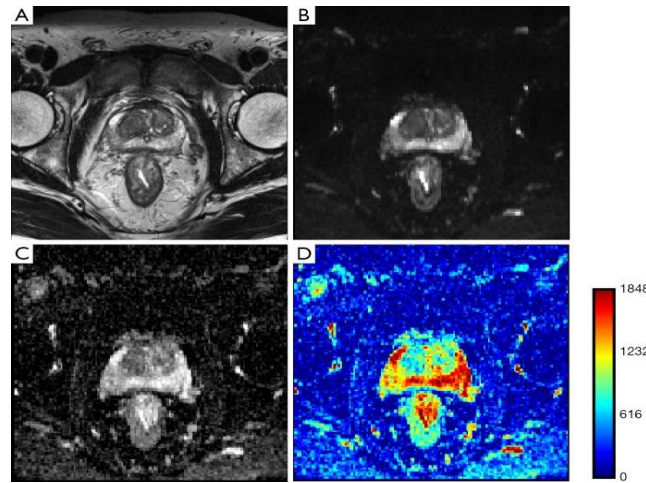

Figure7: conventional MRI and DWI images and their ADC maps

Brain imaging

Diffusion tensor imaging (DTI) is one of the main branches of DWI. Its process is by taking several images from every direction of the region to develop the tensor image. Using DTI enables us to get better images when it comes to fiber tracking. It also helps a lot in studying the white matter of brain depending on the diffusion which assumed to be highest parallel to the tract so it will help in studying the pathways of the brain.

DWI Deficiencies

Theoretically DWI is a perfect tool for tumors and detecting any small change in the region we want to explore. Unfortunately practically the image of DWI depends on a lot of factors which may reduce its efficiency like the field homogeneity, slow gradient changes and the hardware limitations. Also low strength scanners leads to lower resolution which is one of the main reasons that DWI is not efficient alone and needs MRI sequence.

MR FORMATION

 Modern diffusion-weighted (DW) sequences all trace their origin to the echo pulsed gradient spin (PGSE) technique developed by Edward Stejskal and John Tanner in the mid-1960. As shown in the diagram right, symmetric, strong diffusion-sensitizing gradients **(DG's)** are applied on either side of the 180°-pulse. The stationary spin phases are uninfluenced by the DG pair as any phase accumulation from the first gradient lobe is reversed by the second. However, diffusing spins move around in various locations results difference between the first and second lobes, drop out of phase and lose signal.
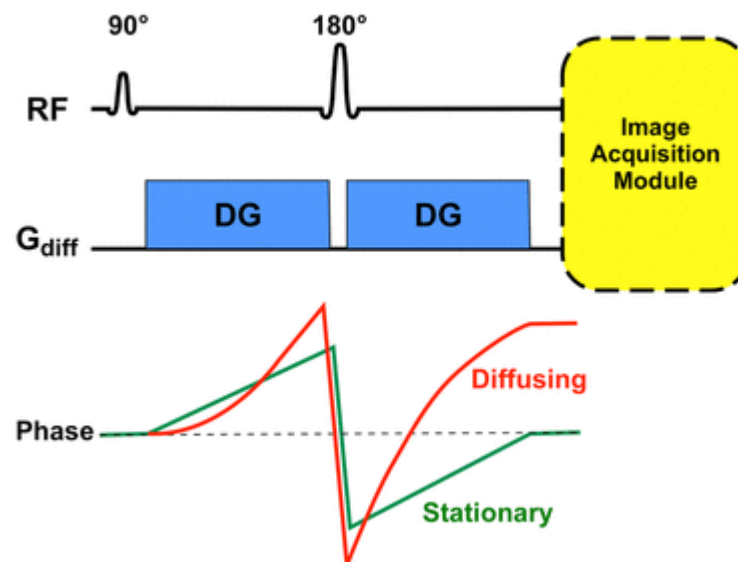
Figure8: Image acquisition module

 Immediately after the second DG a module for image acquisition is played out. That is usually an echo-planar sequence with phase and frequency gradients oscillating rapidly generating multiple echoes of gradients. Generally speedy image acquisition is needed minimizing impacts of bulk motion (such as vascular pulsations) on DW images. Other modules (such as the rapid spin echo) are possible, but are currently not as widely used.

