Title
Rapid Magnetization Prepared Diffusion Weighted Imaging of Articular Cartilage in vivo

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"Rapid Magnetization Prepared Diffusion Weighted Imaging of Articular Cartilage *in vivo*"

by

ADITI GUHA

THESIS

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of

MASTER OF SCIENCE

in

[redacted]

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Abstract

Diffusion Imaging has been primarily focused on brain application with limited applications in the knee. One limitation of diffusion imaging in the knee is the long TE (40-60 ms) in most of the sequences that have been used. While this is not a detriment in brain, it can be a problem in the knee where several tissues have short T2 relaxation times including the cartilage (32 ms) and meniscus (11 ms). Thus imaging of the knee with a short TE diffusion sequence would substantially increase signal to noise, which would in turn be applied to improve diffusion measurements in meniscus and cartilage. Research has shown that diffusion weighted imaging in knee has a strong potential as a biomarker and can act as a new and potent investigation tool for tissue integrity of meniscus and for early diagnosis of cartilage degeneration.

A new sequence for diffusion weighted imaging of knee at 3T has been proposed and evaluated. The proposed stimulated echo with MAPSS acquisition sequence is more signal efficient than the conventional spin echo sequence and can image the whole knee volume in half the acquisition time compared to the most commonly used line scan sequence. The sequence was tested in phantoms, ex-vivo specimens and in-vivo knees with encouraging results. Further optimization and validation of the sequence is proposed for successful acquisition of diffusion values in knee cartilage and meniscus in healthy volunteers and osteoarthritis patient cohorts.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Diffusion, also known as “Brownian motion”, is the random microscopic movement of molecules. It is an important phenomenon by which cells and tissues get important nutrients for growth and survival. In the clinical setting, the type of diffusion being measured is the self-diffusion of water within tissue. Diffusion of water is not entirely random in the body since tissue has microstructure (membranes and organelles) that can restrict diffusion. Thus diffusion in tissue is referred to as “apparent” diffusion. MRI data acquisition techniques that exploit tissue diffusion properties are collectively called diffusion weighted imaging (DWI) sequences. The extent of molecular diffusion is determined by the microscopic tissue structure and can be a powerful biomarker for various pathological and structural changes in the tissue (Figure 1). Previous studies have shown that subtle changes in tissue microstructure correlate with changes in the restricted diffusion of water, which manifest in the signal changes on diffusion weighted MR images (1, 2, 3).

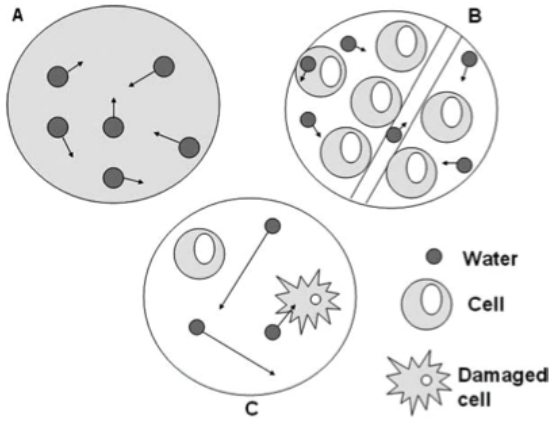


Figure 1: Schematic showing diffusion: in A, water molecules move randomly (Brownian motion). In B, normal cellular structures restrict the movement of water molecules. In C, damaged cellular structure results in greater water movement compared to normal cell (Figure courtesy: 4)

This dynamic diffusion process in cells provides insight into the tissue integrity and structure and DWI has been demonstrated to be a highly sensitive tool for showing pathological changes in the tissue. Diffusion Weighted Imaging (DWI) has become an established tool in neurology, where it has demonstrated sensitivity in brain ischemia even the hyper acute state and is considered the most important clinical application of DWI (5, 6, 7). The brain is well suited to DWI application due to its homogenous composition and minimal motion artifacts compared to other parts in the human body (8). Over the last decade or so, DWI has been used in imaging liver (9), kidneys (10), breast (11), prostate (12), lymph nodes (13) and in soft tissue and vertebral compression tumors (14). Research has also shown that DWI has a strong potential for diagnosing early cartilage and meniscus damage and has clinical implications for joint disorders such as osteoarthritis (3, 15, 16, 17). Osteoarthritis (OA) is a common degenerative joint disorder, which occurs due to aging and wear and tear of the joint especially the protective cartilage (Figure 2). There is currently no effective treatment available to induce new cartilage growth; however, early detection of cartilage damage can help improve quality of life of patients.

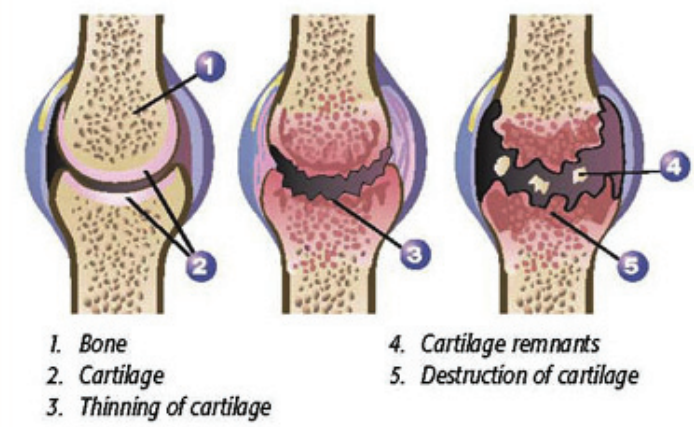


Figure 2: Schematic showing evolution of osteoarthritis. (Figure courtesy: 18)

A diffusion-weighted sequence was first described by Stejskal and Tanner in 1965, in which they introduced an additional pair of diffusion gradient pulses (now called the Stejskal-Tanner diffusion gradients) in a normal spin echo sequence to quantify diffusion (5). Theoretically, the diffusion-weighted gradients can be incorporated into any pulse sequence and this technique or its modified form is still used presently in the majority of the diffusion-weighted sequences.

All diffusion-weighted sequences use two diffusion gradients to provide "diffusion weighting" and signal is measured with and without the diffusion gradient applied. Molecular motion due to diffusion results in loss of signal intensity due to incomplete dephasing of spins that change location between the application of the two gradients. This signal attenuation which, is the measure of molecular diffusion is measured as

$$S = S_0 e^{-bD} \quad \text{(i)}$$

Where, S and S_0 is the signal with and without diffusion weighting, b is the "b-value" that controls the diffusion weighting in the sequence and is determined by the sequence parameters; measured in sec/mm^2. D is the apparent diffusion coefficient (ADC), which quantifies the average mobility of water molecules, expressed in mm^2/sec. Higher ADC values relate to higher diffusion and lower signal intensity in the image while b is the b-value that controls the degree of diffusion weighting in the image and is determined by the sequence parameters. It is expressed in reciprocal units of ADC, i.e., sec/mm^2. Increasing b-value increases the degree of diffusion weighting in an image. Thus to obtain optimal signal in a diffusion weighted image, the optimal b and ADC value and their relationship between the various sub-parameters should be taken into account.

