

Development of Methodologies for Diffusion-weighted Magnetic Resonance Imaging at High Field Strength

Irvin Tze Wei Teh

A dissertation submitted for the degree of
Doctor of Philosophy
for
Imperial College London

February 2009

Robert Steiner MRI Unit
Imaging Sciences Department
MRC Clinical Sciences Centre

Abstract

Diffusion-weighted imaging of small animals at high field strengths is a challenging prospect due to its extreme sensitivity to motion. Periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) was introduced at 9.4T as an imaging method that is robust to motion and distortion. Proton density (PD)-weighted and T_2 -weighted PROPELLER data were generally superior to that acquired with single-shot, Cartesian and echo planar imaging-based methods in terms of signal-to-noise ratio (SNR), contrast-to-noise ratio and resistance to artifacts.

Simulations and experiments revealed that PROPELLER image quality was dependent on the field strength and echo times specified. In particular, PD-weighted imaging at high field led to artifacts that reduced image contrast. In PROPELLER, data are acquired in progressively rotated blades in k-space and combined on a Cartesian grid. PROPELLER with echo truncation at low spatial frequencies (PETALS) was conceived as a postprocessing method that improved contrast by reducing the overlap of k-space data from different blades with different echo times.

Where the addition of diffusion weighting gradients typically leads to catastrophic motion artifacts in multi-shot sequences, diffusion-weighted PROPELLER enabled the acquisition of high quality, motion-robust data. Applications in the healthy mouse brain and abdomen at 9.4T and in stroke patients at 3T are presented.

PROPELLER increases the minimum scan time by approximately 50%. Consequently, methods were explored to reduce the acquisition time. Two k-space undersampling regimes were investigated by examining image fidelity as a function of degree of undersampling. Undersampling by acquiring fewer k-space blades was shown to be more robust to motion and artifacts than undersampling by expanding the distance between successive phase encoding steps. To improve the consistency of undersampled data, the non-uniform fast Fourier transform was employed. It was found that acceleration factors of up to two could be used with minimal visual impact on image fidelity.

To reduce the number of scans required for isotropic diffusion weighting, the use of rotating diffusion gradients was investigated, exploiting the rotational symmetry of the PROPELLER acquisition. Fixing the diffusion weighting direction to the individual rotating blades yielded geometry and anisotropy-dependent diffusion measurements. However, alternating the

orientations of diffusion weighting with successive blades led to more accurate measurements of the apparent diffusion coefficient while halving the overall acquisition time. Optimized strategies are proposed for the use of PROPELLER in rapid high resolution imaging at high field strength.

The work presented in this thesis was conducted by the author at the following locations between October 2005 and February 2009.

- Laboratory of Molecular Imaging, Singapore Bioimaging Consortium, Singapore
- National Neuroscience Institute, Singapore
- Biological Imaging Centre, Imaging Sciences Department, Clinical Sciences Centre, Imperial College London, London, UK

This work has not been presented for the purpose of obtaining any other degree.

Irvin Teh

To Dad, Kevin & Eunice.

Acknowledgements

For the knowledge they have shared and support they have generously given over the course of my PhD, I am deeply grateful to the following people.

My supervisors David Larkman and Xavier Golay have been a constant driving force. Their keen scientific insight and critical feedback have been as invaluable as their encouragement and support for my education and career.

I would like to thank my colleagues with whom I have had many fruitful discussions. In particular, I would like to acknowledge Mustafa Anjari, Martina Callaghan, Shaihan Malik, Helen Marshall, Rita Nunes, Anthony Price, Andrea Protti and So Po-Wah from Imperial College London (ICL). Thanks to Amy Herlihy for accommodating me on their busy scanner and Willy Gsell for his advice on animal handling.

Special thanks to Ivan Zimine for his patient and methodical introduction to MRI, Esben Petersen for his Philips pulse sequence programming wizardry and Lynn Ho for helping with the human data acquisition. I greatly appreciate the hard work of my collaborators Sitoh Yih Yian and Violet Chua from the National Neuroscience Institute, and Anne-Laure Puaux from the Singapore Immunology Network. Thanks also to all patients, volunteers and mice for their time. It was a great pleasure to work with my colleagues Abu Bakar Md Ali Asad, Chuang Kai-Hsiang, Philip Lee, Conny Schmidt and Zheng Bingwen from the Singapore Bioimaging Consortium. Thanks for sharing the frustration and satisfaction of setting up a new lab.

Thanks to the Agency for Science, Technology and Research (A*STAR) for funding, the A*STAR - ICL programme for facilitating this fruitful collaboration, and administrative officers Bun Swee Bee, Pete Campion-Smith, Serene Goh, Jen Martin, April Tan, Vivien Tikerpae and Joyce Yee for their tireless efforts coordinating the programme.

I would like to thank my family and friends for their unwavering support, especially Chng Wen Li, Er Ker Jia and Kevin Teh for their constant faith in me. To my dad, who has steadfastly stood by me and taught me the meaning of hard work, responsibility and family. And finally, thanks to my smu for being my endless source of motivation and mischief.

Table of Contents

Abstract	2
Acknowledgements	6
Table of Contents	7
List of Figures	10
List of Tables	15
List of Abbreviations	16
Introduction.....	18
1 Magnetic Resonance Imaging	20
1.1 Introduction	20
1.2 Bulk Magnetization	20
1.3 The Bloch equation and tissue relaxation	22
1.4 Signal detection	23
1.5 Spatial encoding	24
1.5.1 Slice selection	24
1.5.2 K-space sampling	25
1.5.3 Spin echo sequence	27
1.6 Fast imaging sequences	29
1.6.1 Echo Planar Imaging	30
1.6.2 Fast spin echo	32
1.7 High Field Strength Imaging	35
2 Diffusion Weighted Imaging.....	37
2.1 Introduction	37
2.2 Brownian motion and gaussian behaviour.....	37
2.3 Tissue anisotropy and heterogeneity	39
2.4 Diffusion sensitization	40
2.5 Diffusion tensor imaging	43
2.6 Challenges in DWI	45
2.6.1 SNR	45
2.6.2 Susceptibility	45
2.6.3 Eddy currents.....	45
2.6.4 Imaging gradients and cross-terms	46
2.6.5 Motion	46
3 PROPELLER MRI at High Field Strength.....	47
3.1 Introduction	47
3.2 Materials & Methods	49

3.2.1	PROPELLER Acquisition & Reconstruction	49
3.2.2	Simulations	53
3.2.3	Animal Studies	62
3.2.4	Human Studies	64
3.3	Results and Discussion	65
3.3.1	Simulations	65
3.3.2	Animal Studies	77
3.3.3	Human Studies	84
3.4	Conclusion	88
4	Optimal Strategies for PROPELLER Undersampling at High Field Strength	91
4.1	Introduction	91
4.2	Materials & Methods	94
4.2.1	Simulations	94
4.2.2	Animal Studies	95
4.2.3	Human Studies	96
4.3	Results & Discussion	97
4.3.1	Simulations	97
4.3.2	Animal Studies	117
4.3.3	Human Studies	122
4.4	Conclusion	123
5	Diffusion Weighted Imaging at High Field Strength	125
5.1	Introduction	125
5.2	Materials & Methods	130
5.2.1	B-value simulations	131
5.2.2	Simulations	132
5.2.3	Simulating the Diffusion Tensor	135
5.2.4	Animal Studies	136
5.2.5	Human Studies	138
5.3	Results & Discussion	139
5.3.1	B-value simulations	139
5.3.2	Simulations	140
5.3.3	Animal Studies	148
5.3.4	Human Studies	158
5.4	Conclusion	161
6	Rapid Isotropic Diffusion-weighted Imaging at High Field Strength	164
6.1	Introduction	164

6.2	Materials & Methods	167
6.2.1	Rotating DW gradients.....	167
6.2.2	Comparison of DW Schemes	171
6.2.3	Tumour ADC Simulations	171
6.2.4	Animal Studies.....	172
6.2.5	Human Studies	174
6.2.6	B-tensor simulations	175
6.3	Results & Discussion	175
6.3.1	Comparison of DW Schemes	175
6.3.2	Tumour ADC Simulations	178
6.3.3	Healthy Mouse Studies.....	196
6.3.4	Tumour Mouse Model Studies.....	202
6.3.5	Human Studies	206
6.3.6	B-tensor simulations	207
6.4	Conclusion.....	216
7	Conclusions.....	219
7.1	Summary of findings.....	219
7.2	Concluding remarks.....	223
	References	224

List of Figures

Figure 1-1 Zeeman energy level diagram	21
Figure 1-2 Laboratory vs rotating frame of reference	24
Figure 1-3 Slice selection	25
Figure 1-4 Spin echo pulse sequence	27
Figure 1-5 Acquiring k-space in multiple shots	29
Figure 1-6 Effects of T_2 and motion in simulated data	30
Figure 1-7 Echo planar imaging pulse sequence	31
Figure 1-8 Fast spin echo pulse sequence	33
Figure 2-1 Brownian motion of water	39
Figure 2-2 Diffusion weighted spin echo pulse sequence	41
Figure 2-3 Diffusion weighting mechanism	42
Figure 2-4 Sample DW in-vivo mouse brain data	44
Figure 3-1 Effects of motion on Cartesian and PROPELLER k-space	47
Figure 3-2 PROPELLER motion correction in human brain at 3T	48
Figure 3-3 PROPELLER phase correction process	51
Figure 3-4 NUFFT vs regridding	53
Figure 3-5 Key to Shepp-Logan simulations	55
Figure 3-6 ROIs in Shepp-Logan simulations	57
Figure 3-7 Point spread function of PROPELLER reconstruction	59
Figure 3-8 Mixing of echo times in PROPELLER	60
Figure 3-9 PROPELLER vs PETALS sampling	61
Figure 3-10 ROIs in mouse brain images	63
Figure 3-11 Mouse liver EPI images	64
Figure 3-12 ROIs in mouse liver images	64
Figure 3-13 ROIs in human brain images	65
Figure 3-14 Effects of motion on Cartesian sampled simulated data	66
Figure 3-15 Effects of motion on PROPELLER sampled simulated data	66
Figure 3-16 SNR in differently sampled simulations with centric phase encoding	67
Figure 3-17 Point spread function artifacts associated with PROPELLER	68
Figure 3-18 CNR in differently sampled simulations with centric phase encoding	69
Figure 3-19 Contrast in differently sampled simulations with centric phase encoding	70
Figure 3-20 PSF FWHM in differently sampled simulations with centric phase encoding	71
Figure 3-21 AP in differently sampled simulations with centric phase encoding	71
Figure 3-22 SNR in differently sampled simulations with linear phase encoding	73

Figure 3-23 CNR in differently sampled simulations with linear phase encoding.....	74
Figure 3-24 Contrast in differently sampled simulations with linear phase encoding	74
Figure 3-25 PSF FWHM in differently sampled simulations with linear phase encoding	75
Figure 3-26 AP in differently sampled simulations with linear phase encoding.....	76
Figure 3-27 In-vivo mouse brain images at 9.4T	78
Figure 3-28 Multi-shot FSE vs FSE PROPELLER	78
Figure 3-29 SNR in mouse brain data	80
Figure 3-30 CNR in mouse brain data.....	80
Figure 3-31 AP in mouse brain data.....	81
Figure 3-32 In-vivo mouse liver images at 9.4T	82
Figure 3-33 SNR, CNR and AP in mouse liver.....	83
Figure 3-34 In-vivo mouse brain images: PROPELLER vs PETALS	83
Figure 3-35 SNR, contrast and AP in mouse brain: PROPELLER vs PETALS	84
Figure 3-36 In-vivo human brain images at 3T.....	85
Figure 3-37 SNR, CNR and AP in human brain	86
Figure 3-38 Effects of motion in human brain images.....	87
Figure 3-39 In-vivo human brain images: PROPELLER vs PETALS.....	88
Figure 3-40 SNR, contrast and AP in human brain: PROPELLER vs PETALS	88
Figure 4-1 K-space undersampling strategies.....	92
Figure 4-2 Effects of T_2 on Shepp-Logan simulated images	97
Figure 4-3 Shepp-Logan images with USB undersampling and nPE=8.....	99
Figure 4-4 Shepp-Logan images with USP undersampling and nPE=16.....	100
Figure 4-5 SNR in USB undersampled Shepp-Logan simulations.....	101
Figure 4-6 CNR in USB undersampled Shepp-Logan simulations.....	102
Figure 4-7 PSF FWHM in USB undersampled Shepp-Logan simulations	103
Figure 4-8 AP in USB undersampled Shepp-Logan simulations.....	104
Figure 4-9 Relative SNR in USB undersampled Shepp-Logan simulations	105
Figure 4-10 Relative CNR in USB undersampled Shepp-Logan simulations.....	106
Figure 4-11 Relative PSF FWHM in USB undersampled Shepp-Logan simulations	106
Figure 4-12 Relative AP in USB undersampled Shepp-Logan simulations.....	107
Figure 4-13 Shepp-Logan images with USP undersampling	109
Figure 4-14 SNR in Shepp-Logan simulations: USB vs USP.....	110
Figure 4-15 CNR in Shepp-Logan simulations: USB vs USP	111
Figure 4-16 PSF FWHM in Shepp-Logan simulations: USB vs USP	112
Figure 4-17 AP in Shepp-Logan simulations: USB vs USP.	112
Figure 4-18 Shepp-Logan images with motion: USB vs USP	115

Figure 4-19 AP in Shepp-Logan simulations with motion: USB vs USP	116
Figure 4-20 Undersampled in-vivo mouse brain images at 9.4T	118
Figure 4-21 SNR in USB undersampled mouse brain data.....	119
Figure 4-22 CNR in USB undersampled mouse brain data	120
Figure 4-23 AP in USB undersampled mouse brain data	121
Figure 4-24 Undersampled in-vivo human brain images at 3T	123
Figure 5-1 Diffusion weighted fast spin echo pulse sequence at 9.4T	131
Figure 5-2 Key to anisotropy simulations	133
Figure 5-3 Diffusion weighted fast spin echo pulse sequence at 3T	139
Figure 5-4 Sample DW anisotropy simulation images	141
Figure 5-5 Sample mean ADC image from anisotropy simulation	141
Figure 5-6 Mean ADC vs blade width & FA in simulations with no T_2	142
Figure 5-7 Mean ADC simulation images with no T_2	142
Figure 5-8 Mean ADC vs blade width & FA in simulations at 9.4T with centric encoding	143
Figure 5-9 Mean ADC simulation images at 9.4T with centric encoding	143
Figure 5-10 Mean ADC vs blade width & FA in simulations at 9.4T with linear encoding	144
Figure 5-11 Mean ADC simulation images at 9.4T with linear encoding.....	145
Figure 5-12 Mean ADC vs anisotropy orientation & FA in simulations with no T_2 (I)	146
Figure 5-13 Mean ADC vs anisotropy orientation & FA in simulations with no T_2 (II)	146
Figure 5-14 Mean ADC vs undersampling & FA in simulations at 9.4T	148
Figure 5-15 In-vivo mouse brain DW images at 9.4T	150
Figure 5-16 Mean ADC in mouse grey matter.....	152
Figure 5-17 Mean ADC in mouse white matter	152
Figure 5-18 SNR of mean ADC in mouse brain	153
Figure 5-19 AP of mean ADC in mouse brain	154
Figure 5-20 In-vivo mouse liver DW images at 9.4T	155
Figure 5-21 Mean ADC in mouse liver and muscle	156
Figure 5-22 SNR and AP of mean ADC in mouse liver.....	157
Figure 5-23 Single-shot DW-EPI in stroke patient at 3T	159
Figure 5-24 DW-FSE-PROPELLER in stroke patient at 3T	160
Figure 5-25 DW-FSE-PETALS in stroke patient at 3T	161
Figure 6-1 Rotating DW schemes	168
Figure 6-2 Rotating DW gradients behaviour	170
Figure 6-3 3D projection of effectively isotropic DW gradients.....	170
Figure 6-4 Isotropic DW preparation schemes.....	177
Figure 6-5 Colour FA map of anisotropy simulation (I).....	179

Figure 6-6 Mean ADC simulation images varying nPE & DW scheme	180
Figure 6-7 Mean ADC vs nPE & DW scheme with no T_2	181
Figure 6-8 Mean ADC vs nPE & DW scheme at 9.4T with centric encoding	183
Figure 6-9 Mean ADC vs nPE & DW scheme at 9.4T with linear encoding	183
Figure 6-10 Mean ADC simulation images varying phase encoding & DW scheme.....	184
Figure 6-11 Mean ADC simulation images varying FA & DW scheme (I)	185
Figure 6-12 Mean ADC vs FA & DW scheme with no T_2 (I)	186
Figure 6-13 Mean ADC vs FA & DW scheme at 9.4T with centric encoding	186
Figure 6-14 Mean ADC vs FA & DW scheme at 9.4T with linear encoding	187
Figure 6-15 Colour FA map of anisotropy simulation (II).....	188
Figure 6-16 Mean ADC simulation images varying FA & DW scheme (II)	189
Figure 6-17 Mean ADC vs FA & DW scheme with no T_2 (II)	190
Figure 6-18 Colour FA map of anisotropy simulation (III).....	191
Figure 6-19 Mean ADC vs FA & DW scheme with no T_2 (III)	192
Figure 6-20 Mean ADC simulation images varying nPE & FA	193
Figure 6-21 Mean ADC vs nPE & FA using DW_{alt} with no T_2	194
Figure 6-22 Mean ADC vs nPE & FA using DW_{alt} at 9.4T with centric encoding	194
Figure 6-23 Mean ADC vs nPE & FA using DW_{alt} at 9.4T with linear encoding	195
Figure 6-24 In-vivo mouse brain DW images at 9.4T with linear encoding	197
Figure 6-25 In-vivo mouse brain DW images at 9.4T with centric encoding	197
Figure 6-26 Mean ADC in mouse grey matter with rotating DW	198
Figure 6-27 Mean ADC in mouse white matter with rotating DW	199
Figure 6-28 SNR of mean ADC in mouse grey matter with rotating DW.....	200
Figure 6-29 AP of mean ADC in mouse grey matter with rotating DW	200
Figure 6-30 GM-WM contrast in mean ADC in mouse brain with rotating DW	201
Figure 6-31 Dissections of mouse model of melanoma	203
Figure 6-32 Heterogeneity of tumours in mouse models	203
Figure 6-33 In-vivo mouse brain and tumour DW images at 9.4T.....	204
Figure 6-34 Mean ADC in mouse tumours with rotating DW	205
Figure 6-35 In-vivo human stroke patient DW images at 3T (I).....	206
Figure 6-36 In-vivo human stroke patient DW images at 3T (II).....	207
Figure 6-37 DW gradients in $DW_{ro} G_{z,fix}$	208
Figure 6-38 DW gradients in $DW_{alt} G_{z,fix}$	210
Figure 6-39 DW gradients in $DW_{ro} G_{z,alt}$	212
Figure 6-40 DW gradients in $DW_{alt} G_{z,alt}$	213
Figure 6-41 Percentage error in off-diagonal b-terms.	215

Figure 6-42 Percentage error in on-diagonal b-terms	216
---	-----

List of Tables

Table 3.1 Shepp-Logan simulation specifications	54
Table 3.2 Proton density and T_2 values in-vivo	55
Table 4.1 Effects of undersampling on simulated image quality	113
Table 4.2 Effects of undersampling on mouse brain image quality	122
Table 5.1 Summary of DW publications in rodents $\geq 7T$	128
Table 5.2 Proton density, T_2 , ADC and FA values in mice at high field.....	133
Table 5.3 Scan parameters for in-vivo DWI of mouse brain at 9.4T	137
Table 5.4 Scan parameters for in-vivo DWI of mouse liver at 9.4T	137
Table 5.5 Simulated b-values along FSE echo train	140
Table 6.1 Rotating DW gradient array on Philips 3T scanner	175
Table 6.2 Effects of rotating DW on mouse brain image quality	202
Table 6.3 Effects of rotating DW on mouse tumour image quality	205
Table 6.4 B-values across individual blades using $DW_{ro} G_{z,fix}$	209
Table 6.5 Averaged b-values using $DW_{ro} G_{z,fix}$ and using $DW_{alt} G_{z,fix}$	211
Table 6.6 B-values across individual blades using $DW_{ro} G_{z,alt}$	212
Table 6.7 Averaged b-values using $DW_{ro} G_{z,alt}$ and using $DW_{alt} G_{z,alt}$	214

List of Abbreviations

ADC	Apparent diffusion coefficient
AP	Artifact power
APPEAR	Anti-aliasing partially parallel encoded acquisition reconstruction
AT	Acquisition time
BW	Bandwidth
CNR	Contrast-to-noise ratio
CPMG	Carr-Purcell-Meiboom-Gill
CSF	Cerebrospinal fluid
DFT	Discrete Fourier transform
DTI	Diffusion tensor imaging
DW	Diffusion weighted / weighting
DWI	Diffusion weighted imaging
EPI	Echo planar imaging
ETL	Echo train length
FA	Fractional anisotropy
FFT	Fast Fourier transform
FID	Free induction decay
FOV	Field-of-view
FSE	Fast spin echo
GM	Grey matter
GRAPPA	Generalised autocalibrating partially parallel acquisitions
GRASE	Gradient and spin echo
GROG	GRAPPA operator gridding
IACUC	Institutional Animal Care and Use Committee
IRB	Institutional Review Board
kSPA	K-space sparse matrices
MBP	Multiple bipolar
MCA	Middle cerebral artery
MG	Meiboom-Gill
MRI	Magnetic resonance imaging
MSEPI	Multi-shot echo planar imaging
MSFSE	Multi-shot fast spin echo
MTF	Modulation transfer function
NMR	Nuclear magnetic resonance
NUFFT	Non-uniform fast Fourier transform

PD	Proton density
PE	Phase encode
PETALS	PROPELLER with echo truncation at low spatial frequencies
PGSE	Pulsed gradient spin echo
POCS	Projection onto convex sets
PROPELLER	Periodically rotated overlapping parallel lines with enhanced reconstruction
PSF	Point spread function
RARE	Rapid acquisition with relaxation enhancement
RF	Radiofrequency
RIGR	Reduced encoding imaging by generalised series reconstruction
RO	Readout
ROI	Region-of-interest
SAR	Specific absorption rate
SE	Spin echo
SENSE	Sensitivity encoding
SNR	Signal-to-noise ratio
SPLICE	Split acquisition of fast spin echo signals for diffusion imaging
SS	Slice select
SSEPI	Single-shot echo planar imaging
SSFSE	Single-shot fast spin echo
STEAM	Stimulated echo acquisition mode
TE	Echo time
TE _{eff}	Effective echo time
TR	Repetition time
TRSE	Twice refocused spin echo
TSE	Turbo spin echo
U-FLARE	Ultrafast low angle rapid acquisition and relaxation enhancement
USB	Undersampling by blades
USP	Undersampling by phase encodes
VERSE	Variable-rate selective excitation
WM	White matter

Introduction

There is an ever present drive towards higher field strengths in magnetic resonance imaging (MRI) that is primarily motivated by the pursuit of higher signal-to-noise ratios (SNRs). Improvements in ultra high field magnet technology have enabled field strengths of up to 11.7 Tesla (T) and 17T in human and animal research scanners respectively. The higher signal available allows greater flexibility in imaging as SNR can be traded for shorter acquisition times and higher image resolutions. In the imaging of small rodents such as mice and rats, the latter becomes an essential requirement due to the small dimensions involved. Higher fields have also paved the way for MRI contrast methods that have intrinsically low SNRs such as perfusion and functional MRI.