 Modern DWI implementations maintain the core features of the original PGSE technique used by Stejskal and Tanner with some modifications. All commercial DWI sequences use some form of fat suppression method to suppress artifacts from chemical shifts. This can be a chemical-selective fat saturation pulse or a non-selective inverting pulse "STIR-like" applied immediately before the 90 ° pulse. Alternatively, it is possible to selectively tune the 90 ° -pulse itself to only excites water protons. Suppress eddy currents and decrease artifacts of spatial distortion a "twice-refocused" PGSE sequence

can be used. This technique uses a second 180 ° -refocusing pulse at the use of bipolar (rather than unipolar) DG's is a third common modification to reduce eddy current artifacts.

With the core pulse sequence defined as above, DW images and their associated maps are automatically generated with the following steps:

Bo image

The DW pulse sequence is initially executed with the DG turned off or set the value to very low. This generates a set of T2-weighted **b0 ("b-zero") images** which will serve as the basis for the later calculated maps. (**B50 images** are also collected for abdominal imaging, the low but non-null amplitude gradient helps to block signal in vessels). **Fig. 9** shows an example of b0 images.
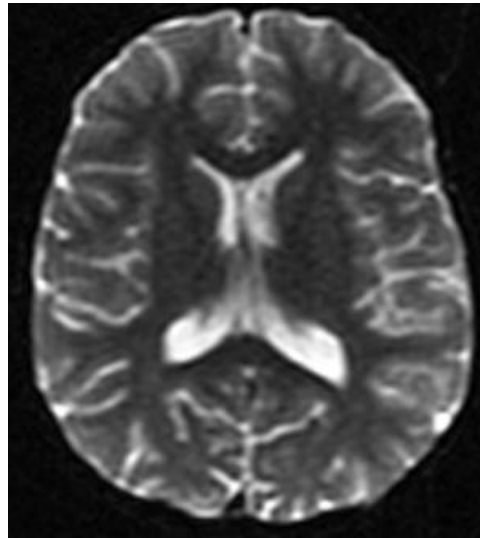

Figure9: B0 image

DW source image

The DW sequence is then executed individually or in combination with the DG's turned on and at different strengths. It produces **DW source images** that are sensitized to diffusion in several different directions. **Fig. 10** shows an example of DW source images.
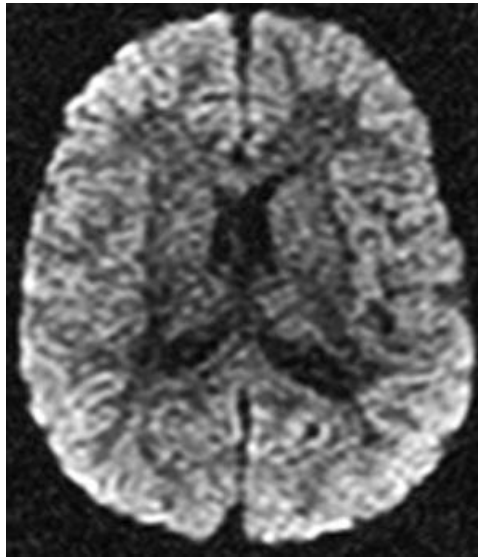
Figure10: DW source image