Currently most MR DWI sequences for knee OA use spin-echo preparation with a single shot echo-planar imaging readout (Figure 3). However, in the presence of B0 inhomogeneities and susceptibility variations, the single shot echo-planar imaging sequence suffers from geometrical distortions due to its long echo train. Also, the long TE values of the sequence can result in low SNR in short T2 tissues such as cartilage and meniscus. A multi shot echo planar sequence may be used instead of a single shot sequence, in which the long echo train can be broken up into small parts. This may result in an increase in resolution and a reduction in geometric artifacts, but on the flip side it is more prone to motion artifacts as there is a greater likelihood of patient motion as a result of increased total acquisition time. Another

proposed method for quantification of molecular diffusion is steady state free precession (SSFP), which allows for relatively high quality images with good signal to noise ratio and an acquisition time comparable to the single shot spin echo sequence. However, due to complicated signal generation and natural T1 and T2 decay dependencies, accurate ADC values cannot be quantified (8, 16, 17, 18, 20, 21, 22, 23). Additionally, sequences with multiple TR periods are susceptible to phase errors since each TR period has a different phase. A modification to the SSFP sequence has been suggested recently called double echo steady state (DESS) sequence where a simultaneous estimation of T2 and ADC value has been proposed. However, the images obtained by this method are of low SNR and the diffusion quantification might be contaminated due to variation in imaging parameters, which affect the T2 and ADC estimates. To improve the estimates, a second modified DESS acquisition is needed resulting in increased acquisition times (24).

Other diffusion acquisition sequences, like line-scan imaging technique proposed by Gudbjartsson et al in 1996 have been used in which only one-dimensional lines of the images volume are excited instead of the whole two dimensional volume (25). Raya et al used the line scan acquisition sequence recently to measure the ADC and Fractional Anisotropy (FA) values in histological samples of degenerated and healthy cartilage and showed a difference in diffusion values in cartilage after degeneration. The ADC value indicates the mean displacement of water molecules and FA value show the degree of anisotropy or how restricted the diffusion is. Additionally, Raya et al used the same sequence on a large cohort of healthy

volunteers and OA patients in vivo at 7T. The results show a significant difference between healthy volunteers and patients for both ADC and FA values. However, the line scan technique is very time inefficient, yields images with low SNR and the technique is not available on most MRI systems (2, 15, 25).

In the past, researchers have proposed new sequences for diffusion imaging of knee but these studies have largely been proof of concept and have not typically been followed up by *in-vivo* imaging for large cohorts, especially at 3T. They also generally suffered from low SNR and poor scan coverage in the knee. Thus, there is a strong motivation for a sequence with lower TE, which will substantially improve signal from short T2 tissues like cartilage and meniscus. Replacing the Spin Echo (SE) preparation with a stimulated echo (STE) preparation can solve many problems of the spin echo EPI sequence and produce relatively high SNR in short T2 tissues (27, 28,29,30).

Typical Stimulated Echo sequence: The normal stimulated echo sequence consists of three pulses (typically 90° pulses). Diffusion gradients are applied after the first and third pulse RF pulse. The first 90° pulse flips the spins from longitudinal (z axis) to the transverse (x-y) plane. The second pulse flips the spins back along the longitudinal axis but in the opposite direction compared to the first pulse. Between the end of the second and beginning of the third pulse a "mixing time (T_{mix})" is allowed. It helps to compensate for the shorter TE and the shorter diffusion gradient time used in the STE preparation compared to SE sequence, which increases the diffusion weighting without increasing the diffusion gradient duration and TE

(Figure 4). The stimulated echo occurs at a time delay after the third pulse equal to the time interval between the first two pulses. The first two pulses are separated by a time delay TE/2. After the same delay TE/2 following the third pulse, a stimulated echo is produced. This type of scheme is beneficial because it does not experience T2 or T2* dephasing during the mixing time (T_{mix}) since the magnetization of the stimulated echo is stored in the longitudinal plane between the second and third RF pulses (28, 29).

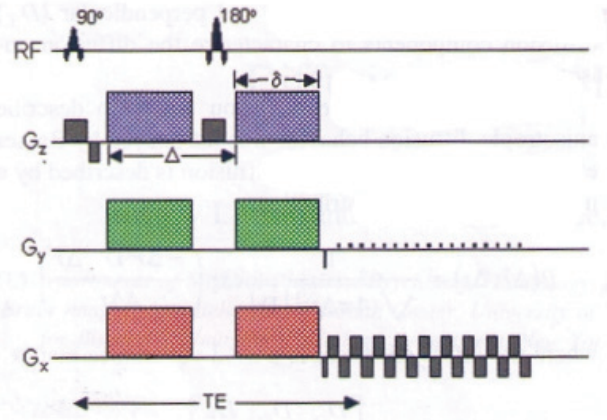


Figure 3: Schematic of a Diffusion Weighted spin echo EPI MR sequence. (Figure courtesy: 26)

Relaxation dependent signal losses are lower in the T_{mix} interval (which is T1 sensitive) compared to that in TE (T2 sensitive) (20,27,28) for tissue with short T2 and long T1 relaxation times, like cartilage and meniscus. Thus, STE preparation can actually provide improved SNR images for diffusion measurement in those tissues. However, the type of acquisition done with a typical STE sequence is EPI, which

again increases the total TE time due to long acquisition period and yields images with geometric distortions.

Therefore the development of an STE prepared diffusion sequence with MAPSS (Magnetization Prepared Angle Modulated Partitioned K-Space SPGR) acquisition, which allows for efficient k-space acquisition is proposed in this research for use in early detection of knee cartilage and meniscus damage.

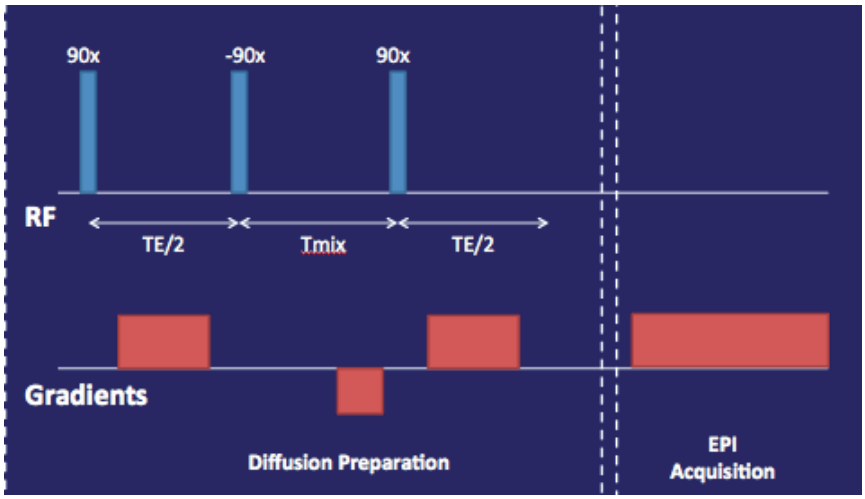


Figure 4: Schematic showing typical stimulated echo sequence

MATERIALS AND METHODS

Proposed Stimulated Echo sequence:

The proposed STE sequence consists of two parts: magnetization preparation imparting the diffusion weighting and a segmented 3D SPGR sequence for image acquisition. The stimulated echo (STE) diffusion preparation used in this research has four 90°("non selective" or hard) RF pulses which are shorter and can reduce TE time. However, the spatially selective pulses of the MAPSS acquisition sequence negate the whole volume excitation by the hard pulses. The fourth pulse also flips the spins back to their original position, thus preparing them for the segmented SPGR acquisition. The residual transverse magnetization is crushed using spoilers and the accumulated longitudinal magnetization is read out immediately using a train of 3D SPGR readouts (Figure 5) (28, 29, 30).