Diffusion weighted imaging (DWI) is one such method that relies on the intentional suppression of signal to generate diffusion contrast. Sufficient SNR is then a prerequisite to reduce systematic biases in the calculated data. DWI is based on the premise that water does not diffuse uniformly in-vivo. In nerve fibres for example, microscopic diffusion of water tends to be higher along the axis of the fibres and lower in the orthogonal directions. As a result, DWI has been used to generate exquisite maps of diffusivity and anisotropy in the rodent brain. These have been used to trace the structure of white matter fibres, which together with other imaging methods, have contributed greatly to our understanding of brain connectivity and function.

While promising, DWI at high fields $\geq 7T$ pose a set of unique challenges that are less of a problem at lower field strengths $\leq 3T$. It becomes necessary to develop methods to address these issues. This thesis explores the use of fast spin echo (FSE) PROPELLER methods as a basis for acquiring high resolution diffusion-weighted and non-diffusion-weighted data that are robust to motion and distortion. Chapter 1 introduces the basic concepts of MRI and principles of image formation. This is followed by an introduction to the mechanism and applications of DWI in Chapter 2. Chapter 3 describes the PROPELLER acquisition and non-uniform fast Fourier transform (NUFFT) reconstruction method. The performance of FSE-PROPELLER is compared against other pulse sequences. Chapter 4 explores various k-space undersampling methods in an effort to reduce acquisition times. The performance of FSE-PROPELLER in diffusion-weighted applications is investigated in Chapter 5, again making comparisons with other imaging sequences. Chapter 6 presents rotating diffusion gradients as a method to reduce the acquisition times in isotropic DWI applications. The overall results and impact of such methods are summarized in Chapter 7. In each of

Chapters 3 to 6, simulations were constructed and validated with in-vivo data acquired primarily in mice at 9.4T and also in humans at 3T. These highlight the field-dependent effects inherent in PROPELLER.

1 Magnetic Resonance Imaging

1.1 Introduction

MRI is a versatile, non-invasive imaging modality that has found widespread use in both clinical and research settings. It is particularly useful for longitudinal in-vivo studies due to the wide range of contrasts available and because subjects are not exposed to ionizing radiation. MRI finds its roots in the pioneering work in nuclear magnetic resonance (NMR) by Bloch and Purcell in 1946 (1,2). It was not until 1973 however, when Lauterbur and Mansfield were able to spatially localize the NMR signal, that the imaging aspect was introduced (3,4). This chapter presents a brief overview of the basic concepts of MRI from the origin of signal to image formation, and is based largely on available texts (5,6).

1.2 Bulk Magnetization

According to quantum theory, atomic nuclei possess a property known as the spin. Spin describes the intrinsic angular momentum of the particle, and early work by Stern and Gerlach (7) showed that its value is quantized. Protons and neutrons have a spin of $\frac{1}{2}$. This means they may be found in one of two energy states defined by spin quantum numbers, $m_s = \pm\frac{1}{2}$. In the presence of a magnetic field, spin couples with the magnetic field B_0 as given in Eqn 1.1, and may align either parallel or anti-parallel to B_0 .

$$\text{Potential energy, } E = -\gamma m_s \hbar B_0 \quad 1.1$$

Where γ is the gyromagnetic ratio and $\hbar$ is Planck's constant divided by 2π . The negative sign indicates that the $m_s = -\frac{1}{2}$ has a higher associated energy than $m_s = +\frac{1}{2}$.

The splitting of atomic energy levels due to spin in the presence of an external magnetic field is described by the Zeeman effect (See Figure 1-1). As a result, the energy absorbed or emitted, ΔE , in a proton spin system during transition from one energy level to another in a constant field B_0 is described by Eqn 1.2.

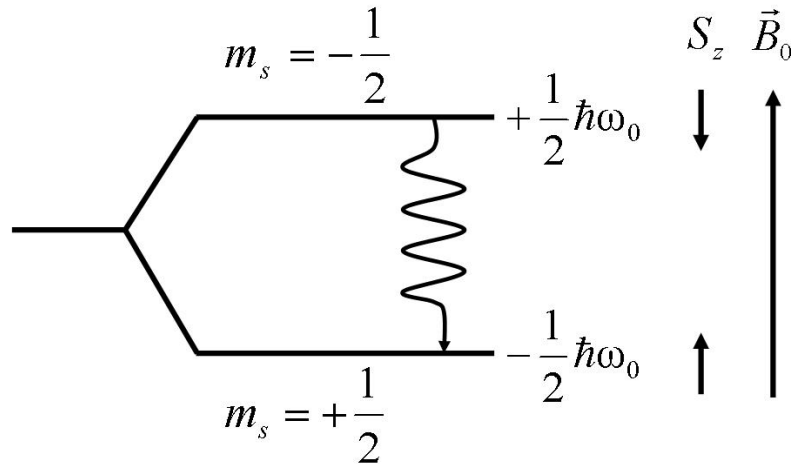


Figure 1-1 Zeeman energy level diagram for a proton spin system in the presence of an external magnetic field, $\vec{B}_0$. Anti-parallel spins (S_z) have a higher energy than parallel spins. Photon emission (wavy line) leads to lower energy state. Figure adapted from Haacke, et al. (6)

$$\text{Transition energy, } \Delta E = \gamma \hbar B_0 = \hbar \omega_0 \quad 1.2$$

Where ω_0 is the frequency of absorption or emission of energy.

The frequency ω_0 is the resonant frequency of the system where energy absorption and emission can take place. This is known as the Larmor frequency (See Eqn 1.3), and corresponds to the equation of motion describing the torque on a magnetic moment arising from an external magnetic field B_0 .

$$\text{Angular precession frequency, } \omega_0 = \gamma B_0 \quad 1.3$$

The manipulation and measurement of proton spins is fundamental to MRI. While other nuclei with non-zero spin exist such as ^{23}Na and ^{31}P , they are found in much lower concentrations in-vivo than ^1H . The amount of signal available depends on the net equilibrium magnetization of the proton spins in the volume of interest. At in-vivo temperatures, ΔE is on the order of $1\text{e-}6$ smaller than the Boltzmann thermal energy. This means that at equilibrium, the number of spins parallel to the magnetic field exceeds those that are anti-parallel to the magnetic field by a very small amount, eg. about five per million protons at 1.5T. However, the abundance and high gyromagnetic ratio of protons leads to measurable effects, and the equilibrium magnetization is given by Eqn 1.4. Proton MRI is most commonly used in imaging, and is the basis for all work herein.

$$\text{Longitudinal equilibrium magnetization, } M_0 = \frac{\rho_0 \gamma^2 \hbar^2}{4kT} B_0 \quad 1.4$$

Where ρ_0 is the number of protons per unit volume or spin density, γ is the gyromagnetic ratio of $^1\text{H} = 42.58\text{MHz/T}$, k is Boltzmann's constant, T is the absolute temperature and B_0 is the external magnetic field.

1.3 The Bloch equation and tissue relaxation

The net magnetization in a tissue of interest due to an external magnetic field is the ensemble effect of a large number of discrete protons. As this number is sufficiently large, classical mechanics may be used to derive the equation of motion.

When the magnetization is perturbed from its alignment along the main magnetic field, two important time constants govern the resultant evolution of the magnetization. T_1 is known as the spin-lattice relaxation time constant and describes the rate of recovery of longitudinal magnetization due to interactions between the proton spins and the environment. T_2 is the spin-spin relaxation time constant arising from local field variations and interactions between proton spins. This leads to a variation in local precessional frequencies and dephasing of the signal. Incorporating these relaxation terms gives the empirical vector equation known as the Bloch equation (See Eqn 1.5). The dependence of relaxation parameters on tissue type contributes to the wide range of contrast available with MRI.

$$\text{Magnetization vector, } \frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B}_0 \hat{z} + \frac{1}{T_1} (M_0 - M_z) \hat{z} - \frac{1}{T_2} \vec{M}_\perp \quad 1.5$$

Where γ is the gyromagnetic ratio, $\vec{M}$ is the equilibrium magnetization, $\vec{B}_0$ is the external magnetic field, $\vec{M}_\perp$ is the transverse magnetization, and T_1 & T_2 are relaxation time constants.

For constant B_0 in the z-direction, solving the Bloch equation gives the magnetization in x, y and z-directions as a function of time, t (See Eqns 1.6, 1.7 & 1.8). As $t \rightarrow \infty$, the transverse magnetization M_x and M_y tend to zero due to T_2 dephasing, and M_z tends to M_0 as longitudinal magnetization is recovered due to T_1 .

$$\text{Magnetization, } M_x(t) = e^{-\frac{t}{T_2}} (M_x(0) \cos \omega_0 t + M_y(0) \sin \omega_0 t) \quad 1.6$$

$$\text{Magnetization, } M_y(t) = e^{-\frac{t}{T_2}} (M_y(0) \cos \omega_0 t - M_x(0) \sin \omega_0 t) \quad 1.7$$

$$\text{Magnetization, } M_z(t) = M_z(0) e^{-\frac{t}{T_1}} + M_0 \left(1 - e^{-\frac{t}{T_1}} \right) \quad 1.8$$

1.4 Signal detection

By Faraday's law of induction, a voltage may be induced in a receiver coil that is dependent on the time rate of change of magnetic flux. Consequently, only the rotating transverse component of the precessing magnetization results in a measurable signal. The induced voltage is referred to as free induction decay (FID). It oscillates at the Larmor frequency and decays with relaxation effects.

In order to generate a transverse component in the magnetization vector, a radiofrequency (RF) pulse at the resonant frequency is used. In the quantum view, the RF energy causes transitions in proton energy states. In the classical mechanics view, the net magnetic field can be described as the vector sum of the main magnetic field, B_0 and the applied RF field, B_1 . If their respective orientations are defined along the z-axis and the x-axis, then the evolution of the magnetization vector according to Eqn 1.5 is illustrated in Figure 1-2. The precession about the z-axis in the laboratory frame of reference may be simplified using a rotating frame of reference. In the latter, it can be seen that the application of an RF pulse rotates the magnetization by some angle about the rotating x'-axis. For an RF pulse that is applied on-resonance and over a short time interval, the angle may be described by Eqn 1.9.

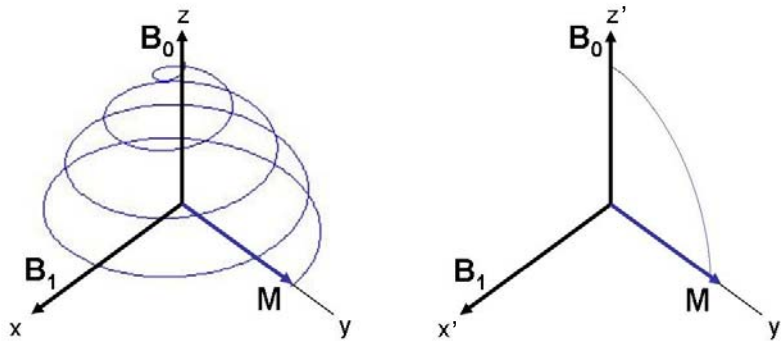


Figure 1-2 The evolution of the magnetization vector M upon application of an RF pulse as observed in the fixed laboratory frame of reference (left) and the rotating frame of reference (right).

$$\text{Flip angle, } \theta = \gamma B_1 \tau$$

1.9

Where B_1 is the applied RF field strength and τ is its duration.

1.5 Spatial encoding

The signal measured in the receive coil comes from the entire sample. In order to reconstruct an image, it is necessary to localize this signal. Eqn 1.3 describes a linear variation in resonance frequency with magnetic field strength. As such, orthogonal magnetic gradients G can be used to add some small magnetic field to spatially encode the signal in three dimensions.

1.5.1 Slice selection

Selection of a two dimensional slice may be achieved by the simultaneous application of a linear gradient perpendicular to the slice and an RF pulse with a limited bandwidth (BW). The gradient results in a linearly varying range of precessional frequencies, such that only a certain thickness of the subject is excited by the RF pulse. For a desired slice in the x-y plane, the variation in angular frequencies along the z-axis is described in Eqn 1.10 and illustrated in Figure 1-3. Slice position may be adjusted by varying the centre frequency of the RF pulse while slice thickness can be adjusted by varying the BW of the RF pulse. Adjusting the gradient G_z affects both the slice position and thickness.

$$\text{Angular frequency, } \omega(z, t) = \gamma B_0 + \gamma z_0 G_z(t) \quad 1.10$$

Where z_0 is the nominal centre slice position and G_z is the gradient strength along the axis through the imaging plane.

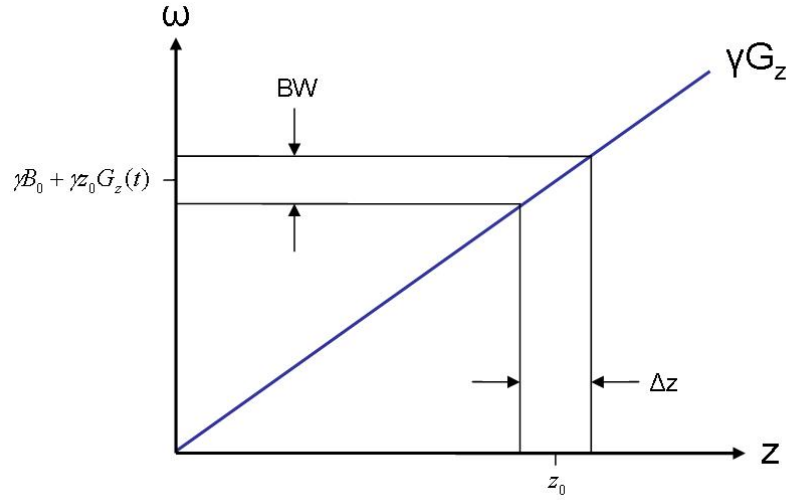


Figure 1-3 Selection of a 2D slice using a linearly varying gradient and RF pulse of limited bandwidth. The slice is perpendicular to G_z , centred at z_0 and with thickness Δz .

1.5.2 K-space sampling

Assuming homogenous B_0 field, a perfect $\frac{\pi}{2}$ excitation pulse and initial equilibrium magnetization, M_0 , the general signal equation for imaging in three dimensions can be expressed as a function of spatial frequencies, $\vec{k}$ (See Eqn 1.11).

$$\text{Signal, } s(\vec{k}) = \int d^3r \rho(\vec{r}) e^{-i2\pi\vec{k}\cdot\vec{r}} \quad 1.11$$

Where $\vec{k}$ is given in Eqn 1.12.

$$\text{Spatial frequencies, } \vec{k} = \gamma \int_0^t \vec{G}(t') dt' \quad 1.12$$

Where γ is the gyromagnetic ratio divided by 2π .

From Eqn 1.11, it can be seen that the measured signal is the Fourier transform of the effective proton density, and that sufficient data as given by $\{\vec{k}\}$ need to be sampled in order for its Fourier transform to be an accurate representation of the image intensities. This collection of spatial frequencies, $\vec{k}$ is known as k-space. It represents the spatial frequency content of the image, which indicates the rate of change of an image feature over a given distance. Low spatial frequencies at the centre of k-space for example correspond to slowly varying general image contrast whereas high spatial frequencies at the periphery of k-space correspond to rapidly varying edge contrast and fine detail. Since MRI data is acquired in k-space, the process of collecting enough data to generate an image is one of filling k-space. This applies similarly in 2D and 3D. Spatial encoding in 2D, as used throughout this thesis, may be achieved through frequency encoding and phase encoding. These entail using orthogonal in-plane imaging gradients to navigate about k-space as data are acquired. This is illustrated in the following example of a spin echo (SE) sequence.

The image and k-space data are related by the discrete Fourier transform. However, applying this may be computationally intensive. In most 2D applications, k-space data are acquired on a Cartesian grid of $2^M \times 2^N$ size where M and N are integers. This facilitates the application of the fast Fourier transform (FFT) which is widely used in MRI reconstruction. Non-cartesian data sampling may also be used. These generally necessitate using gridding or other techniques to resample the data onto a Cartesian grid before applying the FFT. These will be discussed further in Chapter 3.

Both k-space and image space are continuous, however, due to hardware and time constraints, the sampling of k-space is necessarily discrete and limited. This limits the resolution that may be obtained and potentially gives rise to artifacts. One important consideration is that k-space needs to be sampled densely enough to prevent foldover artifacts. This means that the inverse of the sampling step in k-space must be larger than the object to be imaged and is described by the Nyquist sampling criterion (See Eqn 1.13).

$$\text{Sampling step size, } \Delta k < \frac{1}{A} \quad 1.13$$

Where A is the object size.

1.5.3 Spin echo sequence

MRI data are acquired using a carefully timed sequence of RF pulses and imaging gradients. A single echo SE pulse sequence (8) as shown in Figure 1-4 illustrates the basic features of a pulse sequence, and serves as a basis for understanding more complex sequences that follow.

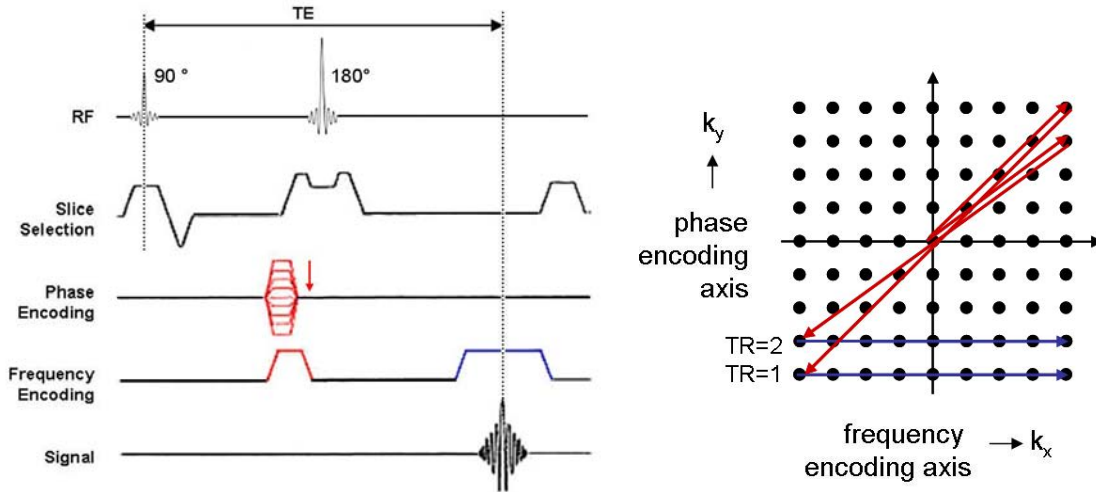


Figure 1-4 Single echo RF spin echo sequence (left) depicting key pulse sequence features. Phase encoding illustrated was linear, from $-k_y$ to $+k_y$. Imaging gradients as highlighted in red and blue navigate through k-space as shown (right). Blue lines indicate where data were acquired. Two repetitions are shown. Figure at left adapted from Bernstein, et al. (5)

Initially, magnetization is at equilibrium and is aligned along the axis of the main magnetic field, usually denoted as the z-axis. Concurrent application of the first positive gradient lobe along the slice selection direction together with a bandwidth limited 90° RF pulse, excites the magnetization of protons in a given slice into the transverse plane. However, slice selective excitation causes dephasing of the signal as a function of slice position z . To rephase the signal, a negative gradient lobe of half the area immediately follows the slice selection gradient. The next step is known as phase encoding and entails application of a gradient in the phase encoding direction to add a suitable phase term in order to move to a suitable k_y position, ie. from centre to top of k-space (See right image of Figure 1-4). A pre-phasing gradient is also applied in the frequency encoding direction to move to a suitable k_x position, ie. from centre to the right of k-space. All this while, relaxation effects T_1 and T_2 contribute to a recovery of the longitudinal magnetization and a dephasing of the transverse magnetization respectively. The term T_2' is introduced which describes additional dephasing due to external

factors such as susceptibility, magnetic field inhomogeneity and imaging voxel size. It is typically shorter than T_2 , hence signal decay due to T_2' is more severe than T_2 .

At time, $t=TE/2$ where TE is the echo time, a slice selective 180° RF pulse is played out. This flips the transverse magnetization by 180° and generates a spin echo at $t=TE$. The phase of the magnetization is reversed and the k-coordinate is flipped about the centre of k-space. By $t=TE$, signal loss due to T_2' is recovered leaving signal loss due to T_2 . As the spin echo occurs, a positive gradient in the frequency encoding or readout direction is applied. This acquires the data from left to right across the readout direction at some velocity determined by the gradient strength, and multiple k-samples are acquired. This is known as frequency encoding. A pair of crusher gradients about the 180° pulse dephases any unwanted transverse magnetization created by imperfect slice refocusing. At the end of the acquisition, a spoiler gradient is applied (seen here in the slice select direction) to dephase any remaining transverse magnetization. A delay is observed before the sequence is repeated to obtain the next line of data using a slightly different phase encoding gradient. The time between successive repeats is known as the repetition time, TR.

Assuming that data is acquired at an instantaneous time TE, then the transverse magnetization measured is given by Eqn 1.14. This describes tissue contrast due to relaxation time constants, T_1 and T_2 . By changing the TR and TE based on the specific tissues of interest, the image contrast can be adjusted so that it becomes more dependent on PD, T_1 or T_2 of the tissues. The data are said to be PD-weighted, T_1 -weighted or T_2 -weighted respectively.

$$\text{Transverse magnetization, } M_{\perp} = M_0 \left(1 - e^{-\frac{TR}{T_1}}\right) e^{-\frac{TE}{T_2}} \quad 1.14$$

Where M_0 is the transverse magnetization due to spin density.