Trace DW image

A collection of **Trace DW images**, the first-line images used for clinical diagnosis, are paired with the DW source images. **Fig. 11** below shows an example of Trace DW images.
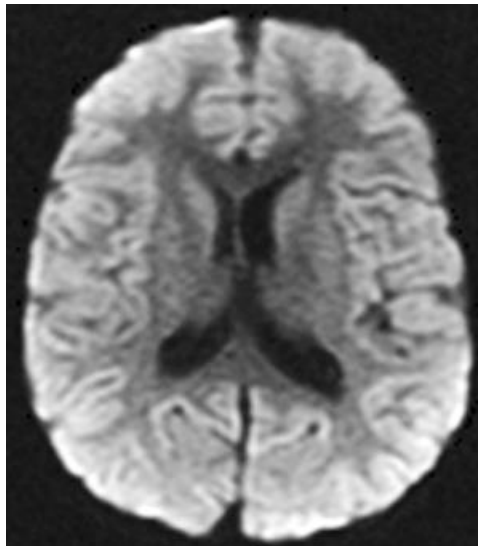

Figure11: Trace DW image

Apparent diffusion coefficient (ADC) map

Then a map of the **Apparent Diffusion Coefficient (ADC)** is calculated using the b0 data and the source images. The ADC chart is used to explain any anomalies found on the trace images. **Fig. 12** below shows an example of ADC map.
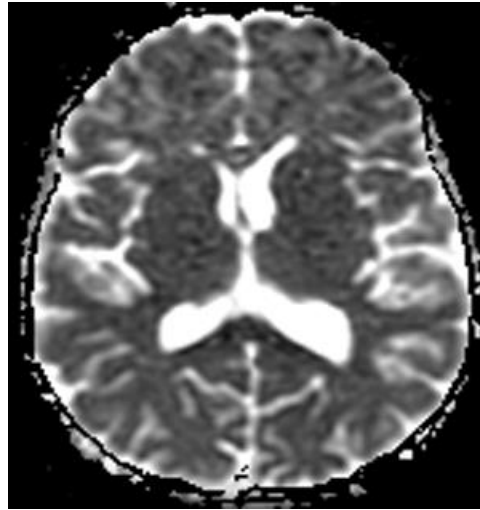
Figure12: ADC map

Additional calculated image sets

Optionally, more advanced processing may be done, generating additional computed image sets for analysis. These may include **exponential ADC maps, fractional anisotropy images**, **principal diffusion direction maps**, and **fiber tracking maps**. **Fig. 13** illustrates these advanced processing and the additional image sets.

Exponential ADC map   Fractional Anisotropy map   Principal Diffusion Direction map   Fiber-tracking map