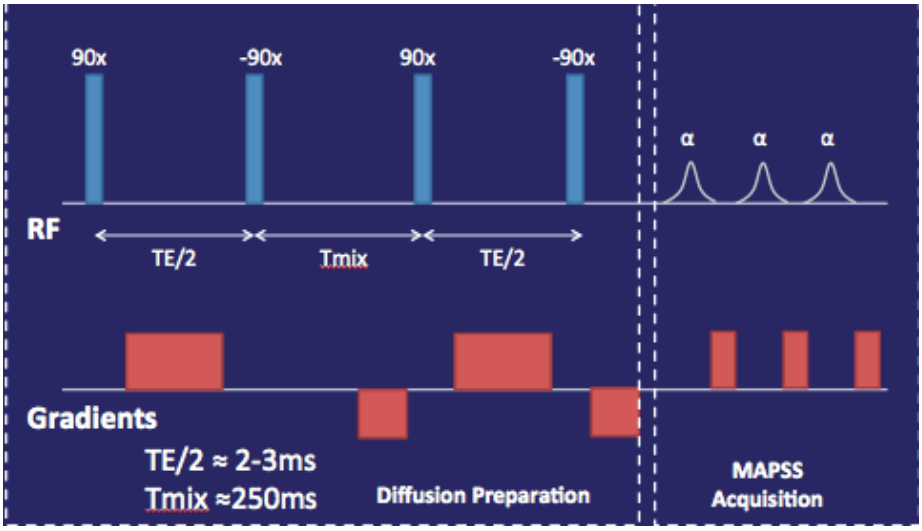


Figure 5: Schematic showing proposed stimulated echo sequence

The image is acquired using a magnetization prepared angle modulated partitioned k-space acquisition (MAPSS) where the k-space is traversed in a segmented and interleaved elliptic centric order. The acquisition starts from the center of k-space, where the overall image contrast and low frequency signal is present. A variable flip angle train is utilized during the acquisition sequence (with the maximum flip angle restricted to 90°) which is an effective way to limit signal intensity variations produced when using a train of RF pulses (31). After each acquisition, a set of magnetization reset pulses are applied to destroy all transverse magnetization. A delay equal to the T1 of cartilage is applied between each preparation and acquisition segment to allow the T1 relaxation to occur. The magnetization reset and T1 recovery time allow for consistent amount of magnetization to be present for each preparation.

I. Optimization of the Diffusion Preparation:

B-value, ADC and variable Parameters:

The b value of the STE diffusion sequence depends on a number of variable parameters including: G (strength of the diffusion gradient), d (duration of the diffusion gradient) and Δ (the total diffusion time). The total diffusion time is the sum of a number of factors including d, r (ramp times: ascent and descent of the diffusion gradients), T_{mix} (mixing time) and RF pulse time (27). Since the maximum signal for a given T1 and T2 is obtained from a particular b value and specific dependent parameter values, it is important to optimize them for getting the best signal.

For a stimulated echo sequence the b value is given as:

$$\boldsymbol{b = \gamma^2 G^2 d^2 \left[\Delta - \frac{d}{3}\right] - \left[\frac{1}{6} r^2 d\right] + \frac{r^3}{30}} \quad \text{(ii)}$$

Where, G is the maximum possible diffusion gradient amplitude of most MR systems is $4x10^{-5}$ T/mm and γ is the gyromagnetic ratio = $2.75x10^8$ $sec^{-1}T^{-1}$

The total diffusion time **(**Δ) is given by

$$\Delta = \boldsymbol{T_{mix} + d + 2r + width\ of\ 90°pulse} \quad \text{(iii)}$$

To observe the dependence of b values and to optimize the sequence parameters Matlab simulations were done by varying the T_{mix}, r (ramp time), d (diffusion gradient duration), total diffusion time, T1 and T2 values and the optimal values for the sequence were obtained.

II. Stimulated vs. Spin Echo Diffusion Preparation signal:

The signal for the stimulated echo sequence is given by:

$$\boldsymbol{Signal_{ste} = 0.5 * S_0 * e^{-\frac{TE_{ste}}{T2}} * e^{-\frac{Tmix}{T1}} * e^{-bD}} \quad \text{(iv)}$$

Where, D is the apparent diffusion coefficient, TE_{ste} is the stimulated echo TE, T_{mix} is the mixing time and b is the b-value. However, for a given optimized b-value for a certain pair of TE_ste and T_{mix} and given T1 and T2 values, the maximum signal as calculated by using the method of Lagrange multipliers is given by the following equation:

$$\frac{T1}{T2} = \frac{\Delta}{d} \quad \text{(v)}$$

The parameters considered for signal calculation were T1 = 900 ms and 1200ms, T2 = 11ms and 32ms (for meniscus and cartilage respectively). The signal was plotted

for different b-value by varying the diffusion gradient duration time, which in turn varied the TE_SE and TE_STE time. ADC values used were $1.4x10^{-3}$ mm^2/sec and $1.6x10^{-3}$ mm^2/sec for meniscus and cartilage respectively and maximum gradient amplitude of 40 mT/m was considered.

III. Determination of Optimal Diffusion Gradient Duration and Mixing Time:

Using Matlab simulations the proposed optimal b-value and the equation (iv) for maximum signal were determined and validated for different values of T1 and T2, total time (Δ), and diffusion gradient duration time (d).

IV. Monte Carlo Analysis and Optimization of Noise of Diffusion Measurement:

Monte Carlo analyses using Matlab were done to assess the validity and precision of the calculated optimal b value. The simulations were performed with b values between 100-2000 sec/mm^2 in 20 sec/mm^2 increments, ADC $=1.4x10^{-3}$ and 1.6 mm^2/sec, T1 = 900 and 1200 ms, T2 = 11 and 32 ms (for meniscus and cartilage respectively), d = 3.2 ms and the M_0 SNR was taken as 1/0.005 (200), 1/0.05 (20), 1/0.03(33.33) and 1/0.0435 (23). 10,000 iterations with independent noise were done. The reverse relationship of ADC value with b-value was also validated.

V. Flip Angle Optimization for the MAPSS acquisition:

The variable flip angle train of the MAPSS acquisition was optimized to work with our proposed stimulated echo sequence. Initially the equation being used for

generating the flip angle train was based on the following formula stated in equation (vi).

$$M0 = (1 - e\left(-\frac{T1recovery}{T1(tissue\ index)}\right)) \quad \text{(vi)}$$

where, M0 is the magnetization present just before the 3D segmented SPGR.