The sequence is repeated nPE times to fully sample k-space, where nPE is the total number of phase encoding steps. The acquisition time is then the TR multiplied by nPE which may be in the order of minutes or hours. Methods to reduce acquisition times are thus highly beneficial.

1.6 Fast imaging sequences

K-space is normally filled as single or interleaved lines on a Cartesian grid. These can be acquired in either multi-shot or single-shot mode by varying the echo train length (ETL) of each shot (See Figure 1-5). The overall acquisition time is proportional to the number of shots, N_s . Data within one shot are acquired rapidly, on the order of $<200\text{ms}$, depending on the length of the echo train. Data acquired between shots are spaced out by one TR, on the order of 2-4s. Consequently, motion and other inconsistencies between shots result in more significant errors in k-space which can cause artifacts that cannot easily be corrected. While single-shot acquisition methods are more resistant to motion due to their rapid filling of k-space, they are more susceptible to T_2 decay and a loss of SNR and image resolution in the phase encoding direction (See Figure 1-6).

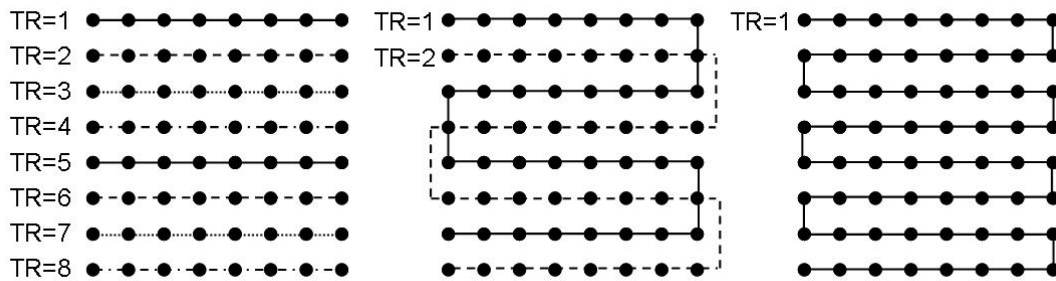


Figure 1-5 Filling of a hypothetical 8 x 8 Cartesian k-space where shots, $N_s=8, 2$ & 1 (left to right). ETLs are inversely related to N_s and equal 1, 4 and 8 respectively.

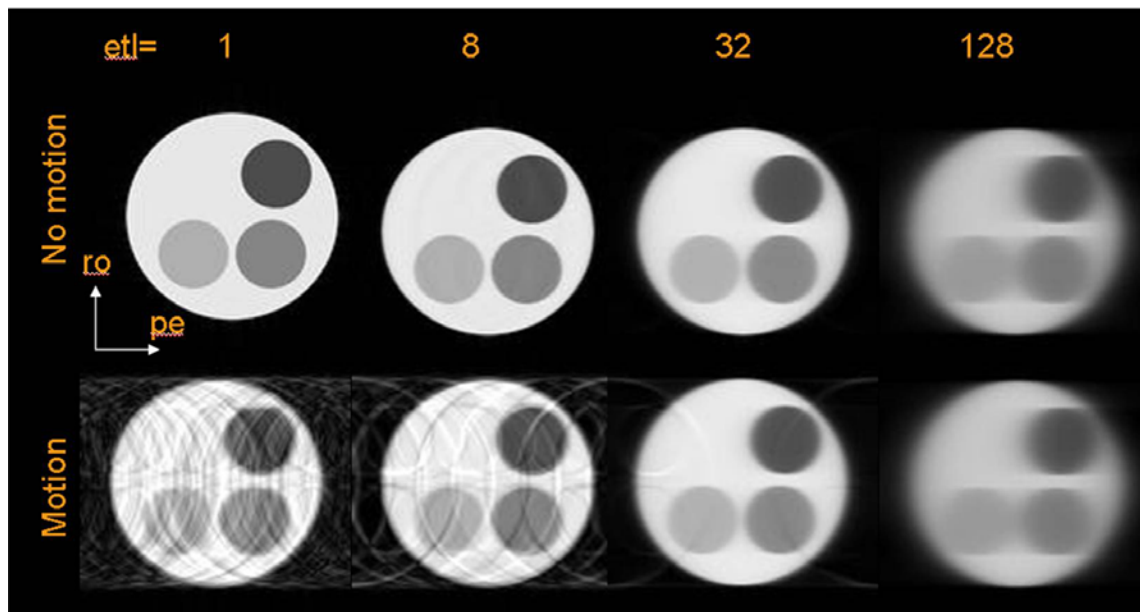


Figure 1-6 Simulation phantom data at varying ETLs (left to right) without and with motion (top and bottom row). Matrix=128 x 128, Cartesian sampling with interleaved phase encoding. Pronounced artifacts were observed in the presence of motion especially at lower ETLs (ie. multi-shot mode). As the simulation approached single-shot mode (right), ghosting artifacts were reduced although there was a loss of SNR and resolution in the phase encoding direction due to T_2 . Intrashot motion was neglected.

1.6.1 Echo Planar Imaging

Echo planar imaging (EPI) is an ultrafast imaging method that is often used to accelerate image acquisition and avoid motion artifacts (9). It has been used extensively in the fields of functional MRI, perfusion, diffusion and cardiac imaging as it facilitates the efficient acquisition of large volumes of multidimensional data. The same concepts of slice selective excitation and refocusing as well as the use of gradients to navigate through k-space apply in EPI imaging. The fundamental difference is the use of gradient echoes to acquire data rather than the spin echo. Gradient echoes can be acquired much more rapidly than spin echoes and typically ETLs of up to 100 within a single-shot can be achieved on clinical systems.

Figure 1-7 shows a spin echo EPI pulse sequence, truncated after the sixth echo. The filling of k-space is shown on the right. Data are acquired in a zig-zag fashion as driven by the readout and phase encoding gradients. Here, the readout gradients rather than RF pulses are used to generate the multiple echoes.

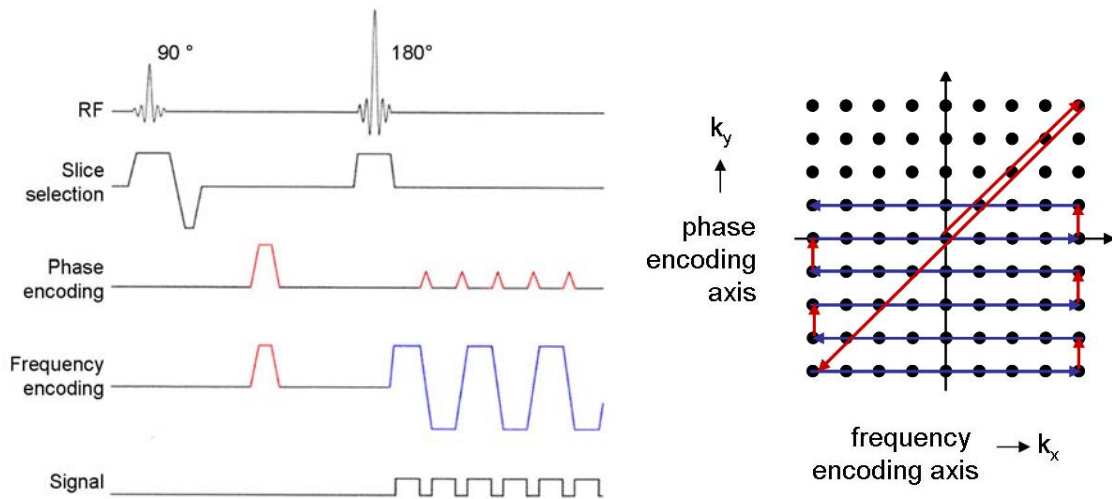


Figure 1-7 Spin echo EPI pulse sequence (left). Imaging gradients as highlighted in red and blue navigate through k-space as shown (right). Blue lines indicate where data are acquired. Figure at left adapted from Haacke, et al. (6)

However, there are several important considerations that limit the use of EPI. As mentioned in the SE pulse sequence, external factors such as susceptibility and magnetic field inhomogeneity contribute to T_2' decay. These combine with T_2 to give T_2^* (See Eqn 1.15). In the case of gradient echoes, signal dephasing is governed by the shorter T_2^* rather than T_2 . This limits the SNR and resolution.

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \quad 1.15$$

Susceptibility describes the degree of magnetization in a material when it is placed in a magnetic field. Adjacent materials with different susceptibilities experience a different magnetization (See Eqn 1.16). This gives rise to local variations in the phase of the signal, which may cause misregistration of the spin positions leading to bright and dark artifacts at tissue interfaces (eg. air-tissue interfaces in the sinuses).

$$\text{Phase difference, } \Delta\phi = -\gamma TE * f(\Delta\chi) \quad 1.16$$

Where TE is the echo time and $\Delta\chi$ is the difference in susceptibility.

Another potential source of artifacts is from chemical shift. Chemical shift is the effect whereby protons in molecules other than water experience a slightly different magnetization due to the shielding effect of the other atomic nuclei. They thus have a slightly different

resonance frequency from protons in water, and this is measured as a relative difference in parts per million (ppm). At 1.5T for example, the chemical shift, Δf_{cs} between water and lipids is 210Hz. Eqn 1.17 shows that in single-shot EPI with echo spacing (ESP) of 1ms and field-of-view (FOV) = 32 x 32cm, the water-fat shift can be as much as 6.72cm. This shift is particularly pronounced in the phase encoding direction where the bandwidth per pixel is much smaller than in the readout direction. To mitigate this, fat suppression techniques are often used (10).

$$\text{Chemical shift in phase encoding direction, } \Delta y_{cs} = \frac{ESP \Delta f_{cs} L_y}{N_s} \quad 1.17$$

Where L_y is the FOV and N_s is the number of shots.

Another consequence of the low pixel bandwidth in the phase encode direction is that EPI is highly prone to eddy current artifacts. Eddy currents are the currents induced in the conducting structures of the MRI scanner by the rapid switching of large magnetic field gradients. These in turn generate their own unwanted, decaying magnetic fields which perturb the applied gradients, resulting in errors in k-space sampling which lead to geometric distortion and ghosting in the image. They can be reduced by limiting gradient slew rates, using gradient pre-emphasis and using pulse sequences that eliminate specific eddy currents.

In EPI, successive lines in k-space are acquired in opposite directions. This commonly leads odd-even echo misalignment and inconsistent data in the presence of magnetic field inhomogeneity that have a $2/\text{FOV}$ periodicity. Uncorrected, this gives rise to ghosting artifacts. Methods to reduce this are better prescan calibration, using reference scans to correct for phase errors (11), and using postprocessing methods to enforce data consistency (12).

1.6.2 Fast spin echo

FSE, also known as turbo spin echo (TSE) or rapid acquisition with relaxation enhancement (RARE), improves acquisition speed by the use of a train of multiple RF spin echoes (13). It reduces acquisition time by a factor equal to the ETL and may be used to acquire single-shot data in humans of up to about $n\text{PE}=64$.

A 2D FSE sequence is illustrated in Figure 1-8 for ETL=2. A slice selective excitation is followed by a slice rephasing gradient as described in previous sequences. A readout pre-phasing gradient is applied, followed by a 180° slice selective refocusing pulse. Prior to the spin echo, a phase encoding gradient encodes the signal in k_y . This is followed by data acquisition and a phase rewinder to return to $k_y=0$. The refocusing, phase encoding and data acquisition is then repeated to obtain another line of data.

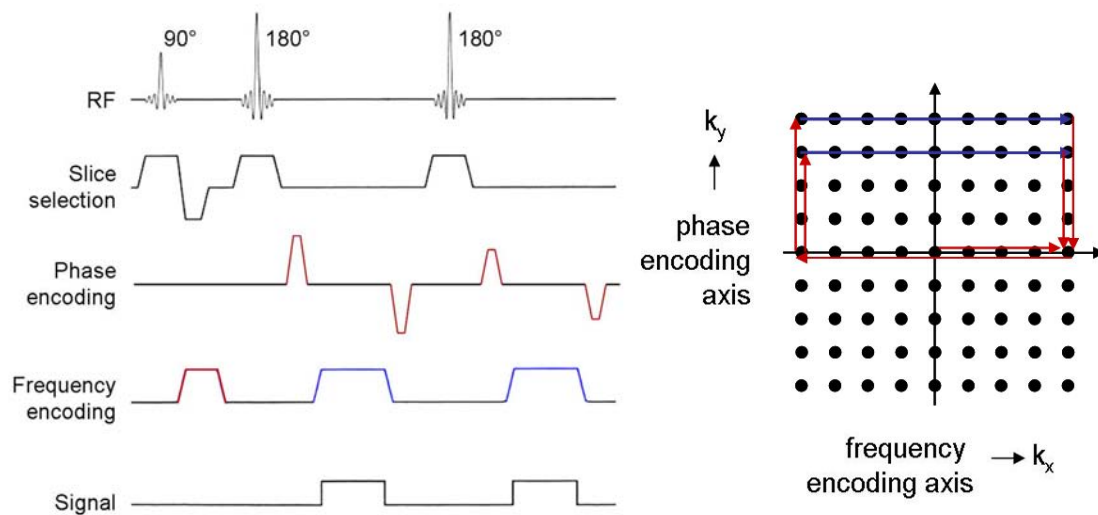


Figure 1-8 FSE pulse sequence with ETL=2 (left). Imaging gradients as highlighted in red and blue navigate through k-space as shown (right). Blue lines indicate where data are acquired. Figure at left adapted from Haacke, et al. (6)

Apart from reducing scan time compared to conventional spin echo imaging, FSE methods are much more robust to geometric distortion due to off-resonance effects, eddy currents, susceptibility and chemical shift as compared to EPI based methods. However, they are subject to increased RF power deposition, altered image contrast and T_2 blurring.

RF pulses deposit energy that causes heating in-vivo. Excessive heating, particularly in patients, is undesirable. RF energy deposition is measured by the specific absorption rate (SAR), and is dependent on the main magnetic field strength B_0 , the flip angle of the RF pulse θ and the RF bandwidth, Δf as shown in Eqn 1.18. Multiple RF refocusing pulses lead to a proportional increase in SAR, which may limit the ETL.

$$\text{Specific absorption rate, } SAR \propto B_0^2 \theta^2 \Delta f \quad 1.18$$

While refocusing pulses of $<180^\circ$ may be used to reduce SAR, careful consideration must be given to the sequence parameters. The multiple RF refocusing pulses in FSE lead to the generation of multiple signal pathways, also known as coherence pathways. When these refocusing pulses are $<180^\circ$ either by design or due to imperfections in implementation, some transverse magnetization gets tipped into the longitudinal axis and some longitudinal magnetization is excited into the transverse plane with every refocusing pulse. As additional refocusing pulses are applied and phase accumulates in the transverse magnetization components, a complex collection of signal pathways develop. In general, these pathways are not in phase and cancel destructively when data are acquired. This leads to a drop in SNR and image artifacts.

To avoid these, echoes should only occur at specified echo times in the pulse sequence and the signal pathways at these time points must be in phase. These requirements are described by the Carr-Purcell-Meiboom-Gill (CPMG) condition (14,15). To fulfil the CPMG condition, the excitation and refocusing RF pulses should be 90° out of phase with each other and the time between consecutive refocusing RF pulses should be twice that of the time between the excitation RF pulse and the first refocusing RF pulse. In addition, the phase accumulated in the transverse magnetization components must be equal between all successive refocusing RF pulses. The portion of the magnetization that satisfies the above requirements is termed the Meiboom-Gill (MG) component and these signal pathways sum constructively across echoes. In contrast, the pathways from the remaining non-MG portion of the signal interact destructively, resulting in signal oscillation and dropout.

Implementing CPMG sequences require the judicious use of crusher gradients about the refocusing RF pulses to eliminate unwanted secondary spin echoes and FIDs. The measured signal then comprises only the primary spin echos and stimulated echoes. Care should also be taken to choose an RF pulse profile that minimizes phase variation across the slice, and motion that may induce phase errors should be minimized.

Spin echo data are acquired at a single TE. In FSE sequences, each echo within one shot is acquired at a different TE. This alters the image contrast depending on the phase encoding scheme used. Since the centre line of k-space contributes most greatly to the overall image contrast, the effective TE (TE_{eff}) is denoted by the TE of the echo at $k_y=0$. In linear phase encoding for example, where k_y is traversed from one end to another, the effective TE is specified by the middle echo in the echo train. In centric phase encoding, where the phase encoding starts from $k_y=0$ and progressively increases while alternating in polarity with each

echo, the effective TE is specified by the first echo. Despite the image contrast being dependent on T_2 rather than the shorter T_2^* , the ESP is lengthened by the presence of the RF refocusing pulses. A T_2 filter is thus present in the data which limits the ETL and leads to blurring in the phase encoding direction.

Many of the problems associated with long echo trains and sensitivity to geometric distortions as in the case of EPI can be mitigated by decreasing the ETL. Multi-shot acquisitions split up the acquisition of data and can be used to reduce T_2 and T_2^* . The tradeoff is that they require N_s longer acquisition times where N_s is the number of shots, increasing the sensitivity to motion (16), and necessitating the use of navigator correction or other methods to correct the phase of the image in between shots (17,18).

1.7 High Field Strength Imaging

A fundamental challenge of MRI is to maximize the SNR and resolution while minimizing the acquisition time and image artifacts. Generally, SNR increases linearly with field strength. Hence, higher field strength systems are of particular interest, especially in pre-clinical research. This increased SNR may contribute to better resolution, better contrast and/or shorter acquisition times. It also provides for longer T_1 relaxation times which can improve magnetic resonance angiography and arterial spin labeling parameters.

There is a trend in MRI to move towards high field strengths to improve image quality. For small animal imaging, high field strength is a basic requirement and this is directly related to the effect of SNR. Basic SNR is proportional to the volume of the voxel (a volume element analogous to a three dimensional pixel) in an image. To image large vessels in humans for example, a voxel of $2 \times 2 \times 5\text{mm}$ may be adequate. For small animals this may be reduced to $0.2 \times 0.2 \times 0.5\text{mm}$. This represents a volume change of three orders of magnitude. Current magnet technology limits the maximum field available to 17 Tesla. Other improvements may be to use smaller coil geometries and cryogenically cooled coils. However, even with cutting edge research systems, imaging in small animals remains inherently more challenging than in humans.

The drawbacks of high field MRI are a lengthened T_1 relaxation time resulting in potentially longer acquisition times where the timescale of the acquisition is dictated by T_1 , and a greater impact of susceptibility and chemical shift artifacts. T_2 is shortened, leading to more rapid T_2 decay and limiting ETLs. Higher field magnets also have less homogeneous main

fields and as these systems are at the cutting edge of MR technology, they often suffer more from system instabilities like eddy currents and RF inhomogeneities. The cumulative effect of these problems often leads to errors in the measured data. In simple applications where only qualitative information is required, many of these problems can be ignored. Where quantitative or functional information is required, acquisition methods capable of monitoring and correcting instabilities due to the system or the subject need to be developed. An emerging application in imaging small animals in-vivo at high field strength is presented in Chapter 2.

2 Diffusion Weighted Imaging

2.1 Introduction

DWI uses the self-diffusion of water in-vivo to generate useful contrast that is well correlated to tissue structure. Introduced in the early 1990s, the field of DWI has grown rapidly and it is now used in standard clinical protocols to detect the presence of stroke (19). Other interesting applications include the study of tumours, trauma, haemorrhage, white matter diseases and development and aging in the brain. In small animal imaging at high fields $\geq 7T$ however, factors like low SNR, severe off-resonance artifacts and motion conspire against using conventional DWI methods. Before addressing these issues, Chapter 2 orientates the reader to a few key concepts in DWI. First, the microscopic and macroscopic origins of the diffusion signal are described. This is followed by a discussion of methods to sensitize pulse sequences to diffusion effects. Finally, the formalization of diffusion as a three dimensional tensor is presented, together with measures of anisotropy that will be used in simulations in later chapters.

2.2 Brownian motion and gaussian behaviour

DWI is based on the premise that water molecules diffuse randomly in-vivo as a result of their thermal properties. This random translational motion, also referred to as Brownian motion, is characterized by the diffusion coefficient, D . This is related to their root mean squared displacement over a given time. In the unrestricted model of diffusion, the displacement profile of water molecules is Gaussian, and can be described by the Einstein equation (20):

$$\text{Diffusion coefficient, } D = \frac{\xi^2}{6\tau} \quad 2.1$$

Where ξ is the displacement length over constant time interval τ .

In the presence of magnetic fields, proton spins are subject not only to relaxation but also diffusion. The use of well defined magnetic field gradients can be used to add a spatially varying phase to the magnetization. In non-moving spins, the phase can subsequently be reversed and the signal recovered. However, diffusion leads to an unknown spatial distribution of spins resulting in irrecoverable signal loss. Torrey reformulated the Bloch

equation (Eqn 1.5) taking diffusion into account (21). Neglecting relaxation, the Bloch-Torrey equation can be expressed as Eqn 2.2.

$$\text{Magnetization vector, } \frac{d\vec{M}}{dt} = \gamma \vec{M} \times \vec{B}_0 + D \nabla^2 \vec{M} \quad 2.2$$

Assuming constant temperature, homogenous media, spatially invariant diffusion and a spatial distribution of spins that is Gaussian, the solution to Eqn 2.2 can be found as Eqn 2.3.

$$\ln S(t) = -D\gamma^2 \int_0^t dt'' \left[\left(\int_0^{t''} \vec{G}(t') dt' \right) \cdot \left(\int_0^{t''} \vec{G}(t') dt' \right) \right] + \ln S(0) \quad 2.3$$

Where S is the signal magnitude and G is the applied magnetic field gradient. Assuming $S(0)=1$, the latter term may be ignored.

Eqn 2.3 suggests monoexponential behaviour of the signal loss due to diffusion. However, in-vivo experiments showed that with high degrees of applied diffusion weighting, the observed signal loss could be characterized by a biexponential function (22,23). This led to the hypothesis that there was a fast and slow diffusing compartment associated directly with the extra and intracellular components respectively of the tissue within a given voxel. This was based on the assumption that intracellular diffusion was subject to greater restrictions than in the extracellular compartment due to the presence of cell organelles and membranes.

However, there was poor agreement between the experimentally determined contributions of the two components and their biological volume fractions. Others argued that there was no biological basis for the two-compartment model, and postulated other methods of modeling the in-vivo diffusion signal. These were restricted diffusion in a single component (24), a multiexponential model (25) and a cumulant expansion model (26). Other recent advances include the use of q-space imaging to determine the full displacement probability distribution of the diffusion signal (27) and measuring the diffusion kurtosis, also the deviation of the signal behaviour from Gaussian (28). However, the focus of this work was on sampling and reconstruction methods, and the conventional monoexponential diffusion model with Gaussian distribution was used in all cases.