Figure13: Additional calculated image sets

IMAGE QUALITY AND ARTIFACTS

Resolution, SNR and contrast Artifacts

DW images tend to be of lower resolution than conventional MR images such as T2WI. This is due to multiple factors such as low resistance scanners, faster image 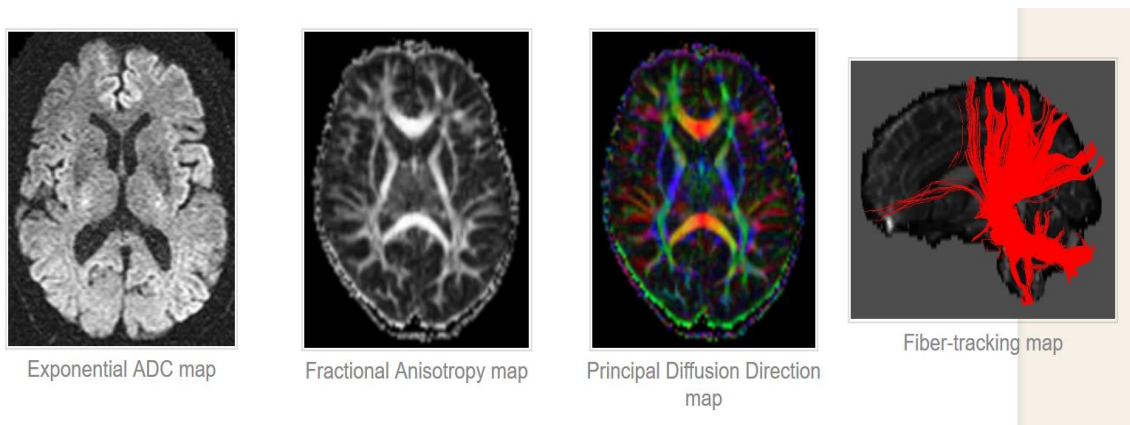acquisition methods such as Single-Shot Echo Planar Imaging and limitations of general acquisition parameters such as field of view (FOV) slice thickness etc. Lower strength scanners contribute weaker signals to the image co pared to high-resistance scanners and thus provide lower resolution than low-resistance scanners. Fast acquisition methods such as SS-EPI focus on image acquisition in a very short time before the complete decline of the signal and thus limit the maximum achievable resolution of DW images. Also related to spatial resolution are general MR acquisition parameters such as FOV, slice thickness, matrix size etc... Increasing FOV but maintaining the same matrix size would reduce image resolution (in-plan spatial image resolution can be calculated by dividing FOV with matrix size) and increase matrix size if FOV remains constant would increase in-plan resolution. In general, the resolution along the direction of the slice (through-plane) is lower than the direction of the image (in-plan). The maximum resolution that can be achieved by optimizing these parameters is therefore constrained by the scanner's hardware limitations. In radiotherapy planning, low resolution can be a challenge since DW images are used in conjunction with T2-weighted images along with ADC maps, which are typically of higher resolution. Despite the disparity between the respective resolutions, if ADC and T2WI were to be superimposed due to ADC / DWI's low resolution, it would overestimate the area of the lesion because of its lower resolution. And in general, images with higher resolution are preferred because compared to images with lower resolution; they offer more data and precise details.

DW images also suffer from low SNR due to the presence of large amounts of noise, in addition to the low resolution. Image contrast is also a crucial issue, since higher contrast is very beneficial in precisely delineating regions of abnormality using diffusion coefficient values from ADC maps. Lower SNR and contrast-to-noise-ratio (CNR) will restrict the capability of accurate interpretation of ADC maps and DW images.

Artifacts

DW images are often susceptible to a variety of artifacts such as distortion, ringing, etc. that arise from a host of factors. Distortion is one of the biggest artifacts in DW images. Distortion of the images may occur due to field inhomogeneity and magnetic susceptibility variations in the area being imaged.

In the early 2000s, widely used 3 T scanners were introduced and quickly adapted by their ability to attain higher spatial resolution, higher SNR, and better contrast than 1.5 T machines. However, increased field strength in the image contributed to higher artifacts related to magnetic susceptibility. The magnetic field B1, in which the patient is placed, becomes more inhomogeneous as the field strength increases, thus contributing to more errors in image acquisition. Sequences like EPI require very homogeneous magnetic fields to ensure that the spins of the proton adhere to the spin rate and do not dephase, thus ensuring accuracy of the signal. However, in some instances, such as at air-tissue interfaces, protons at the interface undergo phase change that is different from the expected due to variations in magnetic susceptibility resulting in geometric distortion of the image. **Figure 14A** shows an image weighted by T2, and **Figure 14B** shows a phantom's corresponding DW image. In the DW image**, Figure 14B**, the phantom is put in the air and scanned because of the distortion occurring around the edges with air-interfacing.
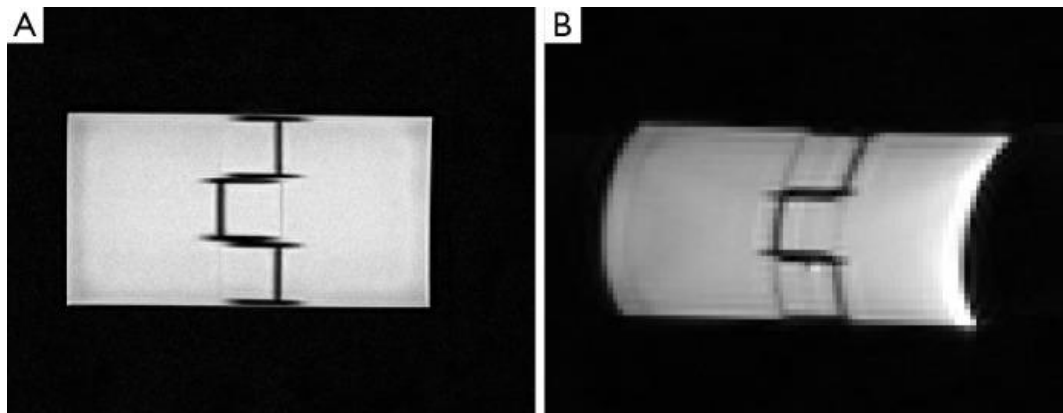