For optimization of the flip train for the proposed stimulated echo sequence, the formula stated in equation (vii) was used.

$$M0 = e\left(-\frac{16}{T2(tissue\ index)}\right) * (1 - e\left(-\frac{T1recovery}{T1(tissue\ index)}\right)) \quad \text{(vii)}$$

where, M0 is the magnetization present after the fourth 90° pulse just before the acquisition.

VI. Phantom measurements:

Agarose phantoms with varying concentrations of agarose (0%, 2%, 2.5%, 4%, 4.5% and 5% in distilled water) were placed inside a head coil in a 7 Tesla GE scanner. B-values and signal were calculated according to the equation (ii) and (iii) mentioned above. A series of images were acquired using the proposed STE sequence by varying diffusion gradient times (from 2ms to 3 or 4ms) or T_{mix} (from 250 ms to 150, 75 or 350ms) or both thus giving multiple b-values (Figure 6a). The linear relationship between the b-values and diffusion gradient duration (d), total time (Δ) and signal were also validated as seen from the table and plots below. The sequence parameters were consistent with knee imaging and included: image matrix was 256x128, field of view=16 cm, receiver bandwidth=62.50kHz, and slice thickness= 3mm. Other sequence parameters were maximum gradient amplitude = $4x10^{-5}$

T/mm, TE ~ 12-15 ms, T_{mix} =250 ms, ramp time =1.068ms, views per segment were 48 and number of slices was 20.

VII. Ex-vivo measurements:

Ex-vivo measurements were done using excised young pig knee. Knees were kept refrigerated and were less than one week old at the time of imaging. A series of images were acquired by varying number of directions, field of view, number of slices, slice thickness and crusher width on a 3T GE scanner located at the Orthopedic Institute at UCSF. The scan parameters were: image matrix = 512x320, field of view = 16 cm, slice thickness = 3mm, bandwidth = 62.5 KHz, crusher duration = 5000-2000μs, number of directions = 12, number of slices = 22-30, diffusion gradient duration = 4ms, diffusion time = 150ms and scan time =12mins.

VIII. In-Vivo measurements:

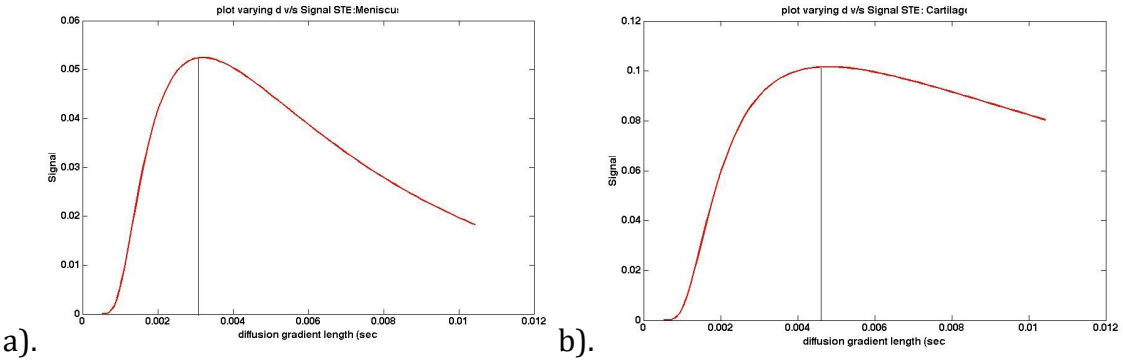
Healthy volunteers were scanned consistently while optimizing the sequence on a 3T scanner at both QB3 and Orthopedic institute at UCSF. The sequence parameters were varied for best image quality. The scan parameters were: image matrix = 256x128, field of view = 14cm, bandwidth = 62.5 KHz, slice thickness = 4mm, number of slices = 22, number of directions = 12, crusher duration = 15000μs, diffusion gradient duration = 4ms, diffusion time = 150ms and scan time =12 mins.

RESULTS AND DISCUSSION

I. Optimization of the Diffusion Preparation:

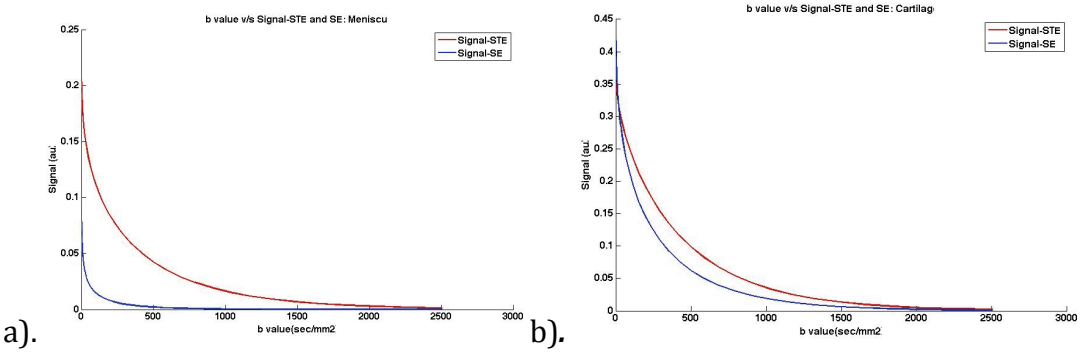
B-value, ADC and variable Parameters:

The optimal b-value for the STE preparation was calculated by varying d and total time (Δ), T1 and T2 values (maximum gradient strength applicable was considered for all calculations). The optimal b-value was calculated to be 504.8 sec/mm^2, while the optimal diffusion gradient duration was 3.2 ms and 4.2 ms for meniscus and cartilage respectively (Figure 6).



a). b).

Figure 6: Plot showing diffusion gradient duration (d) with signal for a). Meniscus and b). Cartilage.



a). b).

Figure 7: Plot showing signal comparison between proposed STE (red line) and SE (blue line) sequences for a). Meniscus and b). Cartilage

II. Stimulated vs. Spin Echo Diffusion Preparation Signal:

Using equation (iv), the anticipated maximum signal was calculated. The value of S_0, which is the initial signal without the stimulated echo preparation, was set to unity. One of the major reasons for proposing the stimulated echo preparation sequence is its signal efficiency over the conventional spin echo sequence especially at lower b-values as seen in Figure 7. For instance, at an optimal b-value of ~500 sec/mm^2, the proposed stimulated sequence signal (0.984 and 0.1161) is 1.5 and 20 times the conventional spin echo signal (0.622 and 0.0762) for cartilage and meniscus respectively. In general, for these parameters, the signal from STE preparation exceeds the signal from SE sequence for b-values higher than 140-150 sec/mm^2.

III. Determination of Optimal Diffusion Gradient Duration and Mixing Time:

Figure 8 shows plots showing maximum signal at the proposed d value of ~3.2 ms and 4.2 ms with varying T2 value keeping T1 constant (900ms and 1200 ms) for meniscus and cartilage. A slight expected shift (shown with an arrow) towards higher d values is seen with increasing T2 values. Figure 9 shows decreasing signal with increasing b-value and an expected slight shift toward higher d value (shown with an arrow) both for meniscus and cartilage; thus validating the expected relationships between the diffusion parameters.