2.3 Tissue anisotropy and heterogeneity

In pure water, where the solution is homogenous and there are no barriers to diffusion, the assumptions used in Eqn 2.3 are valid. However, at in-vivo temperatures and over the diffusion time and voxel length scales used in DWI, interactions between proton spins and physical barriers in-vivo are inevitable. These barriers may be cell organelles, proteins, membranes and others. As such, the measured diffusion does not represent the true intrinsic diffusion, and is termed the apparent diffusion coefficient (ADC).

Diffusion is a three dimensional process. Depending on the structure of any barriers or restrictions within the tissue of interest, diffusion may be greater in one direction than another. Figure 2-1 sketches the path of a randomly diffusing water molecule in pure water, viscous solution and a nerve fibre. In pure water, there are no restrictions and diffusion is isotropic. In viscous solution, the average diffusion is uniformly restricted and remains isotropic. In the nerve fibre, axonal membranes and myelin sheaths restrict diffusion more greatly in the direction perpendicular to the fibres than in the direction parallel to the fibres. Diffusion here is restricted and anisotropic. The associated eigenvalues in the orientations of the eigenvectors are also given, and these will be explained later in the chapter.

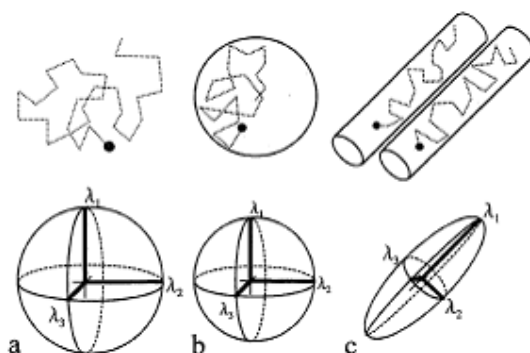


Figure 2-1 Schematic representation of the path traced by a randomly diffusing water molecule (top row) in (a) pure water, (b) viscous solution and (c) along nerve fibre. Corresponding diffusion ellipsoids are presented (bottom row). λ_1 , λ_2 and λ_3 are the eigenvalues oriented along the axes of the respective eigenvectors. Figure from Heemskerk, 2006 (29).

Early experiments in cats showed that diffusion was isotropic in grey matter but anisotropic in white matter and spinal cord (30). It was first proposed that the anisotropic diffusion behaviour in nerve fibres was due to the myelin sheaths and its numerous lipid bilayers (31). It has since been found that axonal membranes, and not myelin, dominate as the basis for anisotropic diffusion in nerve fibres (32,33). Still, other organelles such as microtubules and neurofilaments have been shown to contribute to the measured anisotropy. Anisotropy is not

unique to nerve fibres, and has been identified in muscle, kidneys, tumours and other tissues. The attribution of anisotropy and indeed non-monoexponential behaviour to a particular biological component is complicated by the heterogeneity in size, shape, orientation, T_2 , conformation and interactions of the different components present in-vivo. These are on such a small length scale that individual component contributions are averaged within the larger imaging voxel via partial volume effects. Understanding the sources of anisotropy and non-monoexponential behaviour remains an active field of research, and the reader may refer to this useful review (33).

2.4 Diffusion sensitization

In order to measure the ADC, it is necessary to employ diffusion sensitizing gradients. These were first applied using static field gradient techniques but these were superseded by pulsed field gradient technique (34) that enabled the application of gradients amplitudes of 1-2 higher orders of magnitude. Figure 2-2 shows how this is most commonly combined with a Hahn spin-echo sequence (8) to give a pulsed gradient spin echo (PGSE) DW preparation, also known as Stejskal-Tanner DW. The extra gradients G are used to phase label the transverse magnetization of the water molecules as a function of spatial location. Note that while the gradients G are shown here to be applied in the slice select direction, they can be applied independently along any axis or in combination to obtain diffusion sensitization in any direction.

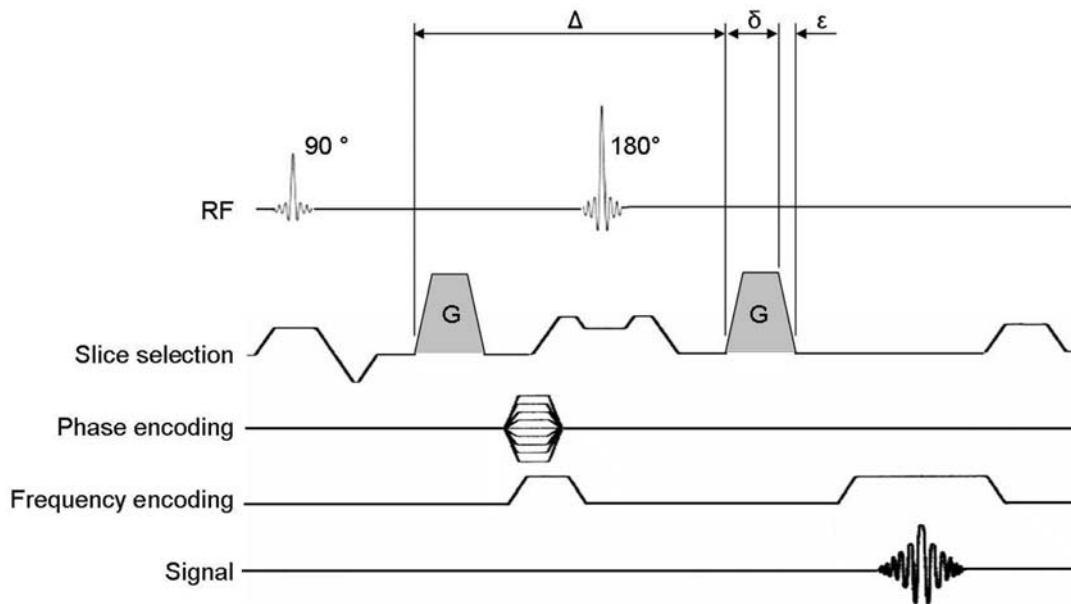


Figure 2-2 Spin echo pulse sequence with PGSE DW preparation. DW gradients G are δ long, separated by Δ and with a slew time of ϵ .

Consider Figure 2-3 where the proton spins begin in phase after the 90° excitation pulse. The first diffusion gradient is applied which leads to a spatially varying dephasing of the spins. In the case of no motion, all the spins are rephased by the 2nd diffusion gradient. In the presence of motion (ie. diffusion), not all the proton spins will be rephased by the second gradient. This leads to a drop in the signal detected.

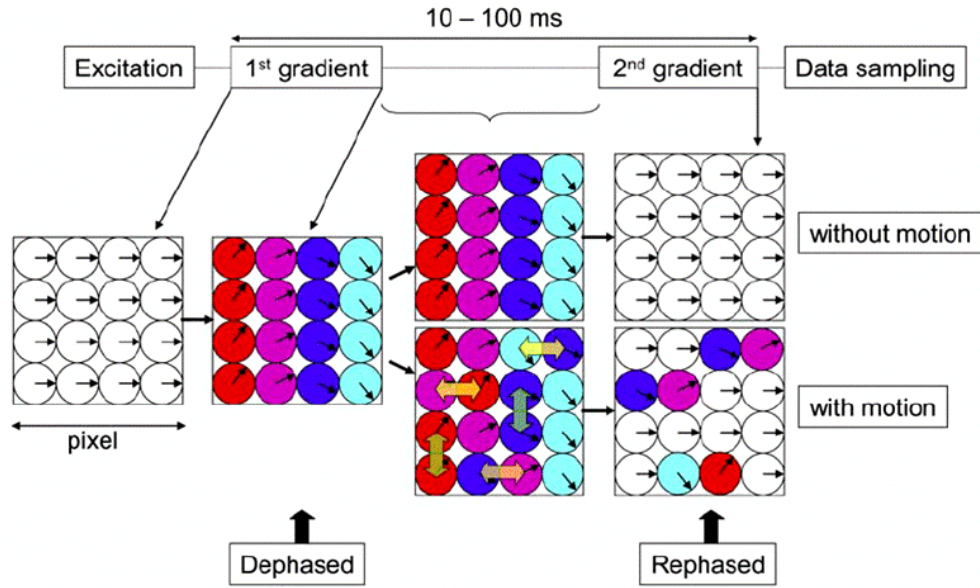


Figure 2-3 Effect of microscale diffusion on diffusion sensitized proton spins. Each pixel contains a distribution of spins that is dephased and rephased by the diffusion gradients. Note the incomplete phase refocusing due to microscale diffusion of the protons. Figure from Mori and Zhang, 2006 (35).

The measured signal decrease is related to the degree of diffusion sensitization, also known as the b-value, and the diffusivity of the given tissue, D. Combining relaxation effects from Eqn 1.14 with diffusion effects from Eqn 2.3 gives:

$$\text{Signal, } S = S_0 \left(1 - e^{-\frac{TR}{T_1}}\right) e^{-\frac{TE}{T_2}} e^{-bD} \quad 2.4$$

Where S_0 is the signal intensity arising from the spin density.

In the case of the spin echo sequence with PGSE DW preparation, the diffusion weighting due to the diffusion gradients G can be analytically derived as Eqn 2.5. For more complicated diffusion weighting schemes, numerical methods may have to be used to determine the b-value.

$$\text{b-value, } b = \gamma^2 G^2 \left[\delta^2 \left(\Delta - \frac{\delta}{3} \right) + \frac{\varepsilon^3}{30} - \frac{\delta \varepsilon^2}{6} \right] \quad 2.5$$

Where γ is the gyromagnetic ratio, G is the applied gradient strength, δ is the gradient pulse duration, Δ is the inter-gradient pulse delay and ε is the gradient slew time.

Keeping TR, TE and other parameters constant, the diffusivity may be obtained, or more rightly the ADC, by acquiring an image at two different b-values. This is usually done by varying the gradient strength G. In practice, one b-value usually comprises no or very low diffusion weighting and the resulting reference image is known as the b_0 image.

$$\text{Apparent diffusion coefficient, } ADC = \frac{\ln(\frac{S_2}{S_1})}{b_1 - b_2} \quad 2.6$$

Where S_1 and S_2 are the signal intensities measured at a given voxel at b-values b_1 and b_2 .

In some applications such as stroke imaging, finding the mean ADC is sufficient for diagnostic purposes. This is commonly found by obtaining the mean of three ADC measurements with DW in orthogonal directions. This usually necessitates acquiring a total of four images - a b_0 image and three DW images. Single-shot isotropic DW methods have been proposed to reduce the number of DW images needed from three to one (36,37). These will be discussed in Chapter 6.

2.5 Diffusion tensor imaging

Although the focus of this work is the development of methods for rapid isotropic DWI, anisotropy terms based on the diffusion tensor are used widely in the simulation data, and warrant introduction. Since diffusion is anisotropic in many tissues in the body, useful information about the 3D orientation and structure of tissues can be obtained by modeling diffusion as a symmetric 3D tensor:

$$\text{Diffusion tensor, } \overline{\overline{D}} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \quad 2.7$$

In order to determine tissue diffusivity in all directions, it would be necessary to obtain diffusion-weighted measurements along a multitude of axes. This would be impractical. A 3D diffusion tensor model was proposed that fitted the data to a 3D ellipsoid characterized by three eigenvalues and three eigenvectors (See Figure 2-1) (38).

By acquiring images with diffusion weighting in at least six non-collinear directions, the six independent unknowns in the diffusion tensor may be found. The tensor can be further

diagonalised to obtain the principal eigenvalues, λ_1 , λ_2 and λ_3 , and eigenvectors. These allow the calculation of parametric maps of the mean ADC (See Eqn 2.8) and anisotropy on a voxel by voxel basis (39). The former describe the average size of the diffusion ellipse while the latter describe the eccentricity of the ellipse. There are several quantitative measures of anisotropy, the most commonly used of which is the fractional anisotropy (FA) (40) as in Eqn 2.9, and is used throughout this text. A number of colour maps have been proposed to better illustrate the 3D directionality of the measured FA in a 2D image (41,42). The most widely used assigns a colour red, green and blue to the left-right, up-down and in-out directions respectively (43). An example of the mean ADC, FA and colour FA maps in the in-vivo mouse brain as acquired at 9.4T are given in Figure 2-4.

$$\text{Mean apparent diffusion coefficient, } ADC_{mean} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad 2.8$$

$$\text{Fractional anisotropy, } FA = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{\sqrt{2} \cdot \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad 2.9$$

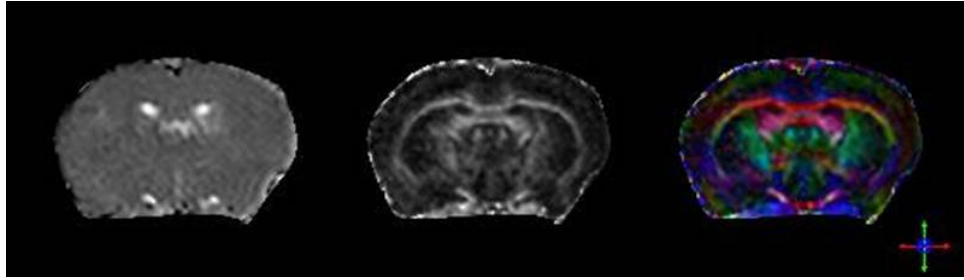


Figure 2-4 Sample in-vivo mouse brain data using spin echo DW-EPI with PGSE preparation. Mean ADC (left), FA (middle) and colour FA (right) maps depicted. FOV = 19.2 x 19.2mm. Images were acquired at 96 x 96 resolution, zero-filled to 192 x 192 and a mask was applied.

The tensor provides information about the orientation of the principal diffusivities, and in the brain, allows one to make inferences about white matter orientation. Consequently, diffusion tensor imaging (DTI) enables the tracking of white matter tracts to better understand brain interconnectivity (44). In small rodents, DTI has been used to investigate normal development and aging in the brain, as well as to study a host of pathological processes such as tumours, stroke, spinal cord injury, Alzheimer's disease, Parkinson's disease, Huntington's disease and others. Further discussion on the limitations of the tensor model and the use of higher DW direction sampling densities may be found elsewhere (45,46).

2.6 Challenges in DWI

DWI is a quantitative measure of diffusion that is highly sensitive to errors in the b-value. These errors arise from a number of sources, and need to be avoided or corrected in order to obtain high quality DW data.

2.6.1 SNR

Since DWI is dependent on the signal attenuation due to loss of intravoxel phase coherence, it is essential to obtain good SNR to reduce noise-induced bias. Low SNR limits the b-values used, and this may result in suboptimal diffusion contrast. While ADC values are not significantly affected, low SNR results in an upward bias in FA (47). Methods to improve SNR include minimizing T_2 and T_2^* , using pulse sequences that maximize the available magnetization and using higher field strengths.

2.6.2 Susceptibility

However higher fields lead to corresponding increases in magnetic susceptibility artifacts. In regions with prominent air-tissue interfaces such as the sinuses, susceptibility-induced B_0 variations act like local diffusion gradients. This causes the b-value to be spatially varying. Artifacts thus induced are much more prominent in gradient echo and EPI sequences than spin echo based sequences, particularly when data are acquired in a single-shot. Parallel imaging techniques have been used successfully to shorten the echo train and improve resistance to susceptibility artifacts (48).

2.6.3 Eddy currents

Due to the presence of large pulsed magnetic field gradients, eddy currents can have a significant impact on the applied b-value. They may also give rise to slowly decaying fields during the readout that result in image distortion. Several methods exist to mitigate the impact of eddy currents. The use of bipolar diffusion gradients for example, was shown to result in eddy currents that tend to cancel out (49). Pre-emphasis adds a compensatory term to the desired gradient waveforms that is opposite to the gradient perturbation due to eddy currents (50). Pulse sequences like the twice refocused spin echo method may also be designed such that eddy currents with specific decay constants can be eliminated (51). Alternatively, postprocessing methods may be used. These may aim to coregister distorted DW data to a common undistorted template (52), or maximize the correlation between a

series of DW data based mutual information (53). Another method derived eddy current field maps from water phantoms, and applied corresponding corrections in human data (54,55).

2.6.4 Imaging gradients and cross-terms

As the amplitude of DW gradients typically greatly exceed those of the imaging gradients, b-values arising from the imaging gradients and their interaction with the diffusion gradients (ie. cross-terms) are often ignored. In practice, these terms are non-negligible. My simulations show that they may add about 2% to the nominal b-value depending on the pulse sequence used. This should ideally be accounted for by using numerical simulations to accurately estimate the b-values based on the sequence parameters, or avoided by designing sequences that minimize concurrent gradients that lead to cross-terms. The latter method may however reduce the efficiency of the pulse sequence. Additionally, poor shimming, gradient non-linearity and miscalibration may lead to B_0 inhomogeneity and errors in calculated diffusion parameters.

2.6.5 Motion

DWI is sensitive to motion on the molecular level, hence it is highly susceptible to artifacts due to bulk motion. This bulk motion may be due to factors including respiration, cardiac pulsation, subject movement, peristalsis and even minor motion such as brain pulsatility. As such, fast imaging methods have to be used to minimize scan time and motion artifacts. Single-shot methods successfully minimize motion but suffer from severe blurring due to T_2 or T_2^* effects. This may be mitigated by reducing the echo train length via the use of multi-shot methods and/or parallel imaging. In the ex-vivo environment, spin echo methods have been applied to obtain high quality data (56). However, multi-shot methods are more time consuming and affected catastrophically by motion in between shots. To ameliorate this, navigator methods that correct for phase errors due to motion have been used (57), along with non-cartesian methods like radial (58), PROPELLER (59) and spiral (60) sampling that oversample the centre of k-space and are inherently self-navigating.

In clinical practice, single-shot DW-EPI is most commonly used due to its robustness to motion and rapid acquisition. At high fields $\geq 7T$, susceptibility and eddy currents lead to severe geometric distortion. Fast spin echo methods are intrinsically more robust to these effects. Coupled with a multi-shot acquisition to minimize T_2 , it becomes necessary to correct for motion in between shots. Chapter 3 introduces PROPELLER as an SNR efficient and motion robust method for acquiring data using a range of contrasts.

3 PROPELLER MRI at High Field Strength

3.1 Introduction

Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER) MRI (61), also known as BLADE (62) or MultiVane (63), was introduced in 1999 as an acquisition method that enabled in-plane motion correction. It was originally based on a FSE sequence that is inherently resistant to B_0 artifacts, and has since been adapted for use with EPI methods as well (64). Data are acquired in blades that are rotated to fill k-space, and subsequently converted to an image via regridding to Cartesian k-space followed by the FFT, or other iterative methods. These blades have low spatial resolution in one direction and high resolution in the normal direction. Like other non-cartesian sequences such as radial (65) and spiral imaging (66), PROPELLER oversamples the centre of k-space. The overlapping central region allows for translation and rotation correction between shots, where each blade is acquired in a single-shot. Specific blades that are corrupted by excess or through-plane motion can be selectively rejected, and motion can be mitigated by a suitable phase correction. Figure 3-1 illustrates the ideal k-space trajectories for multi-shot Cartesian and PROPELLER acquisitions without motion, and an example of the effective k-space when corrupted by motion.

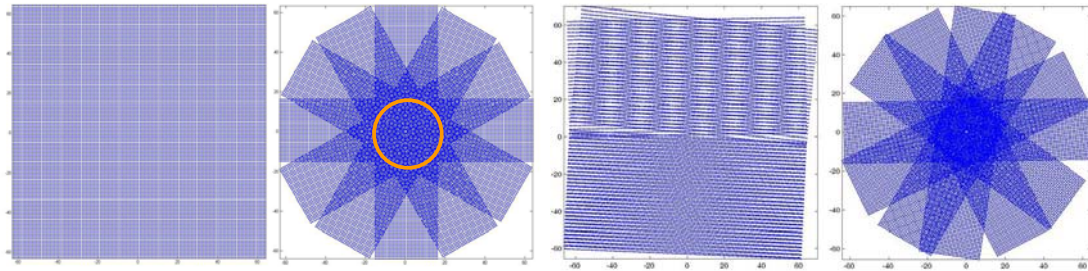


Figure 3-1 Ideal multi-shot Cartesian (leftmost) and PROPELLER (second from left) k-space acquired without motion. Central oversampled region is highlighted. Effective Cartesian (third from left) and PROPELLER (rightmost) k-space with random rotation and translation in between shots.

In multi-shot acquisitions, intrashot motion is often neglected as each shot is acquired rapidly, on the order of 100-200ms depending on the echo spacing and echo train length. The short acquisition time effectively freezes out motion and explains why single-shot methods are more robust to motion than multi-shot methods. Multi-shot acquisitions

however, require intershot motion correction, as each shot may be spaced seconds apart depending on the TR, during which time significant motion could have occurred.

In Cartesian acquisitions, motion mainly gives rise to ghosting artifacts in the more slowly traversed phase encoding direction. In small animal imaging, motion in the healthy mouse brain can be minimized by using suitable anaesthesia, sedation and stereotactic fixation with a nosecone, bitebar and earbars. However, certain strong anaesthetics, paralyzing agents and procedures such as intubation and ventilation carry the risk of injuring or killing the animal. Moreover, fixation is less effective in regions outside the brain. During human clinical studies, patients such as those with major neurological disease can be uncooperative and move in the scanner, yet fixation or sedation may not be recommended for medical reasons.

Motion can also be ameliorated using rapid but resolution-limited single-shot sequences, physiological gating that increases scan time and leads to variable TR, or navigator echoes (67,68) at the expense of a lengthened TE and a drop in SNR. Navigator echoes are typically non-phase encoded echoes that contain phase information as a function of motion in a given shot. The data acquired can then be corrected by the respective navigator phase to enforce consistency in the data. The self-navigated PROPELLER acquisition circumvents the need for additional navigator echoes as motion can be estimated and corrected for by correlating the central overlapping regions between blades. Further, the repeated sampling of the centre of k-space potentially increases SNR. Figure 3-2 shows the results of the motion correction in a volunteer who was asked to rotate his head from side to side during a scan. Data were acquired on a 3T Philips Achieva scanner. Preliminary human studies may be found in Section 3.2.4.