Figure14: Comparison between DW image and traditional MR image

This distortion can also be observed when imaging is done in metal implant tissues, due to region-wide field variation. The gradient system may also cause artifacts related to this susceptibility which could introduce magnetic field inhomogeneity. Strong and rapidly switching gradients because local currents, called eddy currents, which in effect create their own local magnetic fields and thus disrupt homogeneity in the field. Such eddy currents help to distort and shift images by manipulating the gradient strengths encountered by spins, which affect accurate interpretation of the image and ADC estimation and clinical diagnosis thereby. Other artifacts such as ghosting can also be a result from eddy currents.

Apart from distortion, sequences of EPIs are sensitive to motion, whether microscopic or macroscopic, resulting from different factors. Macroscopic motion results in severe motion-related artifacts causing the DW image to ghost or blur. This could

greatly affect the measurements of diffusion for DW imaging, and could render incorrect data. Although precautions can be taken to minimize the voluntary movement of patients, involuntary movements such as breathing, blood flow or mechanical vibrations resulting from the scanner's patient table remain unavoidable.

Technological advancement in addressing the challenges

DW images often have lower image quality compared to other traditional MR images due to problems with image quality such as distortion, noise, poor resolution and the presence of artifacts, most of which result from the use of faster image acquisition techniques such as EPI, necessary to capture the diffusion signal until it becomes null.

Most of these problems can be solved by altering DW-MR protocol variables such as echo time (TE), gradient strengths, adjusting techniques for image acquisition etc. Broadly speaking, the approaches to address the inherent challenges associated with DWI fall into four categories: hardware upgrades or enhancements, use of contrast agents, optimizing acquisition parameters, and post-processing techniques based on software. None of these approaches address all of the challenges individually, as they may present their own challenges such as increased acquisition time, etc.

Challenge	Some common approaches to address challenges
Low resolution	Hardware improvements
	Increasing field strength of scanners
	Multi-shot sequences
	Post-processing
	Interpolation techniques; super-resolution reconstruction
SNR	Hardware improvements
	Increasing field strength of scanners; High strength gradients
	Multi-shot sequences
	Acquisition parameters

	Averaging
Contrast Acquisition time	Contrast agents
	Hardware improvements
	Increasing field strength of scanners; high strength gradients
	Single-shot sequences
	Parallel imaging
	Acquisition parameters
	Optimal TR, TE, number of b-values
Distortion from susceptibility differences and eddy currents	Hardware improvements
	Increasing field strength of scanners; high strength gradients; shimming coils
	Non-EPI based sequences
	Calibration scans and pre-emphasized pulses
	Acquisition parameters
	Increasing receiver bandwidth or decreasing peak gradient amplitudes
	Post-processing
	Acquiring field maps and correction algorithms
Motion artifacts	Hardware improvements
	Single-shot EPI; Non-EPI based sequences;
	Cardiac and Respiratory triggering or bi-polar gradient pulses Navigator based and readout-segmented acquisition methods
	Acquisition parameters
	Averaging
ADC accuracy	Acquisition parameters
	Optimal number of b-values

	Diffusion modelling in tissue
	Post-processing

Table1: Challenges of DWI and some approaches to address these challenges

Conclusion

References