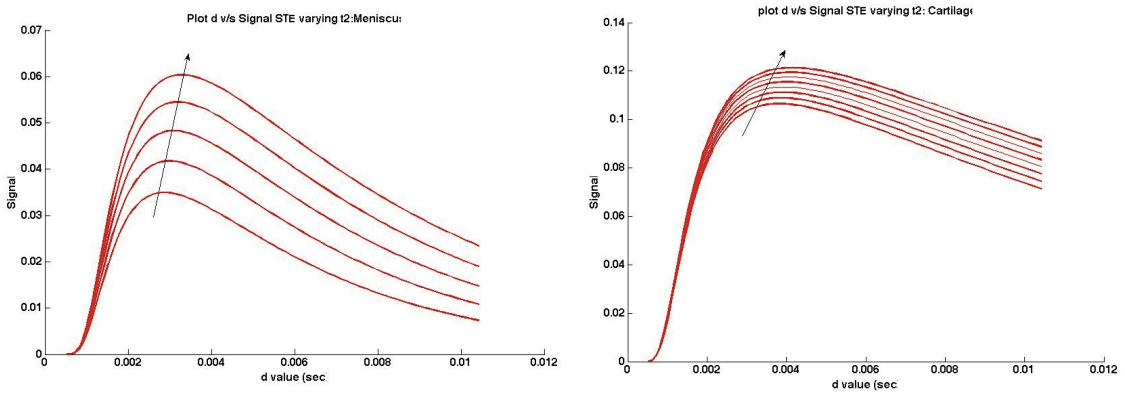


Figure 8: Plot showing maximum signal at the proposed d value with varying T2 value keeping T1 constant for meniscus (left) and cartilage (right)

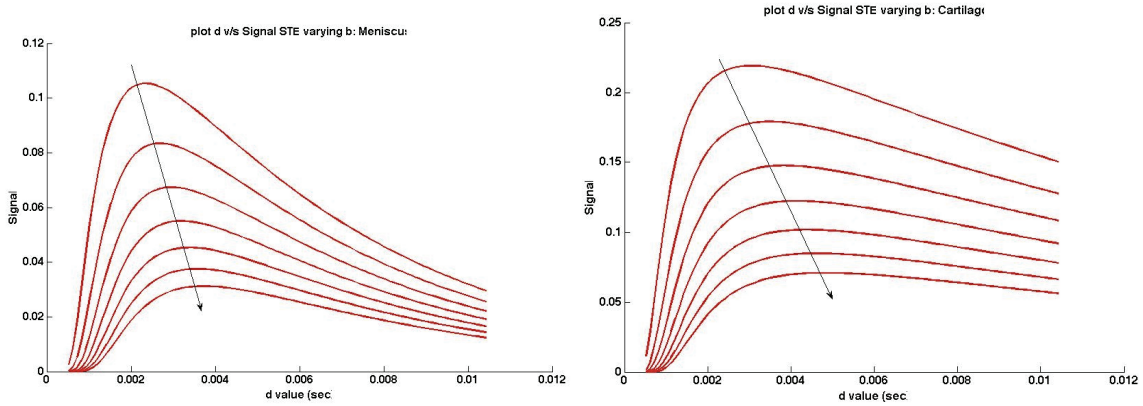


Figure 9: Plot showing decreasing signal with increasing b-value for meniscus (left) and cartilage (right)

IV. Monte Carlo analysis and optimization of noise of diffusion measurements:

The Monte Carlo simulation for optimization of b-value and Mixing time (T_{mix}) is shown in Figure 10 and 11. Based on Figure 10, the optimal b-value at which minimum noise of ADC measurement occurs (shown by arrow) appears to be between 500 to 550 sec/mm^2, which falls well within the proposed optimal b value and will result in a best fit for diffusion for both meniscus and cartilage. This wide area of high signal and low noise will allow for accurate measurement for a range of

scan parameters. This optimization analysis also validates the proposed optimal b-value and mixing time value for both cartilage and meniscus.

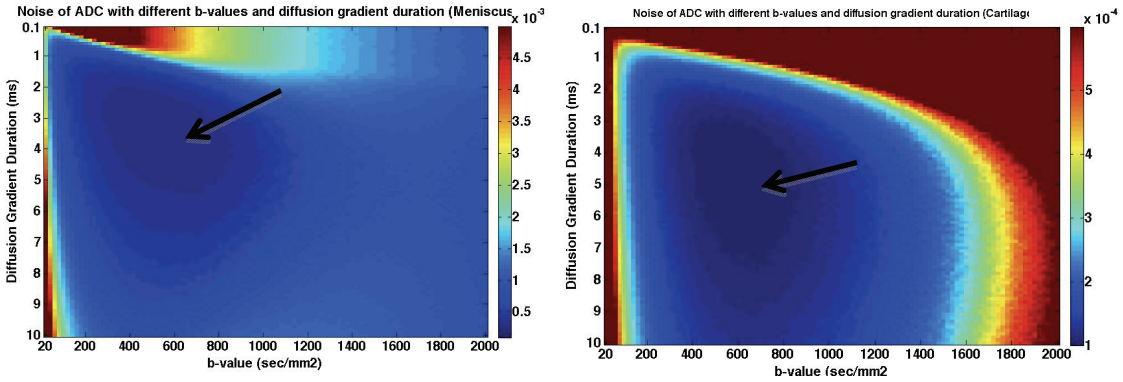


Figure 10: 2D colormap showing the noise of ADC measurement with different b-values plotted against the diffusion gradient duration (d) for meniscus and cartilage. The color bar (right) shows spectrum used in color-coding to represent probability for highest signal, from lowest indicated by red to highest, which is indicated by blue.

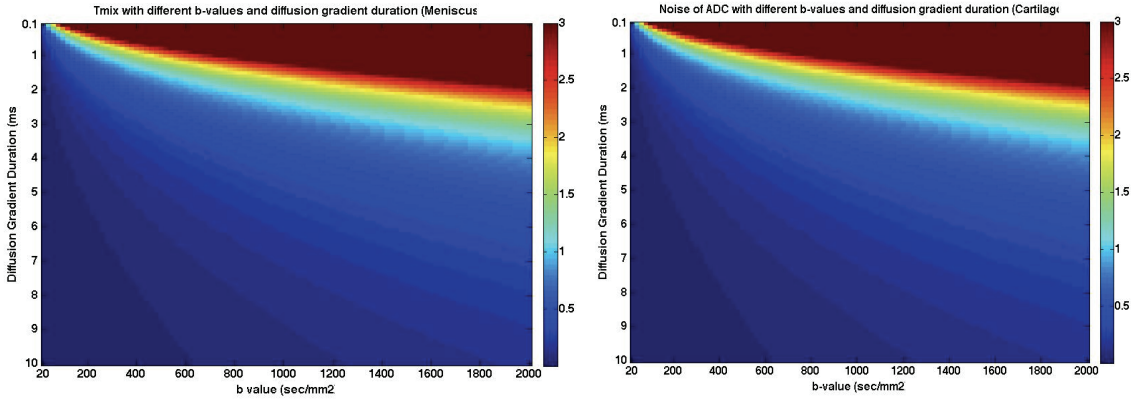


Figure 11: 2D colormap showing the T_{mix} (mixing time) with different b-values plotted against the diffusion gradient duration (d) for meniscus and cartilage. The color bar (right) shows spectrum used in color-coding to represent probability for highest signal, from lowest indicated by red to highest, which is indicated by blue.