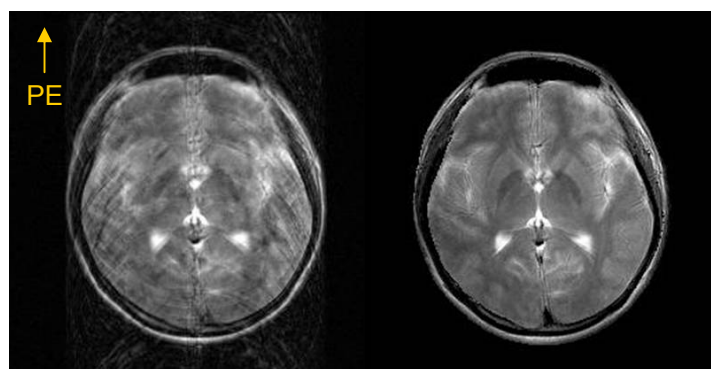


Figure 3-2 Human brain images acquired at 3T with a Cartesian FSE sequence (left) show marked ghosting in the phase encode (PE) direction in the presence of motion. The FSE-PROPELLER sequence (right) demonstrates effective motion correction.

The majority of work in PROPELLER has been performed at 1.5T (59,61) with increasing numbers of studies at 3T (62,64). Recently, the use of PROPELLER at higher field strengths such as 7T (63,69,70) and 9.4T (71) has been explored by others and myself respectively. While higher field increases SNR, there are several potential disadvantages. First, T_1 is lengthened, leading to longer acquisition times, while T_2 is shortened, enhancing T_2 decay. This suggests that shorter echo trains may be needed, increasing the number of blades required for full k-space coverage and limiting motion correction in PROPELLER. Second, susceptibility and chemical shift are both enhanced leading to a marked increase in associated artifacts. This will present a problem particularly with EPI based methods that are sensitive to off-resonance effects.

This chapter explores the hypothesis that FSE-PROPELLER is highly suited for PD-weighted and T_2 -weighted imaging in-vivo at high resolution and high field strength. To investigate this, a series of simulations were constructed and experiments were conducted in both mice at 9.4T and humans at 3T, as the MultiVane sequence became available on the Philips Achieva scanner during these studies, humans at 3T. In particular, FSE-PROPELLER was compared to other acquisition methods including single-shot, Cartesian and EPI. Due to limitations of the commercial implementation and to make comparison between systems more accessible, all reconstructions were performed offline using the same reconstruction algorithm as outlined in this chapter.

The chapter begins with a description of the acquisition and reconstruction of PROPELLER data. This is followed by an outline of the simulations and the experimental protocols that were used. Data from simulations and in-vivo experiments are presented, together with a k-space based sampling strategy to improve contrast at the expense of SNR. The applicability and limitations of FSE-PROPELLER are discussed.

3.2 Materials & Methods

3.2.1 PROPELLER Acquisition & Reconstruction

Data were acquired in N_b blades, each consisting of n_{PE} phase encode steps and n_{FE} frequency encode steps. On both the Varian and Philips scanners, data were twice oversampled in the frequency encoding direction and truncated to the central n_{FE} data to avoid foldover artifacts in that direction. For the fully sampled case, as determined by acquiring sufficient blades such that the gap between k-space data at the corners of adjacent blades is no greater than the gap in between successive phase encode steps within the

same blade, N_b is given by Eqn 3.1 (61). N_b necessarily was rounded off to the nearest integer in implementation, usually resulting in a slight over or undersampling of the data using this criterion. For convenience, fully sampled PROPELLER as used in this work refers to data using the rounded value of N_b . PROPELLER acquisition matrices will subsequently be described in the format $nFE \times nPE \times N_b$ (eg. $256 \times 32 \times 12$).

$$\text{Number of blades, } N_b = \frac{nFE}{nPE} * \frac{\pi}{2} \quad 3.1$$

The image FOVs were periodically rotated for each successive blade, leading to k-space data as shown in Figure 3-1. The central region of k-space was multiply sampled while the periphery of k-space was sampled only once. Each blade was acquired within a single-shot.

In 2D MRI, in-plane bulk motion can be described in terms of a rotation matrix, $\mathbf{R}_a$ and a translation vector, $\mathbf{T}$ as follows:

$$S_{cj,T_j}(k_j) = S_{ref}(R_{cj}^{-1}k_j) \exp[-2\pi(R_{cj}^{-1}k_j) \cdot T_j] \quad 3.2$$

Where S_a is the motion-corrupted signal in k-space, S_{ref} is the actual signal and k_j is the location in k-space.

From Eqn 3.2, it can be found that a rotation of the object in image space is the same as a rotation of k-space about its centre, while a translation in image space translates to a linear phase ramp in k-space and vice versa.

In order to combine information from different blades, phase errors need to be first corrected. A 2D triangle window was applied to each blade in k-space, and the resultant image phase was removed from the original blade data (61) as shown in Figure 3-3. This removes spurious phase information due to motion, imperfect gradient balancing and eddy currents. The triangle window was used because the FT of a triangular window is a $\text{sinc}^2(x)$ function that has no negative values. This avoids introducing 180° phase shifts from Gibb's ringing into the windowed image, which should not be removed from the raw image phase.

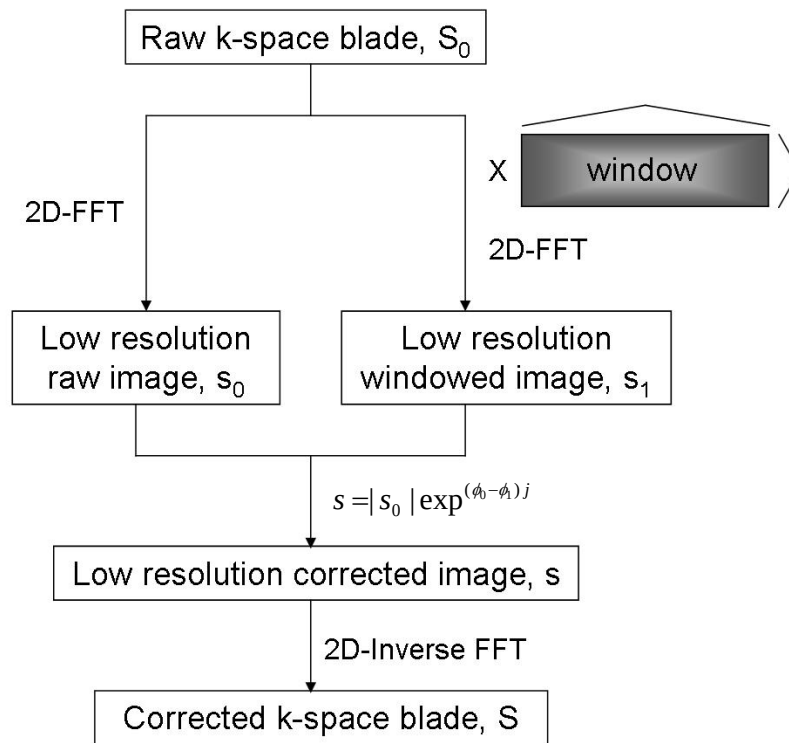


Figure 3-3 Phase correction process for each PROPELLER blade

Subsequently, each of the coordinates of the peak k-space magnitudes were found. The blades were then shifted in k-space by subtracting the corresponding x- and y-coordinates for every $k_{x,y}$, such that the peak intensity for all blades were aligned at (0,0).

Blades that were deemed to have been overly corrupted by intrashot motion were discarded. This was determined by identifying blades whose k-space peak magnitude was less than 0.6 of the largest k-space peak magnitude among all blades – the assumption being that uncorrectable through-plane motion had occurred. These blades were excluded from further analysis, reducing SNR and resolution in the direction parallel to the missing blades. The effect of removing blades will be discussed further in Chapter 4. In practice, this arbitrary threshold meant that only blades with severe motion were discarded.

Rotation and translation correction may subsequently be applied. First, a central disc of k-space data of diameter equal to the blade width was extracted, gridded and rotated by the nominal blade angle such that the low-resolution data across all blades were oriented similarly. Due to intershot rotation, the data are offset by some angle. To estimate this angle, each blade was rotated progressively from -5° to $+5^\circ$ in 1° intervals. The range and intervals

of rotation would depend on the range of anticipated subject rotation and desired accuracy respectively. The correlation of k-space magnitude data at each angle with respect to reference k-space magnitude data, as obtained from the blade with the highest peak signal intensity, was found. To reduce the heavy weighting at the centre of k-space, each point in k-space was multiplied by the square of its distance from the centre of k-space. The correlation values were then fit using a fourth-order polynomial and the rotation was found based on the peak correlation. The blades were then corrected by a rotation of the appropriate angle. Translation was estimated by finding the peak value of the convolution of the central image data of the respective blade with that of the reference blade. This was done by multiplying their k-space values, followed by a Fourier transform. Second-order polynomial fits in the x and y directions were used to find the peak value, also the translation. The corresponding linear phase was removed from the data in each blade. Due to imperfect estimation, motion correction was turned off in simulations without added motion.

To combine this non-cartesian data, the discrete Fourier transform (DFT) may be used, but this is computationally inefficient, requiring $O(N^2)$ operations. For efficiency, non-cartesian data are often regridded onto a Cartesian grid using some well chosen density compensation function and convolution function, followed by the FFT which requires $O(N \log N)$ operations. Typically, a Kaiser-Bessel interpolation kernel is used for gridding. Depending on the nature of the data, other interpolation kernels such as sinc, spline, Gaussian or polynomials may be used (72).

There exists a wide range of methods that may be used to reconstruct non-Cartesian data. Both non-iterative methods such as the use of k-space sparse matrices (kSPA) (73) and iterative methods such as projection onto convex sets (POCS) (74), GRAPPA operator gridding (GROG) (75) and conjugate gradient methods (17,76,77) have been shown to substantially reduce approximation errors over simple interpolation methods.

One effective method is the use of NUFFT, the aim of which is to derive an oversampled FFT of a given image and optimally interpolate onto the specified non-uniform k-space using small local neighbourhoods in k-space. NUFFT has been used with interpolation kernels that are Gaussian (78) or derived by minimizing the approximation error in a least squares sense (79) or a worst case (min-max) sense over all signals of unit norm (80). Fessler, et al. showed that NUFFT with min-max interpolation reduced interpolation errors by four orders of magnitude compared to bilinear interpolation and was faster than the DFT by more than 100 times in Shepp-Logan simulations with randomly generated k-space sampling. Figure 3-4

illustrates data reconstructed using bilinear interpolation and the griddata function, which is based on Delaunay triangulation, in Matlab v7.4 (The Mathworks, Natick, MA) versus the min-max NUFFT algorithm. Reconstructions were performed on a shared dual core 1GHz AMD Opteron Processor 254 platform with 16Gb RAM and Linux operating system.

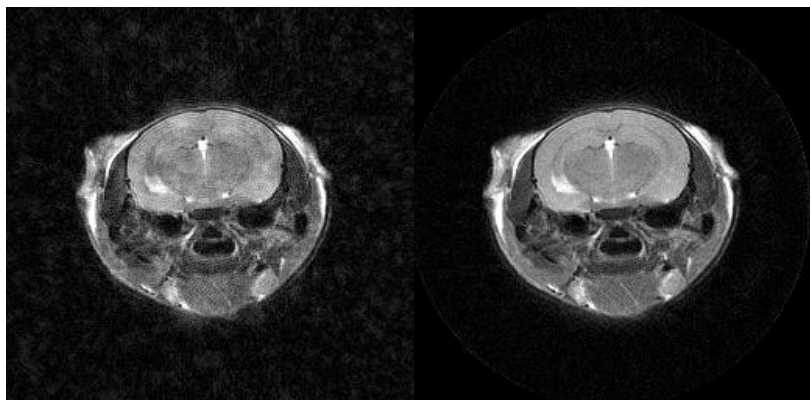


Figure 3-4 In-vivo mouse brain PROPELLER images reconstructed at a resolution of 256 x 256 using griddata (left) and NUFFT (right) show significant improvement in image quality. Griddata and NUFFT reconstruction times for 5 slices were 97s and 313s respectively.

Here, min-max NUFFT was identified as an effective tool for the robust and reliable reconstruction of PROPELLER data. It was employed in all subsequent PROPELLER reconstructions. Detailed analyses of image reconstruction methods may be found in the papers cited above. One drawback of NUFFT is the long processing time. Griddata and NUFFT reconstruction of 5 slices of 256 x 256 data required 97s and 313s respectively, while equivalent Cartesian data could be reconstructed in 2.2s. However, neither anatomical nor diffusion data require real time reconstruction and this can be done offline. If required, improvements in processing speed may be achieved through more efficient code parallelization, the use of dedicated computing resources or reducing accuracy specified by the NUFFT algorithm. However, this was not the focus of this work.

3.2.2 Simulations

The Shepp-Logan phantom was created to simulate the head and brain for 2D computerized tomography (CT) (81). It comprised a number of ellipsoids used to represent different tissues in the brain such as grey matter (GM) and white matter (WM). Its analytical form and k-space representation were presented as a summation of the k-space for individual ellipsoids (82). This facilitated MRI reconstruction with arbitrary k-space trajectories. In order to adapt the image contrast from CT to MRI, each ellipsoid had to possess a discrete set of MRI

parameters such as spin density and T_2 . Since the ellipsoids were overlapping, this necessitated the subtraction of the background 'tissue' from the foreground 'tissue'.

The simulation used here follows work by Gach, et al (83) with the following exceptions. Tissue parameters for scalp were substituted with cerebrospinal fluid (CSF) and tissue parameters for bone were substituted with cartilage. This was due to the wider availability of the latter T_2 parameters at different field strengths in the literature. Table 3.1 presents the geometry and tissues represented in the simulation used. Following their convention, the column *Portion Subtracted* refers to the background subtracted within a given ellipsoid. For example, consider *Ellipsoid 2* where the k-space representation of a region with the geometry of *Ellipsoid 2*, but parameters of *Ellipsoid 1*, is subtracted from the total k-space. This removes the mixing of tissue properties where ellipses overlap. Simulations were implemented on Matlab v7.4 (The Mathworks, Natick, MA) using existing code (84) modified to include T_2 effects.

Ellipsoid	Centre		Half Axis		Angle	Portion Subtracted	Tissue
	x	y	a	b	θ		
1*	0	0	0.72	0.95	0	NA	CSF
2	0	0	0.69	0.92	0	1	Cartilage
3*	0	-0.0184	0.6624	0.874	0	2	CSF
4	0	-0.0184	0.6524	0.864	0	3	GM
5	-0.22	0	0.41	0.16	-72	4	CSF
6	0.22	0	0.31	0.11	72	4	CSF
7	0	0.35	0.21	0.25	0	4	WM
8	0	0.1	0.046	0.046	0	4	Tumour
9	-0.08	-0.605	0.046	0.023	0	4	Tumour
10	0.06	-0.605	0.046	0.023	-90	4	Tumour
11	0	-0.1	0.046	0.046	0	4	Tumour
12	0	-0.605	0.023	0.023	0	4	Tumour

Table 3.1 2D Shepp-Logan specification. *Regions not included in the original Shepp-Logan phantom, Ellipsoids 1 & 3 represent the scalp and CSF in the subarachnoid space respectively.

Relative proton density and T_2 were simulated at different field strengths and these are given in Table 3.2. TR was assumed to be sufficiently long in all cases such that T_1 could be

neglected. T_2 decay was assumed to be zero within each phase encoding step. Since T_2 at 1.5T and 3T were similar, simulations at 1.5T were excluded.

	Field	Cartilage	WM	GM	CSF	Tumor
PD	All	0.12 ⁽⁸³⁾	0.617 ⁽⁸³⁾	0.745 ⁽⁸³⁾	0.98 ⁽⁸³⁾	0.95 ⁽⁸³⁾
T_2 (ms)	1.5T	30 ⁽⁸⁵⁾	72 ⁽⁸⁵⁾	95 ⁽⁸⁵⁾	290* ⁽⁸⁵⁾	111 ⁽⁸⁶⁾
	3T	27 ⁽⁸⁵⁾	69 ⁽⁸⁵⁾	99 ⁽⁸⁵⁾	275* ⁽⁸⁵⁾	111 ⁽⁸⁶⁾
	9.4T	8** ⁽⁸⁷⁾	35.4 ⁽⁸⁸⁾	40.3 ⁽⁸⁸⁾	111 ⁽⁸⁸⁾	62 ⁽⁸⁹⁾

Table 3.2 MRI parameters used in simulations. T_2 values reported for 1.5T and 3T were from human data while those at 9.4T were from mouse and rat data. *Blood T_2 was used here. **Measurement was at 8.5T instead of 9.4T.

Figure 3-5 serves as a key for identifying the various ellipsoids. A binary mask was applied in all cases to exclude regions outside Ellipsoid 1.

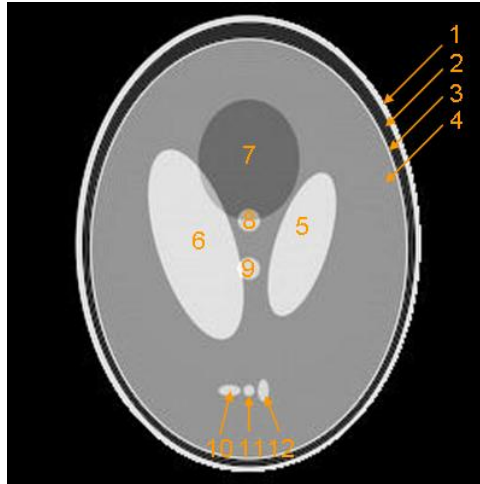


Figure 3-5 Shepp-Logan reference identifying various tissue ellipsoids as given in Table 3.1.

All simulations described were tested with no T_2 , T_2 at 3T and 9.4T, over two sets of TE. Echo spacing was set to 6.38ms to match in-vivo experiments at 9.4T. Gaussian noise with a mean of zero was added to each k-space blade. The SD of this added noise was such that the SNR within Ellipsoid 1 of the reconstructed image was 20, in data with Cartesian sampling, no T_2 and a single average. Phase encoding scheme in Cartesian sampling was interleaved.

To illustrate the effects of field strength, motion and sampling method on image fidelity, data were simulated at a resolution of 256 x 256 (Cartesian), and 256 x 64 x 6 (PROPELLER), where ETL=64, in the absence and presence of motion. Here motion was a $\pm 0.5\text{mm}$ random translation in x- and y-directions, and a ± 5 degree random rotation, where the FOV was 25.6 x 25.6mm.

Previous works have argued for the use of phase encoding schemes that are centric (90), customized (91,92) and that segregate odd and even echoes into the centre and periphery of each blade (59,93), in an effort to improve contrast, resistance to artifacts and/or reduce sensitivity to non-CPMG effects. Out of these, two sets of simulations were constructed. The first used TE=6.38ms and a centric phase encoding scheme to maximize SNR and to allow a large range of ETLs at the same TE to be tested. Reconstructed matrix size was 256 x 256 and ETL = [8, 16, 32, 64, 128, 256]. PROPELLER blade widths were set to match the corresponding ETL. The second set used TE=51.0ms and a linear phase encoding scheme to obtain good T_2 -weighted contrast while keeping the total echo train duration minimal. Linear phase encoding was found to produce images that were visually equivalent to those produced using the phase encoding scheme by Pipe, et al. (59), and was used due to its general availability on scanners. Due to linear sampling and restraints on TE, only ETL = [8, 16] were simulated.

To quantify image SNR, contrast-to-noise ratio (CNR) and artifact power (AP), Cartesian and PROPELLER simulations were repeated ten times without motion and for a range of ETLs. The parameters were measured using Eqns 3.3, 3.4 and 3.5. To normalize theoretical scan times, two averages were simulated for the Cartesian scans and PROPELLER scans were oversampled by a factor of 33%. This meant that for ETL = [8, 16, 32, 64, 128, 256], $N_{s,\text{Cartesian}} = N_{b,\text{PROPELLER}} = [64, 32, 16, 8, 4, 2]$ respectively.

$$\text{Signal to noise ratio, } SNR = \frac{\frac{1}{N} \sum_{j=1}^N I_j^A}{\sqrt{\frac{1}{N-1} \sum_{j=1}^N ((I_j^A - I_j^B) - \overline{(I_j^A - I_j^B)})^2}} \quad 3.3$$

Where j is the pixel index within a Region-of-interest (ROI) drawn in the simulated whole brain, corresponding to Ellipsoid 1. See Figure 3-6 for geometry of the relevant ROIs used. I^A and I^B are the pixel intensities in the two separate identical measurements (94).

$$\text{Contrast to noise ratio, } CNR = SNR_{\text{greymatter}} - SNR_{\text{whitematter}} \quad 3.4$$

Where grey matter was defined by non-overlapping regions in Ellipsoid 4 and white matter was defined by non-overlapping regions of Ellipsoid 7.

$$\text{Artifact Power, } AP = \frac{\sum_j \|I_j^{\text{reference}} - I_j^{\text{simulated}}\|^2}{\sum_j |I_j^{\text{reference}}|^2} \quad 3.5$$

Where j is the pixel index within the ROI (Ellipsoid 1), $I^{\text{reference}}$ is the reference image and $I^{\text{simulated}}$ is the simulated image.

AP is conventionally measured by the ratio of signals obtained from 2 ROIs – one in a region of noise with no ghosting or artifacts, and one in a region of noise with artifacts present. However, the rotational symmetry of PROPELLER spreads out artifacts in all directions, precluding this method of AP measurement. Instead the normalized sum of squares error approach used by Park, et al. was employed as a measure that was equally applicable to Cartesian and PROPELLER data (95). The reference image used was the ideal Shepp-Logan phantom as described, with uniform T_2 that were matched to the corresponding simulation images. Before subtraction, the mean signal intensity of the simulated image was normalized to that of the reference image to account for scaling factors in the NUFFT algorithm.

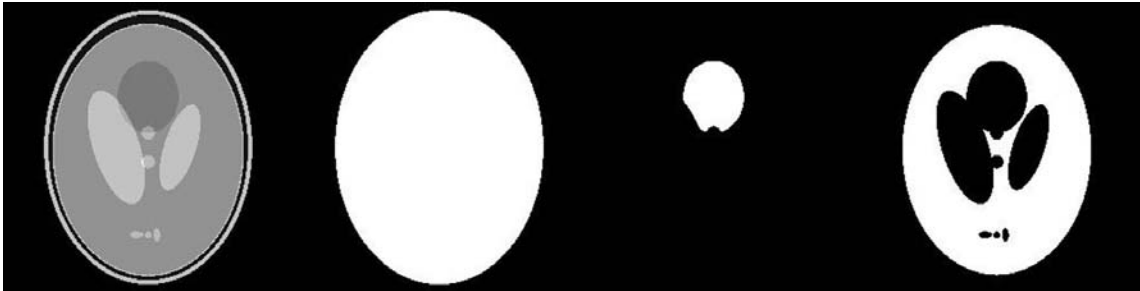


Figure 3-6 Sample phantom image (leftmost) and corresponding regions-of-interest in simulated whole brain (second from left), white matter (third from left) and grey matter (rightmost).