V. Flip Angle optimization for MAPSS:

Figure 12 shows the images obtained using un-optimized and optimized flip angle train. Initially the un-optimized flip angle train leads to large signal intensity variations, resulting in filtering effects, which manifested themselves as artifacts in the image (shown by arrow). But with the flip angle train optimized and the signal intensity constant, the image quality improved.

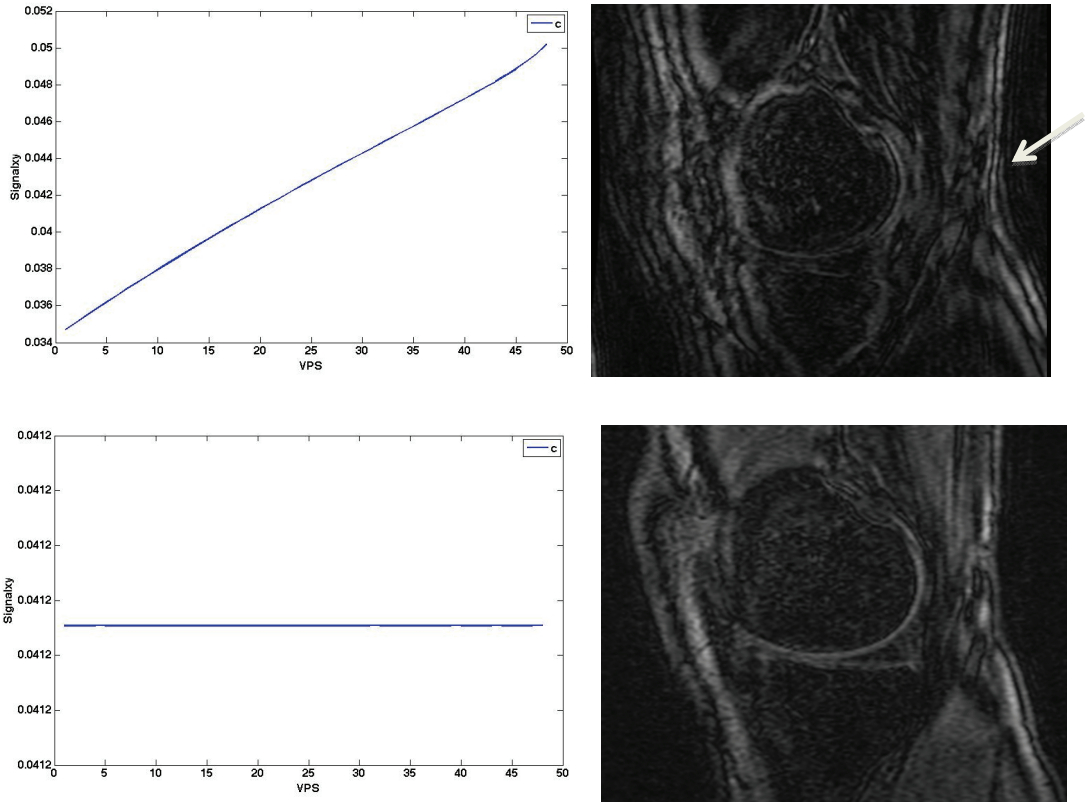
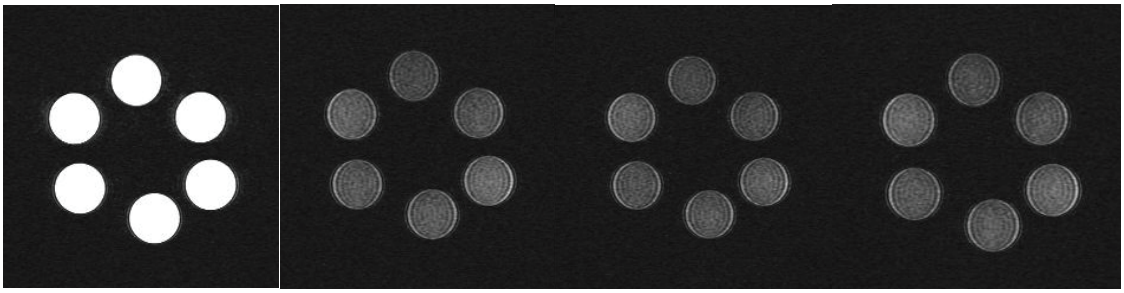


Figure 12: Signal intensity graph and the corresponding image obtained using un-optimized flip train (top) and optimized flip train (bottom)

V. Phantom measurements:

The phantom images obtained using proposed sequence and the natural log of the mean signal in each of the diffusion weighted images is plotted against the respective b-value in Figure 13a and b. The mean signal was the geometric mean of three diffusion weighted images taken to remove the orientation dependence. A linear fit between ln (S2/S1) and the corresponding b-values is plotted. The linear regression yields apparent diffusion coefficient (ADC) value, which in this case is 1.6 mm^2/sec, close to the expected value of 1.8-2 mm^2/sec (Figure 13b) (33). The linearity of the values (R^2 = 0.99028) suggests that proper scaling of the diffusion weighting is present in this sequence.

a).



b).

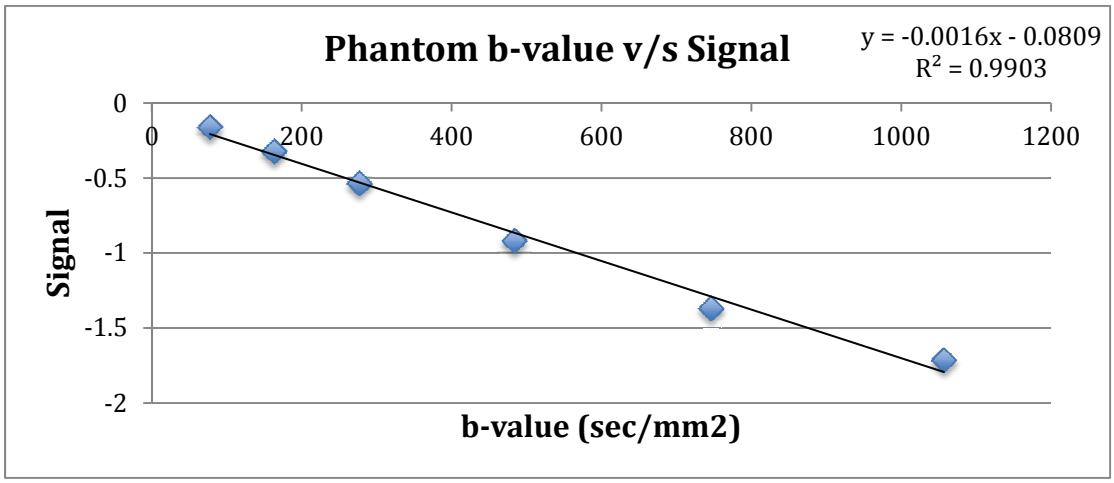


Figure 13 a): Phantom images from left to right: B0 image and 3 corresponding images in 3 directions. b). Plot showing the inverse relationship between b-value and signal as validated in phantom measurements

VI. Ex-vivo Images:

Figure 14-15 shows the *ex-vivo* pig knee images with the ADC and FA colormap overlaid. The mean ADC and FA values obtained are shown in Table 1. The ADC values may be lower than *in-vivo* pig knee values, due to the low temperature of the excised knee at the time of scanning. More importantly, the ADC values obtained validate the diffusion gradient that exists in the cartilage starting from high ADC and low FA values in the superficial layer near the articular surface due to loosely connected collagen fibers facilitating diffusion compared to low ADC and high FA values in the deep zone near the subchondral bone where neatly stacked collagen fibers allow only restricted diffusion to take place (Figure 16) .

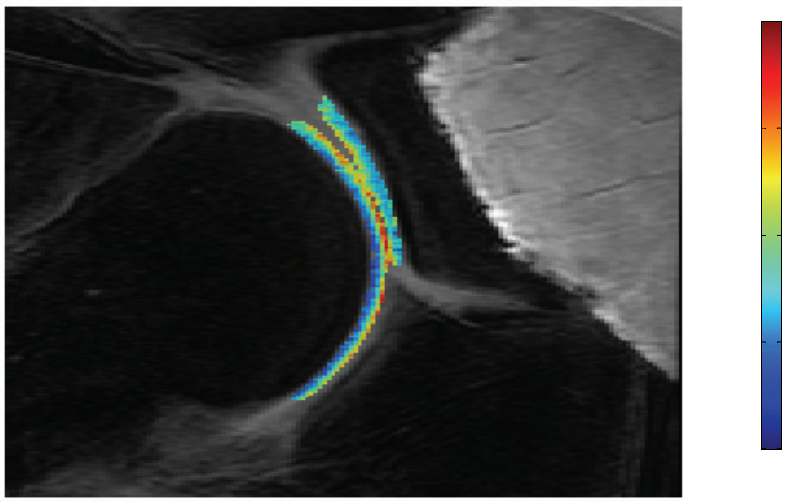


Figure 14: *Ex-vivo* pig knee images obtained using proposed sequence with ADC colormap overlaid.

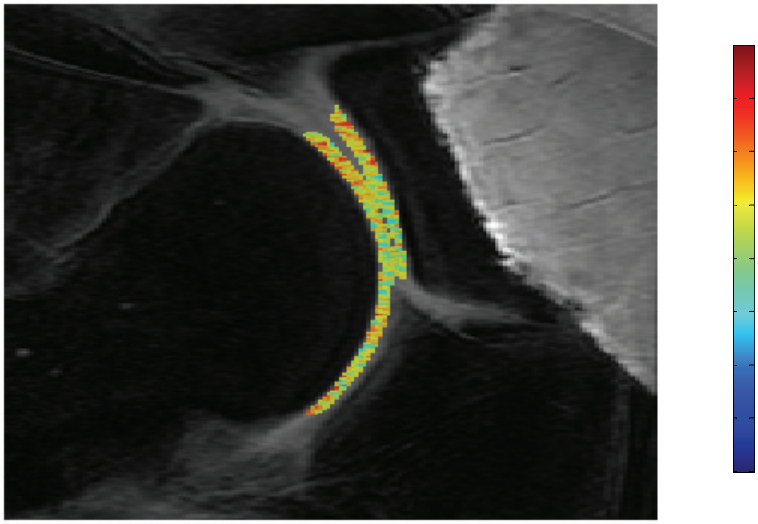


Figure 15: *Ex-vivo* pig knee images obtained using proposed sequence with FA colormap overlaid.

	Mean Diffusivity (ADC) value		FA value	
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**
Trochlea	1.33	0.31	0.48	0.08
Patella	1.33	0.21	0.47	0.08

Table 1: Table showing the mean and standard deviation values of *ex-vivo* pig knee images obtained using proposed sequence.

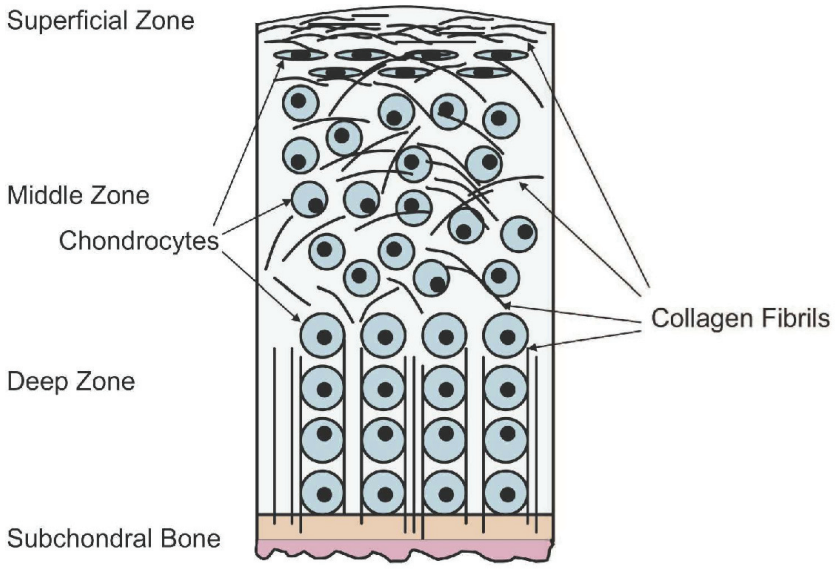


Figure 16: Schematic showing the layered cartilage structure leading to a diffusion gradient from superficial to the deep zone. (Figure courtesy: 32)

VII. In-vivo Images:

Figures 17-20 show the lateral and medial images obtained from a healthy volunteer with ADC and FA colormap overlaid using the proposed sequence. The ADC and FA values are elevated overall compared to literature (Table 2) (2, 15). There are a number of factors that could contribute to the differences between our measured values and those published in the literature. The fact that that this study is first of its kind on a 3T GE scanner and the published values were calculated with images obtained using a 7T Siemens scanner might be a factor (15). Another reason might be the presence of fluid, phase errors due to volunteer motion. Since these images are preliminary, further optimization of the sequence might help understand the elevated values and get ADC and FA values within the expected range.