The point spread function (PSF) was also calculated for the k-space sampling trajectories. The PSF is a measure of the degree of blurring due to the reconstruction method and filters such as T_2 . The reconstructed image, $s(x)$ can be said to be a convolution of the actual image, $s_0(x)$ with the PSF, $h(x)$ as shown in Eqn 3.6. (6)

$$\text{Reconstructed image, } s(x) = s_0(x) \otimes h(x) \quad 3.6$$

For example, in Cartesian acquisitions with finite and discrete sampling, the PSF may be given as Eqn 3.7, where W is the width of the k-space window and Δk is the individual k-step size.

$$\text{Point spread function, } h(x) = W \frac{\text{sinc}(\pi W x)}{\text{sinc}(\pi \Delta k x)} e^{-i\pi \Delta k x} \quad 3.7$$

The PSF for the PROPELLER acquisition in the presence of T_2 filter however, is not straightforward. In order to measure the PSF, $s_0(x)$ was set to $\delta(x)$, in which case, $s(x)$ was equal to $h(x)$. Conventionally, the PSF can be quantified by measuring the full-width at half maximum (FWHM) of the PSF at $k=0$ in a specified direction. In Cartesian sampling, blurring is expected to be least in the readout direction and largest in the phase encode direction, and taking the average of the FWHM in these directions gives a good measure of the overall blurring. Due to the rotational symmetry and overlapping central region in PROPELLER, the smallest and largest degree of blurring no longer occur along the readout and phase encode direction of any particular blade. In order to obtain an estimate of overall blurring, the FWHM of the PSF was instead measured parallel to one blade and in between blades, then averaged. A sample PSF and FWHM measurements taken from a $256 \times 64 \times 6$ PROPELLER reconstruction is shown in Figure 3-7.

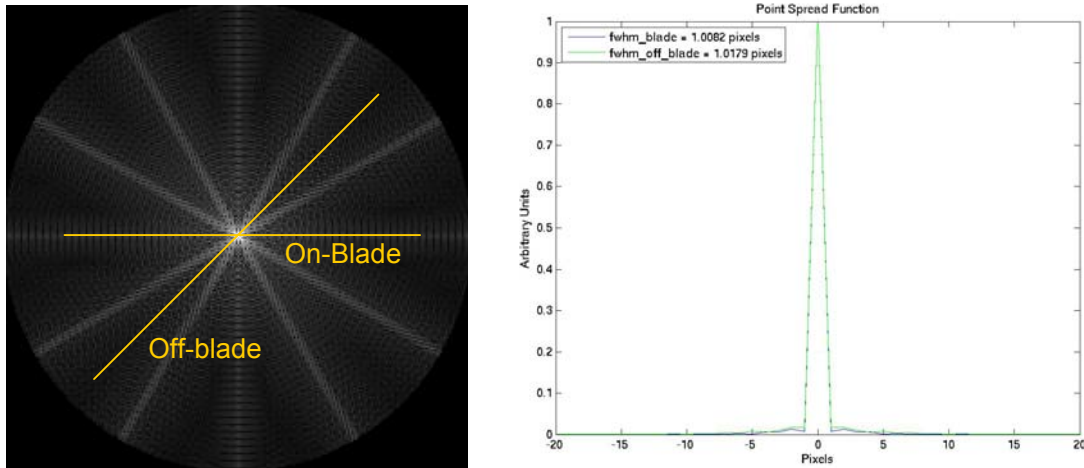


Figure 3-7 Point spread function of a PROPELLER reconstruction with 6 blades (left), raised to $1/3$ power for display. Cross-sections of the PSF were taken along one blade and in between blades and displayed as 2D plots (right). FWHM were measured as the average of the FWHM along these two directions.

It is expected that the repeated sampling of the centre of k-space may improve SNR in PROPELLER over Cartesian sampling. In view of the respective PSFs, Cartesian FSE data will be prone to blurring in the phase encode direction while blurring in PROPELLER will be spread radially. The effect may be to reduce contrast and increase artifacts, and this will be dependent on ETL, T_2 and field strength. In addition, there will be a mixing of TEs near the centre of k-space as blades overlap as shown in Figure 3-8. This may potentially cause artifacts.

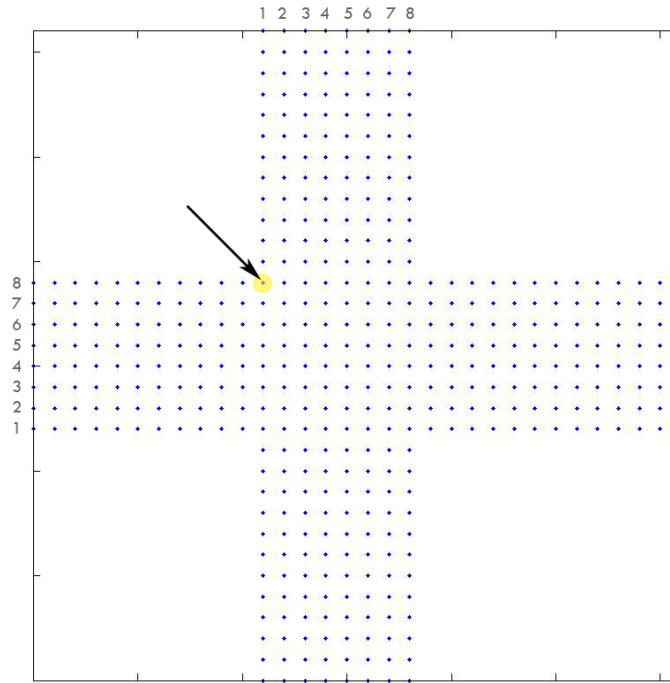


Figure 3-8 Low-resolution k-space data with two PROPELLER blades showing the overlap of samples from different blades with different echo times. For example, data from the 1st echo of the vertical blade coincides with data from the 8th echo in the horizontal blade at the highlighted k-coordinate. Mixing of TEs occurs similarly in other central overlapping data.

As a further investigation, a new k-space sampling approach was explored. In order to reduce the effect of mixed T_2 contrast, each k-space blade was truncated progressively towards the centre after the motion correction step, such that the remaining blade looked like two opposing petals on a flower. The multiple blades were then combined with NUFFT as before. Previous work had weighted PROPELLER k-space data in a similar way in order to optimize contrast (96). However, only human brain data at 1.5T and ETL=15 were acquired where blurring due to mixed T_2 contrast, and hence resultant improvements, were limited. The resultant k-space trajectory was coined PROPELLER with echo truncation at low spatial frequencies (PETALS). K-space trajectories, sample images, modulation transfer functions (MTFs) and PSFs are given in Figure 3-9 for comparison. The MTF is the Fourier transform of the PSF and illustrates the sampling density. Simulations of PETALS were compared to Cartesian and PROPELLER data.

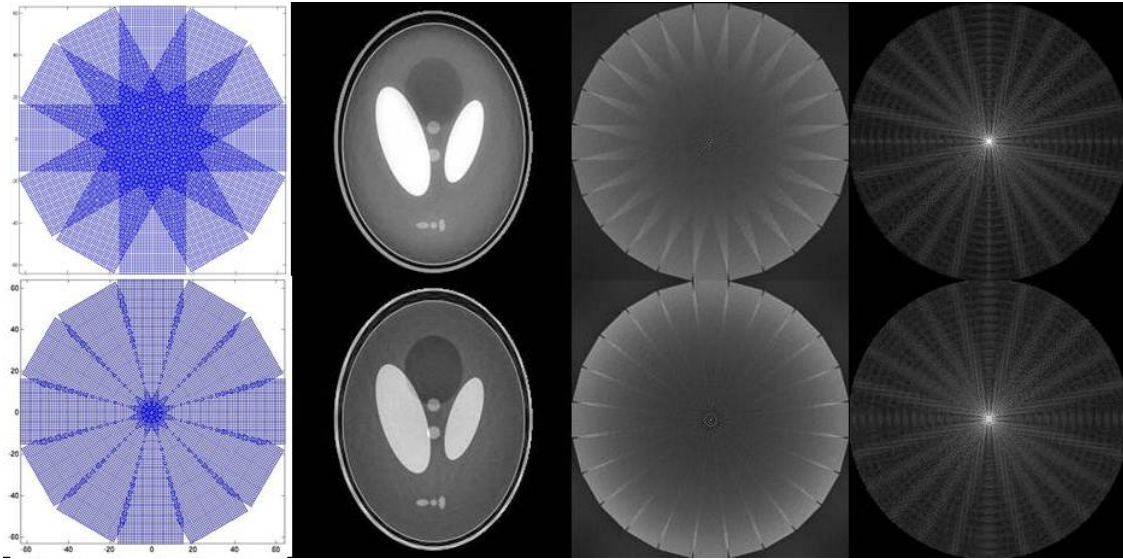


Figure 3-9 K-space trajectories (leftmost column), images (second column), MTFs (third column) and PSFs (rightmost column) for PROPELLER (top row) and PETALS (bottom row). For clarity, k-space trajectories were displayed using a matrix of 128 x 32 x 6. Other data were simulated at 256 x 32 x 12 and 9.4T. Remaining untruncated central portion of each PETALS blade was 7 k-space samples wide, expanding linearly towards the periphery of the blade at an angle that avoided creating Nyquist holes.

Since an SNR reduction would arise from the truncation of k-space, there could be an associated reduction in CNR. Contrast, as defined by Eqn 3.8, was used instead of CNR to examine the PETALS data.

$$\text{Contrast, } C = \frac{1}{N} \sum_{j=1}^N I_j^{GM} - \frac{1}{N} \sum_{j=1}^N I_j^{WM} \quad 3.8$$

Where j is the pixel index and I_j^{GM} and I_j^{WM} are the pixel intensities in the ROIs of grey matter and white matter respectively.

EPI methods suffer from geometric distortions due to low effective bandwidth in the phase encoding direction that scale with field strength. They are also resolution-limited due to short T_2^* - 25ms in human brain at 7T (97). Acquiring high resolution EPI images at high field is challenging, and requires the use of very strong and fast gradients, sophisticated parallel imaging, distortion correction, fat saturation and shimming methods to generate any usable images (98). In the absence of some or all of these techniques, the image quality obtained using EPI is dramatically inferior to similar nominal resolution FSE methods. Moreover, the

artifacts associated with EPI acquisitions are very hard to predict. Hence only FSE acquisitions were simulated.

In these simulations, T_1 and SNR changes due to field strength were neglected so that the dependence of image fidelity on blade configurations and T_2 could be isolated. These latter factors depend highly on the choice of imaging parameters by the operator and have a large impact on contrast and artifacts. For this reason, off-resonance, eddy currents and motion were also neglected. In practice, SNR and T_1 increase with field strength (99). Smaller coil geometries in small animal imaging also improve SNR. However, the reduction in voxel size on the scale of 500x from human to small animal imaging negates this and overall SNR is lower in the latter for acquisitions of equal time.

3.2.3 Animal Studies

The PROPELLER sequence was implemented on a 9.4T MRI scanner (Varian, Palo Alto, CA) by adaptation from a conventional 2D-FSE sequence. FOVs with low resolution in the phase encode direction were arrayed and progressively rotated. Complex data were exported, and the images were reconstructed offline. A transmit-receive quadrature volume RF coil with an internal bore of 26mm was used (Rapid Biomedical, Rimpar, Germany). The Varian 205/120 HD gradient coil used had an internal bore of 205mm, a maximum gradient strength of 40G/cm and a rise time of 130 μ s. 8 healthy wildtype C57/Bl6 mouse datasets were acquired in-vivo, in accordance to local Institutional Animal Care and Use Committee (IACUC) guidelines. Experiments were performed at the Lab of Molecular Imaging, Singapore Bioimaging Consortium, Singapore. In order to compare the ultimate fidelity of various scan protocols listed below, in the presence of minimal motion, brain data were acquired with animals secured with a nosecone and bitebar. To investigate the effectiveness of PROPELLER motion correction, similar data were acquired in the liver. Anaesthesia was induced with 3.5% isoflurane and maintained at 1-1.5% isoflurane in a 55%:45% mixture of N_2 : O_2 . Respiration was monitored using an air pillow transducer and controlled between 60-80 breaths/min. Animals were free breathing. Body temperature was measured using a rectal probe and maintained at 36.5°C by circulating warm air.

Each animal was scanned using the following sequences: single-shot (ss) FSE, multi-shot (ms) FSE, FSE-PROPELLER, ssEPI, msEPI and EPI-PROPELLER. Cartesian sampling was used unless otherwise specified. In the brain, all sequences used TR=4000ms, TE=51ms, FOV=25.6 x 25.6mm, reconstructed matrix=256 x 256, thickness=1mm, gap=0.5mm, slices=5, slice order=interleaved, orientation=axial and readout bandwidth=208kHz.

Exceptions were $TR_{ssFSE} = 10000\text{ms}$ due to high RF deposition, and $TE_{ssEPI} = 60.6\text{ms}$ due to the long echo trains. For multi-shot sequences, $ETL=16$ and acquisition time (AT) was equalized to 2m 16s by acquiring two averages for Cartesian sampling and acquiring an additional 33% number of blades for PROPELLER sampling. This time-normalised data would facilitate more direct quantitative comparison of SNR, CNR and other parameters between datasets. For single-shot sequences, $AT=20\text{s}$.

All experiments were repeated to obtain SNR, CNR and AP information based on manually drawn ROIs for each subject. ROIs were drawn to encompass as much of the anatomy of interest as possible to minimize the effects of local signal fluctuations and operator bias. ROIs of whole brain, WM (corpus callosum) and GM (cortex) are given in Figure 3-10. Each ROI was manually drawn using the FSE-PROPELLER image data as a reference and subsequently applied as a mask across corresponding image data acquired using the various sequences. Of interest were $SNR_{\text{whole brain}}$, GM-WM contrast, and $AP_{\text{whole brain}}$ that was calculated with Eqn 3.5, by substituting the reference and simulation image with the data acquired from the first scan and repeated scan. P-values were cited using one way ANOVA and $p<0.05$ was used to determine if a result was significant.



Figure 3-10 Sample mouse brain image (leftmost) and corresponding regions-of-interest in whole brain (second from left), white matter (third from left) and grey matter (rightmost).

In the liver, TE and reconstructed matrix were reduced to 40.3ms and 128×128 respectively primarily due to shorter T_2 . Additional averages or blades were acquired and $AT_{\text{multi-shot}}$ was maintained at 2m 16s, while $AT_{\text{single-shot}}$ was 16s. High T_2^* and susceptibility in the mouse body led to severe degradation of images using EPI methods as shown in Figure 3-11, and these were excluded from further analysis. Instead, msFSE images were acquired with respiratory triggering to compare efficacy of motion correction of triggering against PROPELLER. A 90° spectrally selective fat saturation pulse was applied in the preparation

phase to minimize off-resonance effects due to fat. ROIs of whole body, liver and muscle are given in Figure 3-12. $SNR_{\text{whole body}}$, liver-muscle contrast, and $AP_{\text{whole body}}$ were measured.

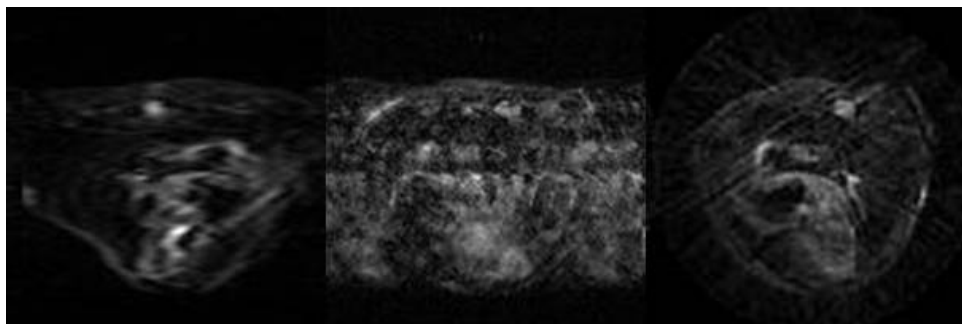


Figure 3-11 Liver images acquired in a free breathing mouse in-vivo at 9.4T with ssEPI (left), msEPI (middle) and EPI-PROPELLER (right).



Figure 3-12 Sample mouse liver image (leftmost) and corresponding regions-of-interest in whole body (second from left), liver (third from left) and muscle (rightmost).

Experiments in the mouse brain were repeated at a lower nominal resolution of 128×128 using centric phase encoding in order to investigate the performance of PETALS in mouse data. Acquisition matrix = $128 \times 16 \times 16$, ETL=16, TE=28ms and acquisition time = 1m 4s.

3.2.4 Human Studies

Similar work was carried out on a 3T Achieva scanner (Philips, Best, Netherlands) and 7 human brain datasets were acquired in healthy volunteers. A whole body transmit coil and 8-Ch birdcage receive coil were used. Studies were carried out in accordance to the sequence development protocol under local Institutional Review Board (IRB) guidelines.

Each volunteer was scanned using three sequences: msEPI, msFSE and FSE-PROPELLER. EPI-PROPELLER was not tested as MultiVane was not compatible with EPI on the Philips system. Preliminary studies showed that single-shot methods suffered from severe blurring or distortions, partly due to the reduced acquisition matrix and partial Fourier

needed to maintain TE. They were better suited for lower resolution applications. Exemplar images are shown.

All experiments were repeated to obtain SNR, CNR and AP information based on specific ROIs as shown in Figure 3-13. ROIs in whole brain, WM, GM and noise were manually drawn for each subject based on the anatomy. Of interest were $SNR_{\text{whole brain}}$, GM-WM contrast, and $AP_{\text{whole brain}}$. To observe the effects of motion, volunteers were also asked to rotate their heads from side to side during one set of experiments. In all sequences, $TR=2000\text{ms}$, $TE=80\text{ms}$, $ESP=7.6\text{ms}$, $ETL=20$, $FOV=240 \times 240\text{mm}$, reconstructed matrix= 256×256 , thickness=5mm, gap=1mm, slices=14, slice order=interleaved, orientation=transverse and no fat saturation was used. $AT_{\text{multi-shot}}$ were set to about 1m 44s by acquiring 2 averages in Cartesian acquisitions and by acquiring one third more blades in PROPELLER.

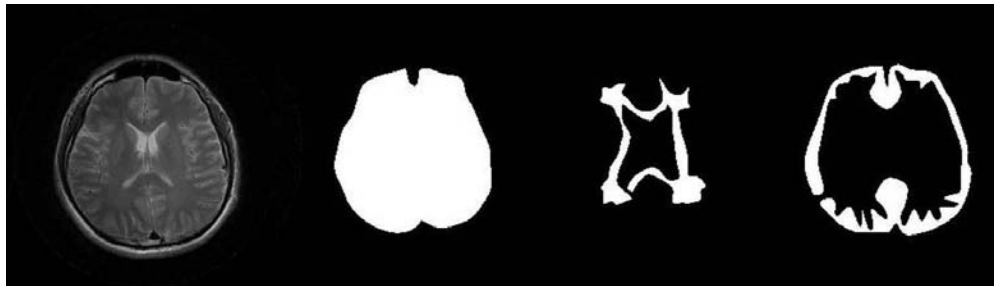


Figure 3-13 Sample human brain image (leftmost) and corresponding regions-of-interest in whole brain (second from left), white matter (third from left) and grey matter (rightmost).

Experiments were repeated in 2 volunteers at a lower nominal resolution of 128×128 using centric phase encoding in order to investigate the performance of PETALS in human data. $TR=3000\text{ms}$, $TE=45\text{ms}$, $ESP=7.8\text{ms}$, Acquisition matrix = $128 \times 24 \times 10$, $ETL=24$ and acquisition time = 30s.

3.3 Results and Discussion

3.3.1 Simulations

Figure 3-14 shows that for Cartesian multi-shot acquisitions, SNR decreases and blurring increases in the phase encode direction as field strength increases. This corresponds to increasing T_2 decay. Motion gives rise mainly to ghosting in the phase encode direction which can also be seen in Figure 3-14. Figure 3-15 shows corresponding images

reconstructed from fully sampled PROPELLER. In this case, a reduction in contrast is apparent, but motion artifacts are greatly reduced.

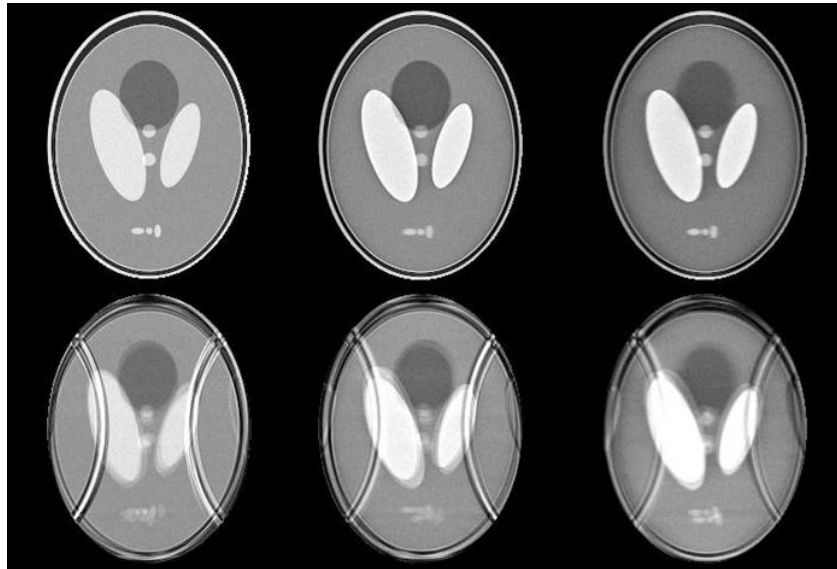


Figure 3-14 Simulations with Cartesian sampling with no T_2 , T_2 at 3T and T_2 at 9.4T (left to right columns) without motion (top row) and with motion (bottom row). Matrix size = 256 x 256, ETL=64 and phase encoding was interleaved. Figures were masked and normalized to noise.