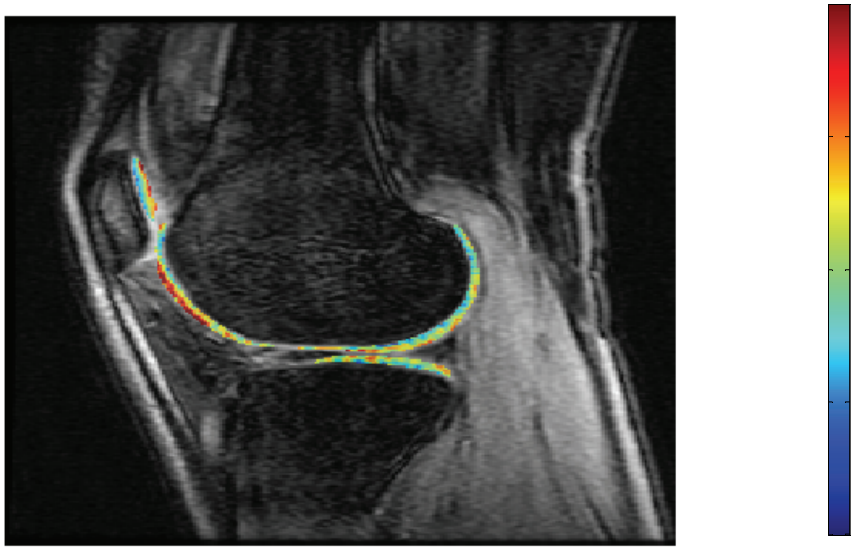


Figure 17: Lateral *in-vivo* image of a healthy volunteer knee with ADC colormap overlaid.

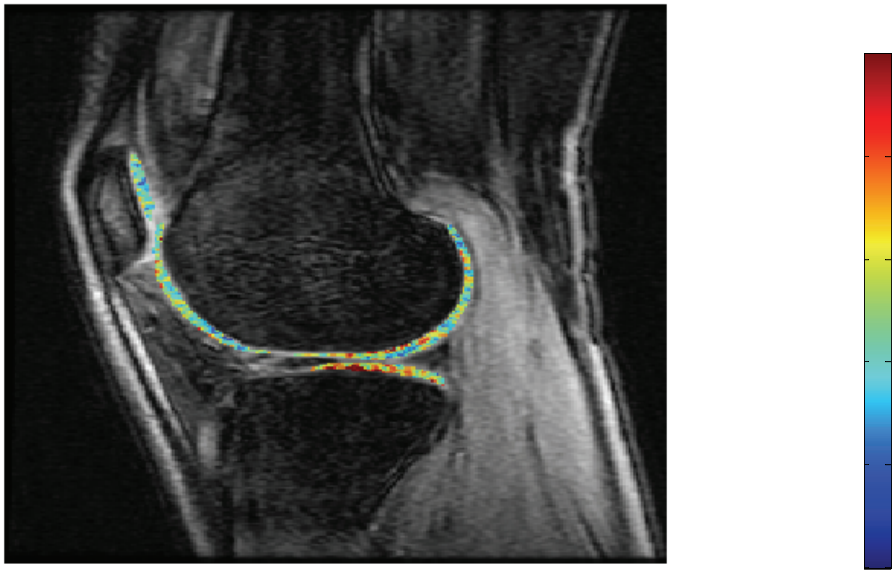


Figure 18: Lateral *in-vivo* image of a healthy volunteer knee with FA colormap overlaid.

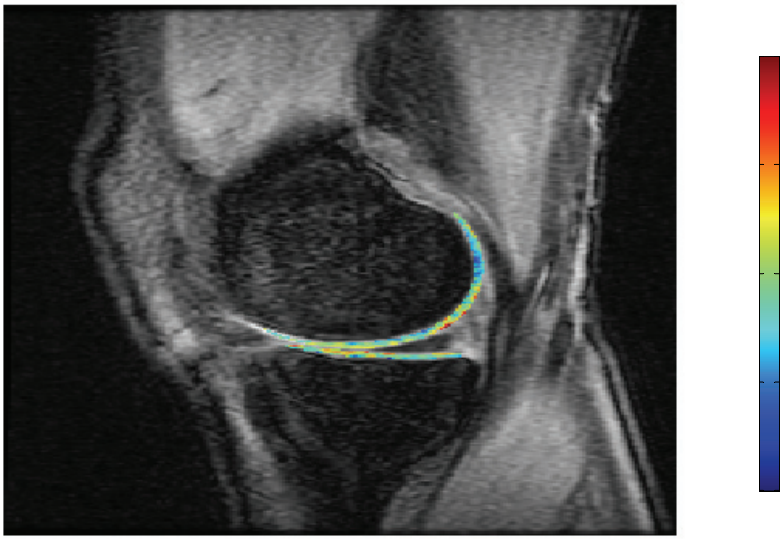


Figure 19: Medial *in-vivo* image of a healthy volunteer knee with ADC colormap overlaid.

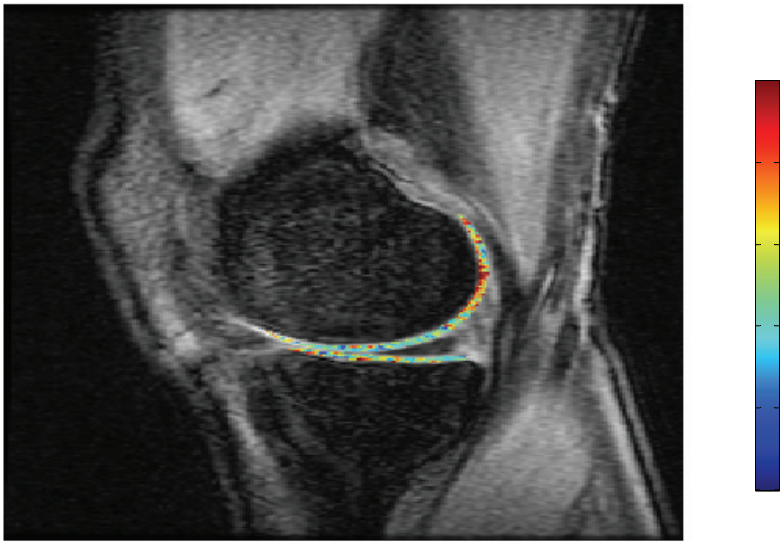


Figure 20: Medial *in-vivo* image of a healthy volunteer knee with FA colormap overlaid.

	Mean Diffusivity (ADC) value		FA value	
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**
Medial Femoral	1.43	0.3	0.29	0.11
Medial Tibia	1.53	0.26	0.25	0.09
Lateral Femoral	1.55	0.3	0.28	0.1
Lateral Tibia	1.64	0.29	0.33	0.1
Trochlea	1.69	0.34	0.28	0.08
Patella	1.48	0.36	0.26	0.08

Table 2: Table showing the mean and standard deviation values of *in-vivo* knee images obtained using proposed sequence. The average of four slices was taken for the entire cartilage except patella where six slices were averaged.

CONCLUSION

A new optimized 3T MR sequence for *in-vivo* diffusion imaging of knee for diagnosis of early cartilage degeneration is proposed. The phantom and preliminary *ex-vivo* and *in-vivo* results and images obtained are encouraging. The inverse relationship of the ADC and FA values as well as the correlation of the values with the diffusion gradient present due to the layered structure of cartilage has been observed. Our *in-vivo* measures of cartilage ADC and FA values were elevated compared to those reported in the literature. This requires additional investigation and future studies will aim to address this discrepancy and further optimizing and validating the proposed sequence in *ex-vivo* and *in-vivo* settings. Presently, the main focus of this research project is on imaging cartilage but in the future, further scope exists for imaging meniscus as well.

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