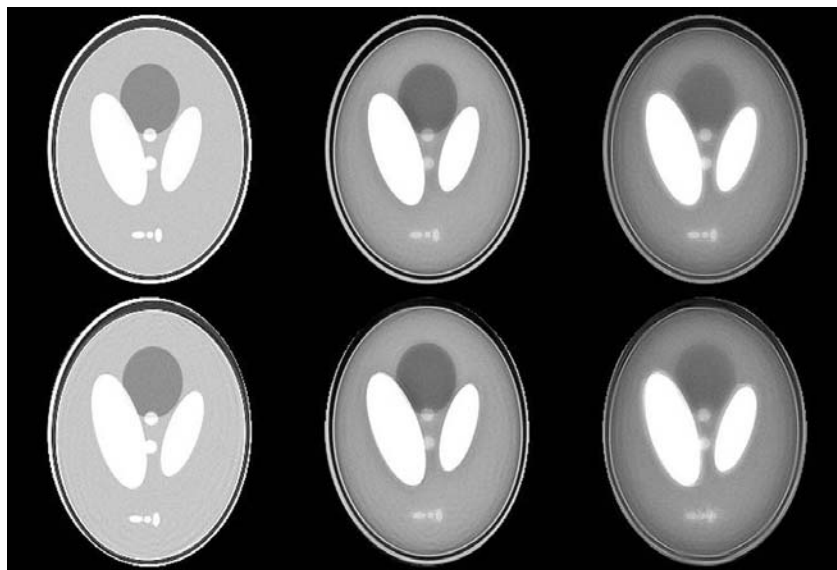


Figure 3-15 Simulations with PROPELLER sampling with no T_2 , T_2 at 3T and T_2 at 9.4T (left to right columns) without motion (top row) and with motion (bottom row). Matrix size = 256 x 64 x 6, ETL=64 and phase encoding was centric.

Figure 3-16 shows the simulated SNR for Cartesian, fully sampled PROPELLER and PETALS acquisitions without T_2 , and at 3T and 9.4T, at echo train lengths ranging from 8 to 256. PROPELLER acquisitions consistently exhibited highest SNR across the range of ETLs followed by PETALS then Cartesian. This was due to the repeated sampling of the central part of k-space. In PETALS, the central k-space data were truncated and SNR was lower compared to PROPELLER. SNR generally decreased with increasing ETL due to T_2 . However, there is an unexpected dip in SNR in PETALS at ETL=8, as well as in PROPELLER at higher field strengths. Closer inspection of the PSF as shown in Figure 3-17 revealed prominent side lobes that contributed to a strong ringing artifact that degraded image SNR, CNR and AP. As ETL increased to 16, the side lobes diminished markedly, restoring image fidelity.

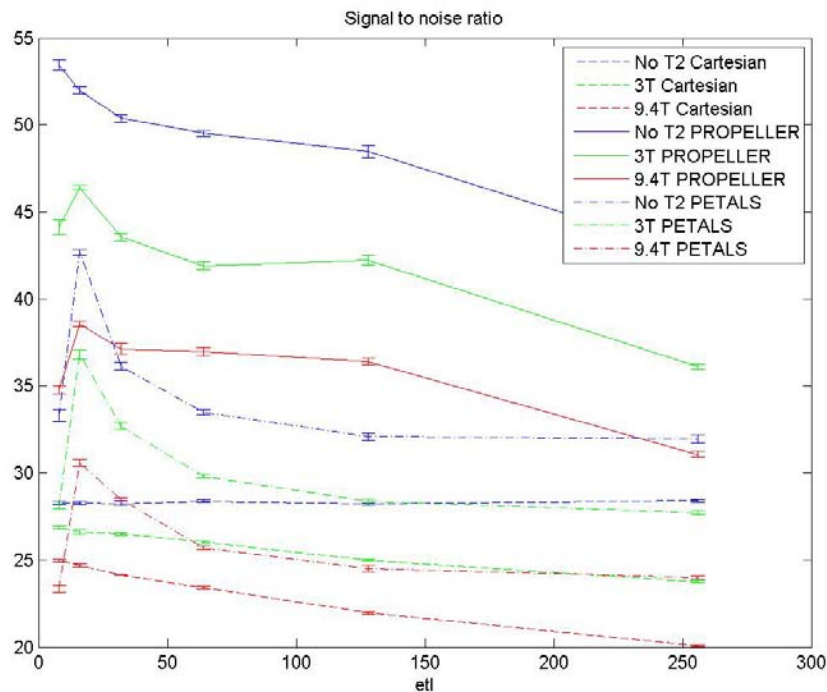


Figure 3-16 SNR for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 256. Images had effective TE of 6.38ms corresponding to the first echo. Phase encoding was interleaved in the Cartesian acquisition and centric in the PROPELLER and PETALS acquisitions.

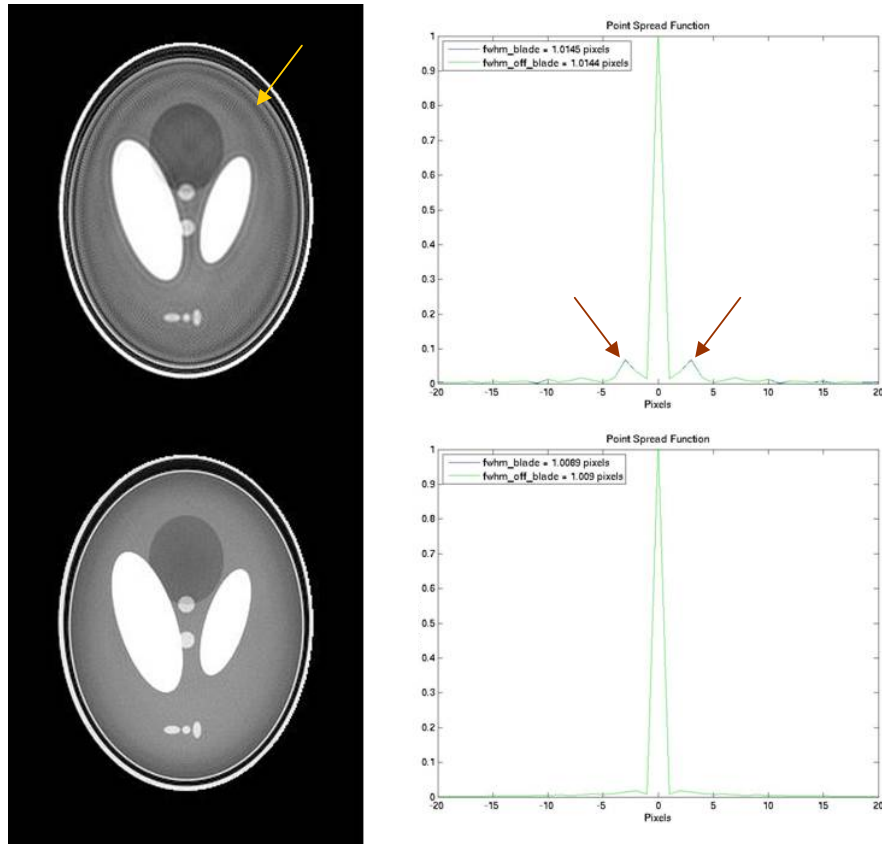


Figure 3-17 Shepp-Logan PROPELLER simulations with ETL=8 (top left) and ETL=16 (bottom left) and their corresponding PSF cross section plots. Image degradation including ringing artifacts caused by side lobes in the PSF as highlighted.

CNR was generally higher in PROPELLER compared to PETALS and Cartesian acquisitions with no T_2 and at 3T, corresponding to decreased noise levels. This can be seen in Figure 3-18. However at 9.4T, there was poorer CNR in PROPELLER compared to Cartesian despite the better SNR. This resulted from the severe TE modulation and mixing of central k-space regions of long and short TEs from different blades.

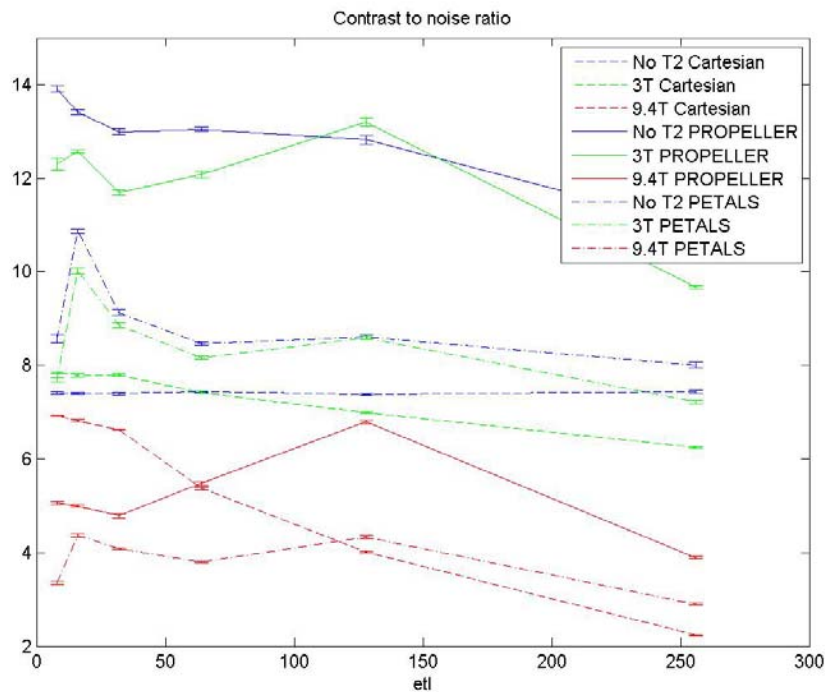


Figure 3-18 CNR for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 256.

However, contrast as defined by taking Eqn 3.8, decreased from $1.1e-6$ to $0.92e-6$ in PROPELLER as ETL increased from 8 to 32. In PETALS, it remained steady at $1.1e-6$. This explains the higher apparent contrast in Figure 3-9 where SNR was adequate. Contrast data is presented in Figure 3-19. It shows that PETALS offers a modest improvement in contrast for the practical range of ETL for PROPELLER from 16 to 64 at 9.4T. This effect was field strength dependent and may account for the limited improvement observed by a similar study at 1.5T (96). A local maximum was observed in the PROPELLER and PETALS contrast at ETL=128. This was an artifact arising from the severe blurring of the simulated CSF into the GM region, artificially raising the apparent GM signal and resultant GM-WM contrast.

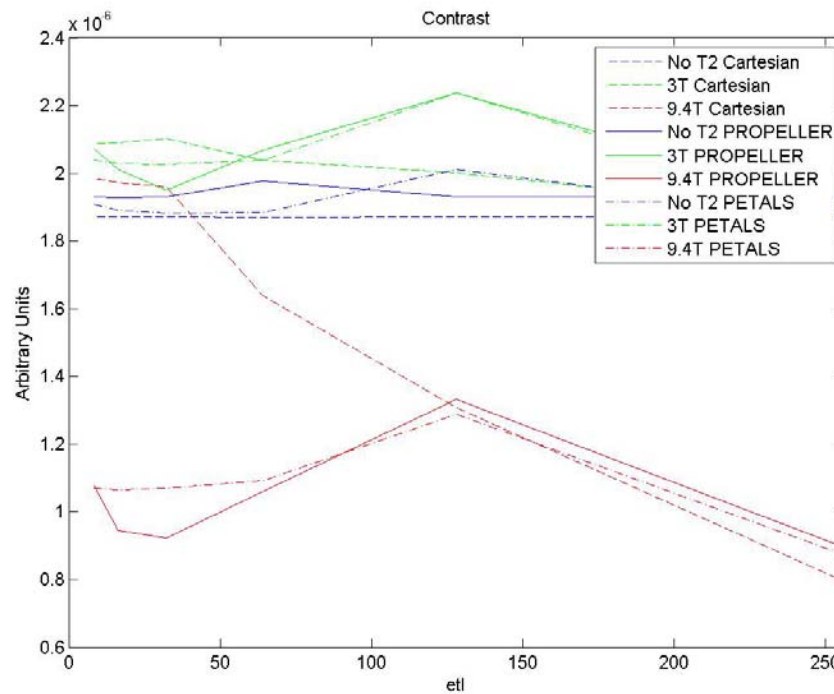


Figure 3-19 Contrast for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 256. A modest improvement was observed for a limited range of ETLs as field strength increases.

Predictably, the increased blurring shown in Figure 3-20 resulted in AP scaling with ETL and field strength as in Figure 3-21, which is evidenced by the corresponding raised mean FWHM of the PSF. The mixing of T_2 contrast accounted for the higher AP in PROPELLER sampling. This effect was mitigated using PETALS, and a reduction in AP at ETL from 16 to 64 was observed.

The reason for the improvement was principally due to the reduced mixing of TEs near the centre of k-space, this relates to the dependence on k-space sampling, tissue T_2 and field strength. The more homogenous modulation transfer function in PETALS as seen in Figure 3-9 may have contributed partly to the improvement, as seen by the improved AP (but not contrast) with no T_2 .

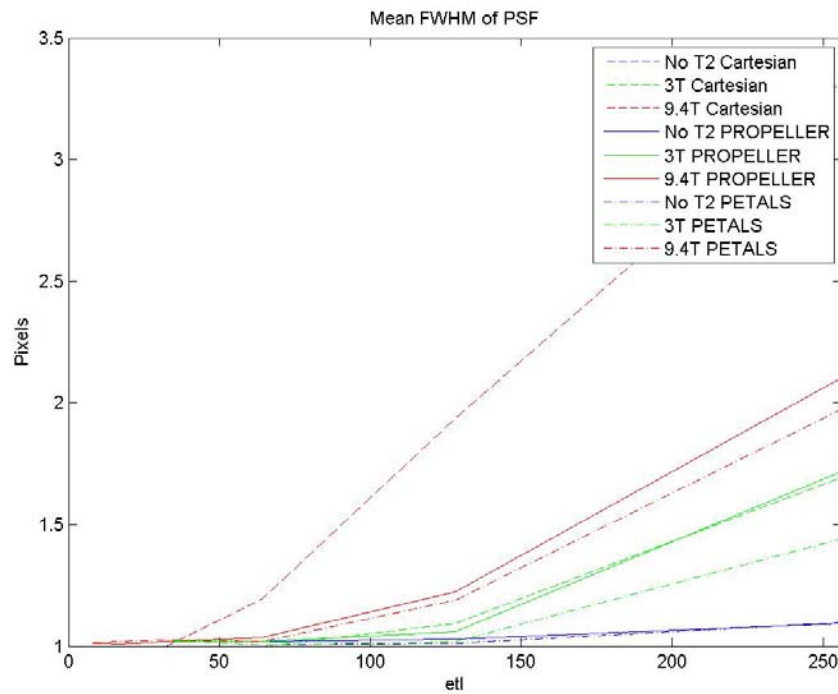


Figure 3-20 Mean full width half-maximum of PSF for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 256.

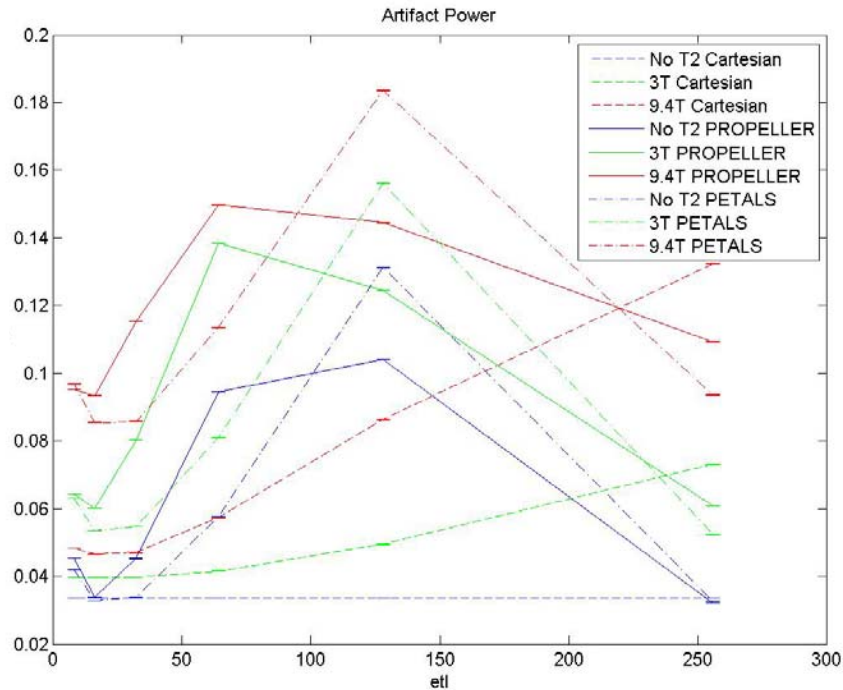


Figure 3-21 AP for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 256.

A drop in AP in PROPELLER and PETALS at ETL=256 occurred as the wide blades meant they were effectively Cartesian scans. The data here did not align with the Cartesian data though, as the two blades were acquired orthogonal to one another whereas the Cartesian sampling acquired data twice in the same orientation. The apparent improvement in AP and PSF using this orthogonal wide blade sampling, suggests that it may be useful in multiple average single-shot imaging methods.

Motion correction was unaffected as correction was performed prior to truncation of k-space. It is expected that PETALS may be useful in improving image reconstruction accuracy and contrast over PROPELLER where T_2 is short. This may be due to tissue properties, echo train lengths or field strength. However, it should only be applied where the reduction in SNR is tolerable.

In order to obtain T_2 contrast, the experiments were repeated with TE extended to 51.0ms and a linear phase encoding was used in PROPELLER simulations for ETL=8 and 16. While SNR was lower than previous data at TE=6.38ms due to T_2 , it can be seen from Figure 3-22, that SNR for PROPELLER and PETALS remained higher than the corresponding Cartesian data at ETL=16. SNR in the former two dip when ETL was reduced to 8, due to PSF artifacts as explained earlier.

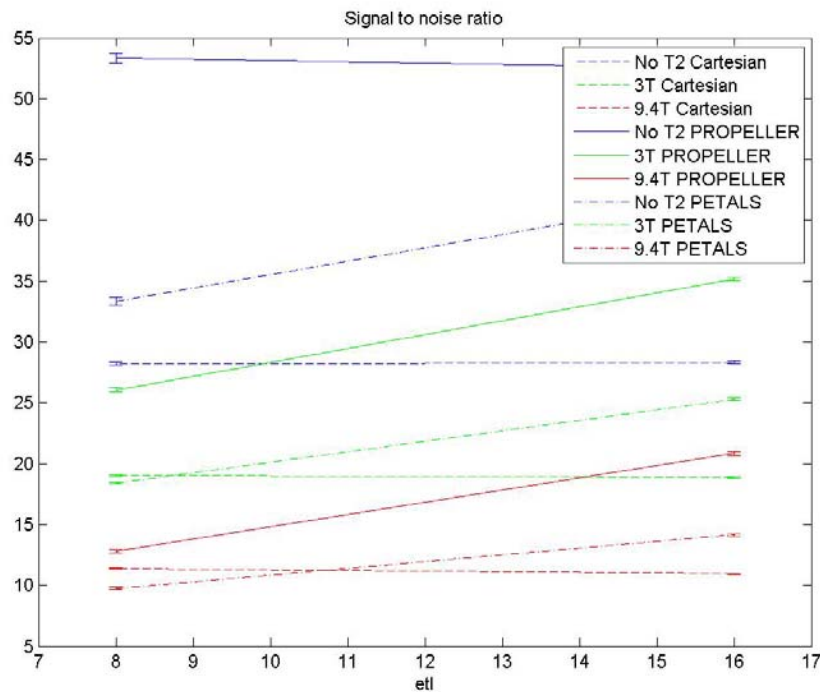


Figure 3-22 SNR for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 16. Images were T_2 -weighted with effective TE of 51.0ms corresponding to the eighth echo. ETL = 8 and 16. Phase encoding was interleaved in the Cartesian acquisition and linear in the PROPELLER and PETALS acquisitions.

PROPELLER data exhibited higher CNR than Cartesian data, owing to less detrimental mixing of T_2 contrast (See Figure 3-23). CNR in PETALS was lower than PROPELLER, but higher than Cartesian at ETL=16. A check of the contrast as given in Figure 3-24 showed that this was due not just to increased noise in PETALS, but also a drop in the signal intensity ratio between WM and GM, seen particularly at 9.4T. This may have been due to the linear phase encoding and the sudden discontinuities in TE modulation from the trailing edge of one blade to the leading edge of the next adjoining blade.

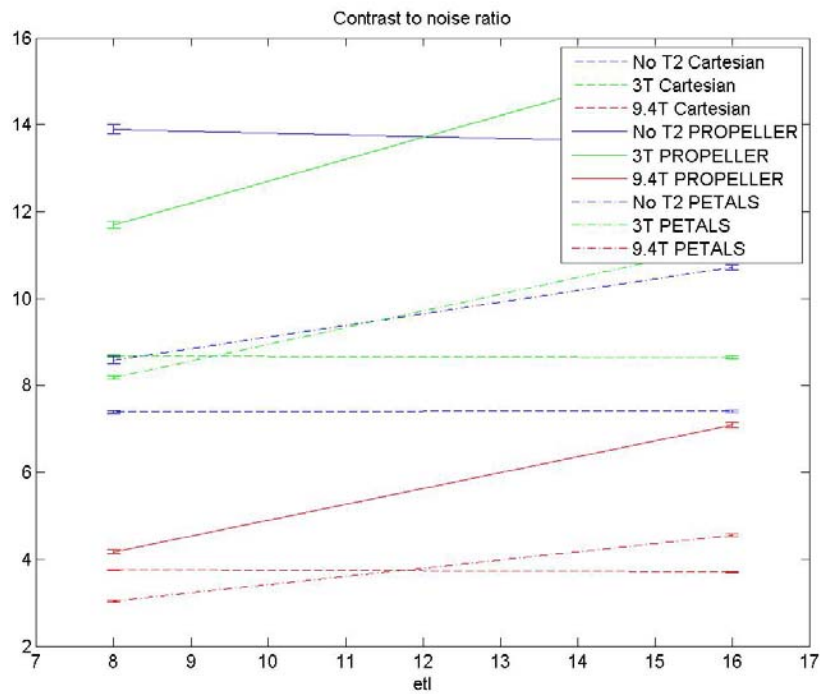


Figure 3-23 CNR for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 16.

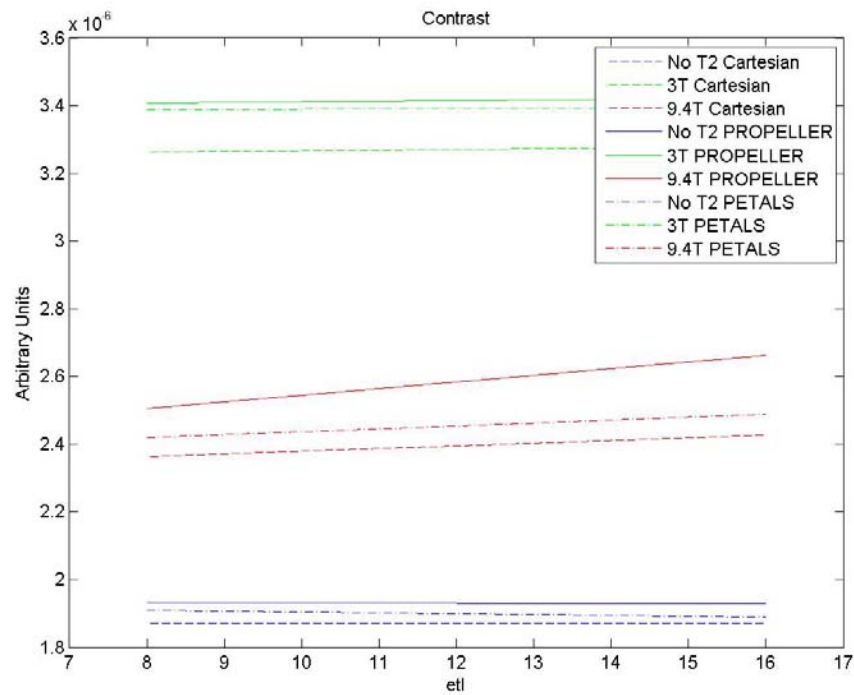


Figure 3-24 Contrast for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 16.

The PSF data in Figure 3-25 showed marginally greater blurring in PROPELLER and PETALS as compared to Cartesian sampling. The AP data in Figure 3-26 showed that the PROPELLER image quality improved increasingly over Cartesian as ETL and field strength were increased, suggesting that the increased blurring of the PSF was compensated by the reduction of blurring and coherent artifacts in the phase encode direction.

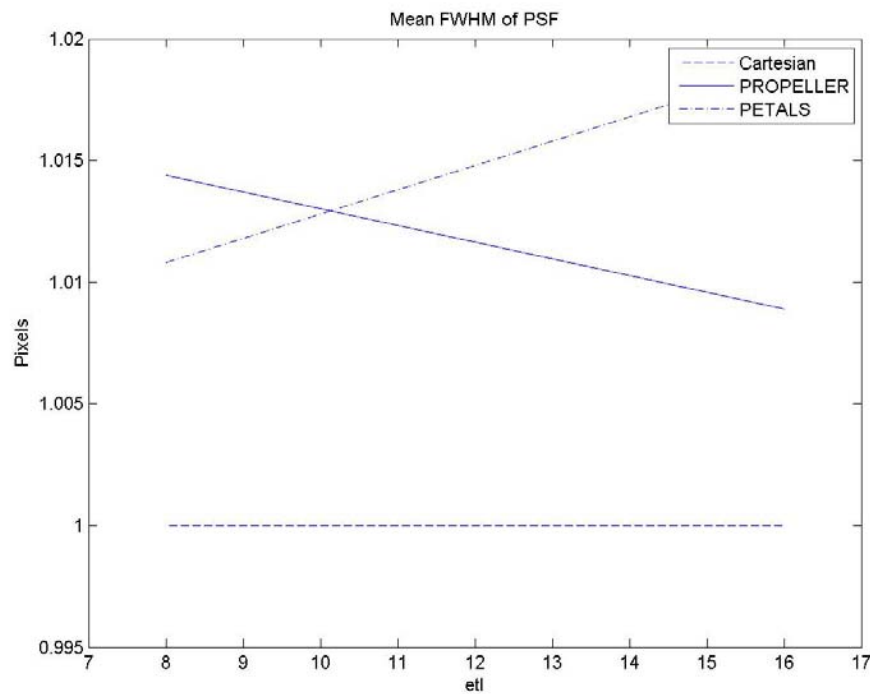


Figure 3-25 Mean FWHM of the PSF for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 16.

The simulation datasets demonstrated that PROPELLER improved SNR across ETLs and field strengths in comparison to a Cartesian acquisition of equal acquisition time. This was primarily due to the repeated sampling of the central region of k-space. Artifacts in the PSF prevent the use of blades that are too narrow, which in any case would be undesirable due to poorer motion correction and increased acquisition time.

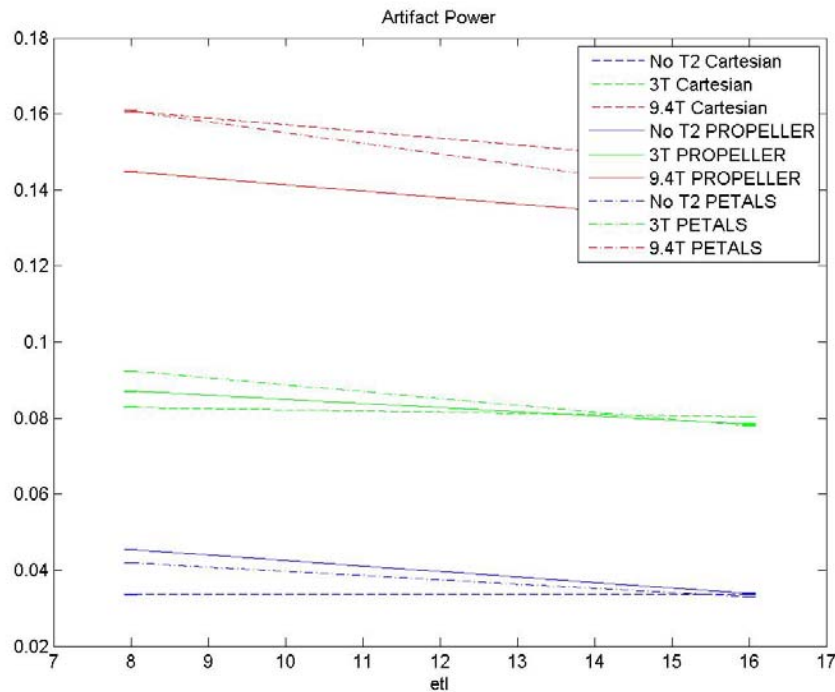


Figure 3-26 AP for Shepp-Logan simulations with Cartesian (256 x 256), PROPELLER (256 x ETL x N_b blades) and PETALS sampling where ETL ranged from 8 to 16.

The severe reduction in contrast in PROPELLER images at 9.4T and TE=6.38ms due to mixing of T₂ contrast, can be mitigated using the PETALS sampling scheme for a practical range of ETLs from 16 to 64. The tradeoff in improving contrast and AP is the reduction of SNR by the truncation of k-space. However, CNR and AP at 9.4T remain poorer using PROPELLER or PETALS, and should be utilized mainly in applications where motion is present. At lower fields, the CNR using PROPELLER and PETALS is higher than Cartesian, and this may compensate for the increased AP for general imaging applications. It is proposed that PETALS may also be useful in DWI with centric encoding (See Chapter 5).

In T₂-weighted imaging, SNR and CNR can both be improved over Cartesian sampling, by using PROPELLER sampling with a linear phase encoding scheme. At 9.4T, AP is lower when PROPELLER is used, suggesting that it may outperform Cartesian imaging for high resolution in-vivo imaging at 9.4T in general, and even more so when motion is present.

In practice, motion correction generally improves with blade width to a point due to greater blade correlation (100), as does acquisition time due to fewer blades needed to fill k-space. At lower fields, ETLs from 16 to 33 have typically been used (59,62). At 9.4T, severe T₂

places greater limitations on ETL and phase encoding scheme than at lower field strengths. One optimized solution that improved SNR, CNR and AP over Cartesian methods was demonstrated using T_2 -weighted PROPELLER imaging with ETL=16 and linear phase encoding. This was subsequently employed in animal experiments.

3.3.2 Animal Studies

Figure 3-27 shows data acquired in a mouse brain in-vivo at 9.4T using single-shot, multi-shot, EPI, FSE, Cartesian and PROPELLER methods. The severe subsampling of k-space in the case of ssEPI in order to match the TE of the other scans, combined with geometric distortions due to off-resonance and resulted in poor image quality. The reduced EPI train length in the msEPI acquisition reduced geometric distortions significantly. However, signal dropout from local field inhomogeneities and T_2^* decay can be seen, particularly in areas outside the brain.

Using EPI necessitates adjusting readout delays in order to align the odd and even echoes and minimize N/2 ghosts. Each calibration scan is done manually on the Varian system and takes about a minute. However, rotating the FOV in an EPI-PROPELLER scan changes the magnitude of the odd-even k-space shifts and necessitates a separate EPI calibration scan for each FOV. The time spent on manual calibration quickly exceeds any time savings through the use of EPI methods. Additionally, geometric distortions are oriented differently across blades, leading to blurring and signal dropout if uncorrected, as can be seen in the data. EPI echo alignment and distortion correction may be achieved during acquisition or postprocessing. For example, Chuang, et al. used parallel imaging to reduce the EPI train length and a twice refocused spin echo preparation to reduce eddy currents (64), while Skare, et al. estimated phase correction parameters based on minimizing total image entropy (101). However, these methods were applied in human brains at 3T and 1.5T respectively. It is expected that enabling EPI-PROPELLER at 9.4T in small animals, particularly in regions outside the brain, would entail significant development work to automate one or more of these corrections and even then is not expected to achieve the fidelity readily achievable using FSE. Due to this limitation the comparison between PROPELLER and Cartesian approaches at 9.4T was wholly undertaken using FSE sequences.

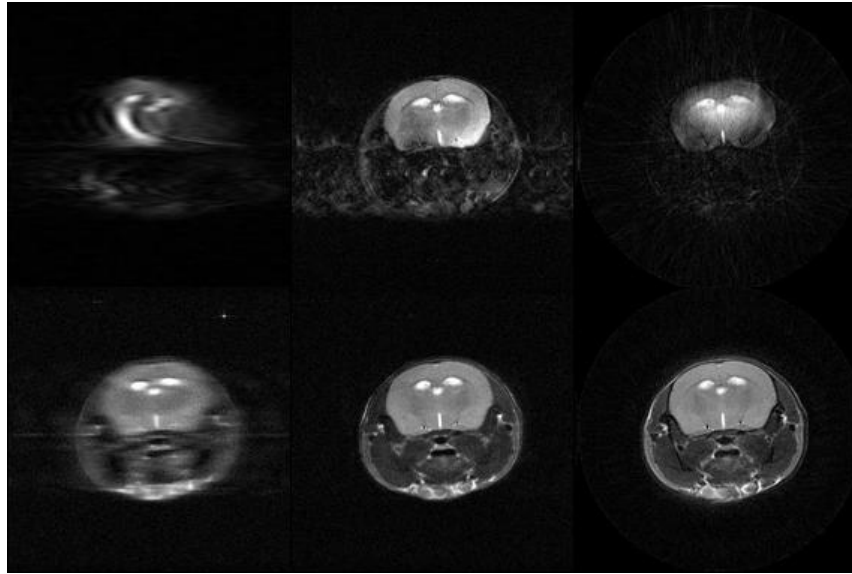


Figure 3-27 In-vivo mouse brain images at 9.4T with ssEPI (top left), msEPI (top middle), EPI-PROPELLER (top right), ssFSE (bottom left), msFSE (bottom middle) and FSE-PROPELLER (bottom right).

Severe blurring in the phase encode direction was observed in the ssFSE acquisition due to T_2 and the long ETL. A closeup of msFSE and FSE-PROPELLER data as in Figure 3-28 showed improvements in resolution, SNR and contrast in the latter.

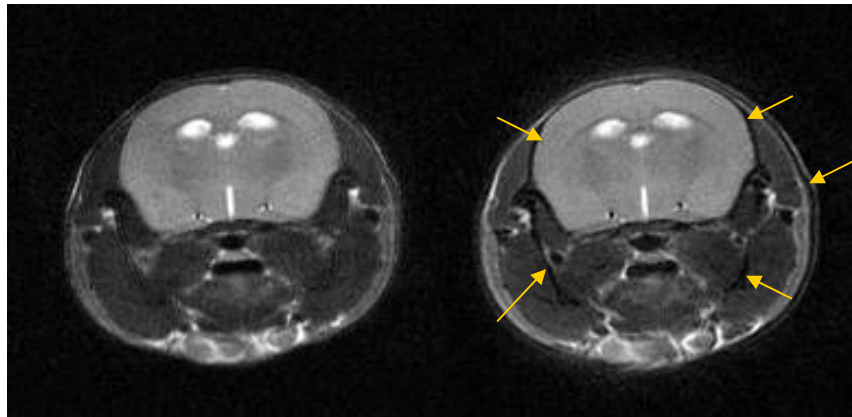


Figure 3-28 Closeup of msFSE (left) and FSE-PROPELLER (right) data. Improvements in resolution are highlighted.

The improvements are reflected in Figure 3-29, Figure 3-30 & Figure 3-31. As a result of T_2^* , susceptibility, chemical shift and N/2 ghosting, there was generally a larger spread in SNR, CNR and AP data for EPI compared to FSE methods. While mean SNR in EPI methods were fairly comparable, CNR and AP were inferior to FSE methods.

Single-shot EPI and single-shot FSE offer rapid acquisition and good SNR at the expense of image distortion and image blurring respectively. While both exhibited negative GM-WM contrast, ssFSE was more reproducible with lower error across samples. Multi-shot EPI data looked somewhat anomalous to other EPI data. It had lower mean SNR and higher CNR and AP. The higher CNR was indicative of the reduced geometric distortion due to the shorter EPI train lengths, while the reduced SNR and elevated AP were due to some datasets where N/2 ghosting were very apparent. This underscored the need for good EPI prescan calibration and phase correction. The coherent N/2 ghosts were removed in the EPI-PROPELLER data and replaced with radially oriented blurring and distortion. This improved the SNR and reduced the AP. CNR however suffered from signal dropouts due to combinations of blades with uncorrected and variable geometric distortions.

Note that due to the lack of a gold standard reference dataset, AP as calculated here was more a measure of data consistency between measurements, rather than agreement with ideal data. As such, the AP in ssEPI was found to be lower compared to that of msEPI, despite the more severe image artifacts.

Multi-shot FSE gave positive GM-WM contrast, with moderate SNR and low AP. This was due to the robustness of FSE methods to geometric distortions, and the mouse being well restrained. In all three respects however, FSE-PROPELLER performed significantly better ($p_{\text{SNR}}=3.7\text{e-}8$, $p_{\text{CNR}}=7.0\text{e-}7$ and $p_{\text{AP}}=1.8\text{e-}5$), and data were consistent with simulation results.

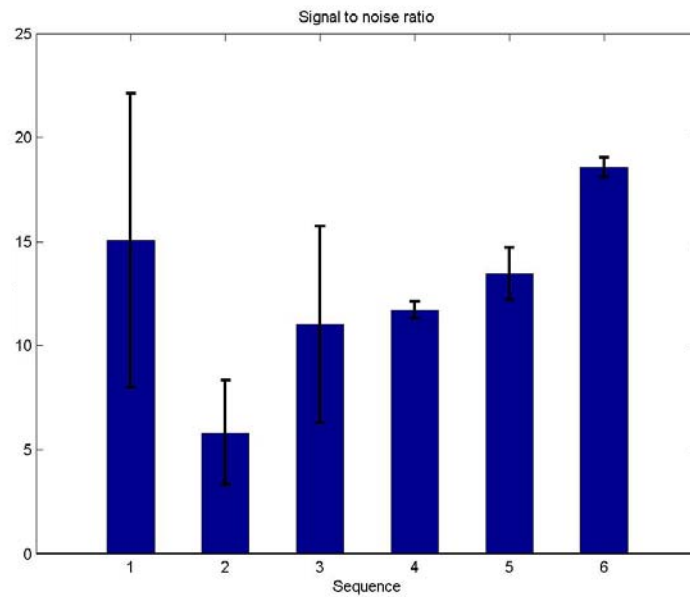


Figure 3-29 Measured SNR in mouse brain imaged in-vivo at 9.4T using six acquisition methods: 1. ssEPI, 2. msEPI, 3. EPI-PROPELLER, 4. ssFSE, 5. msFSE & 6. FSE-PROPELLER.

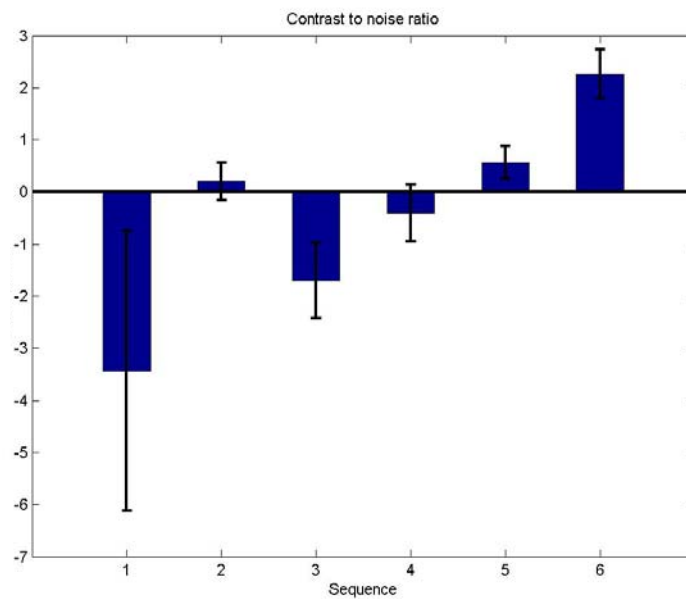


Figure 3-30 Measured GM-WM CNR in mouse imaged in-vivo at 9.4T using six acquisition methods: 1. ssEPI, 2. msEPI, 3. EPI-PROPELLER, 4. ssFSE, 5. msFSE & 6. FSE-PROPELLER.

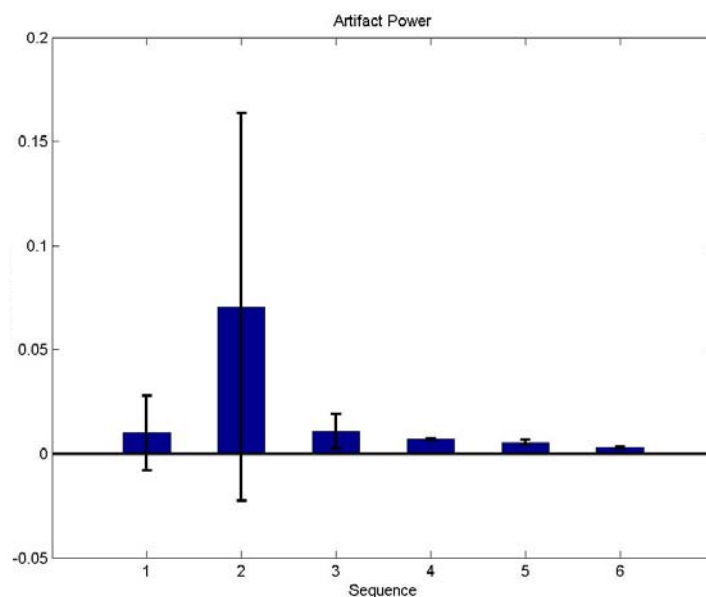


Figure 3-31 Measured AP in mouse brain imaged in-vivo at 9.4T using six acquisition methods: 1. ssEPI, 2. msEPI, 3. EPI-PROPELLER, 4. ssFSE, 5. msFSE & 6. FSE-PROPELLER.

The mouse liver data are presented in Figure 3-32. The in-vivo data showed severe blurring in ssFSE. This was greatly reduced in msFSE. Both scans however exhibited marked signal loss and ghosting due to motion. The corresponding ex-vivo data give the expected signal and contrast without motion. Combining respiratory triggering with msFSE was an effective method to reduce motion artifacts. However, doing so entails either tolerating variable TRs or risking injury to the animal by intubation and ventilation. FSE-PROPELLER provided similar contrast to the respiratory triggered msFSE while maintaining contrast and excluding the need for additional animal preparation. It also appeared to improve resolution and contrast in the ex-vivo scans.

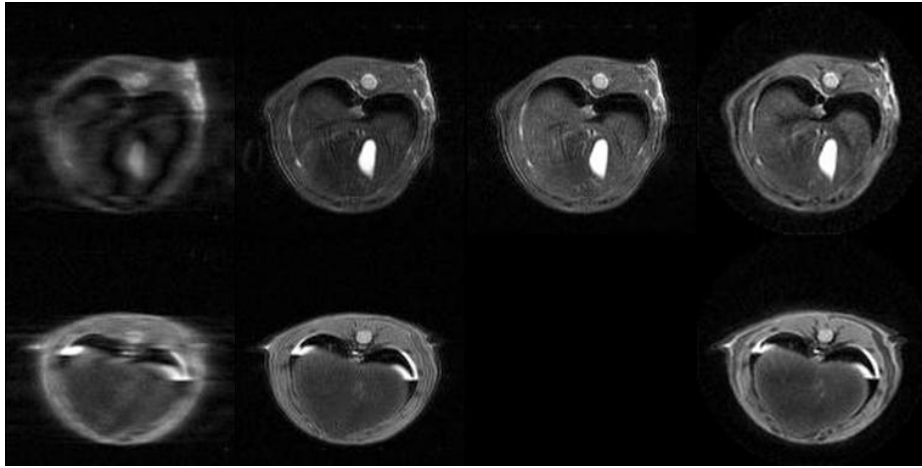


Figure 3-32 Mouse liver images at 9.4T acquired in-vivo (top row) and ex-vivo (bottom row) with ssFSE-Cartesian (leftmost column), msFSE-Cartesian (second column), msFSE-Cartesian with respiratory triggering (third column) and FSE-PROPELLER (rightmost column) sampling schemes. Triggered images not acquired for ex-vivo data.

SNR was in general about 50% lower in the liver than the brain due to greater T_2 decay, despite the voxel sizes having been quadrupled. AP was on the order of four times higher due to respiratory motion and vessel flow. Figure 3-33 shows that ssFSE offered similar SNR to msFSE but using only 15% of the scan time. However blurring and motion artifacts led to a loss in CNR and increased AP. Less blurring in msFSE due to shorter ETL resulted in better contrast. Triggering greatly reduced motion artifacts resulting in a reduced AP. Contrast was maintained while SNR was increased, partly due to more consistent data, but mainly due to greater T_1 relaxation due to variably long TRs. This increased scan time by a variable amount and would degrade any quantitative data measurement. FSE-PROPELLER failed to reduce the AP to that achieved with triggering, but it managed to do so with a gain in SNR ($p=0.042$) and CNR ($p=0.018$) over msFSE methods.

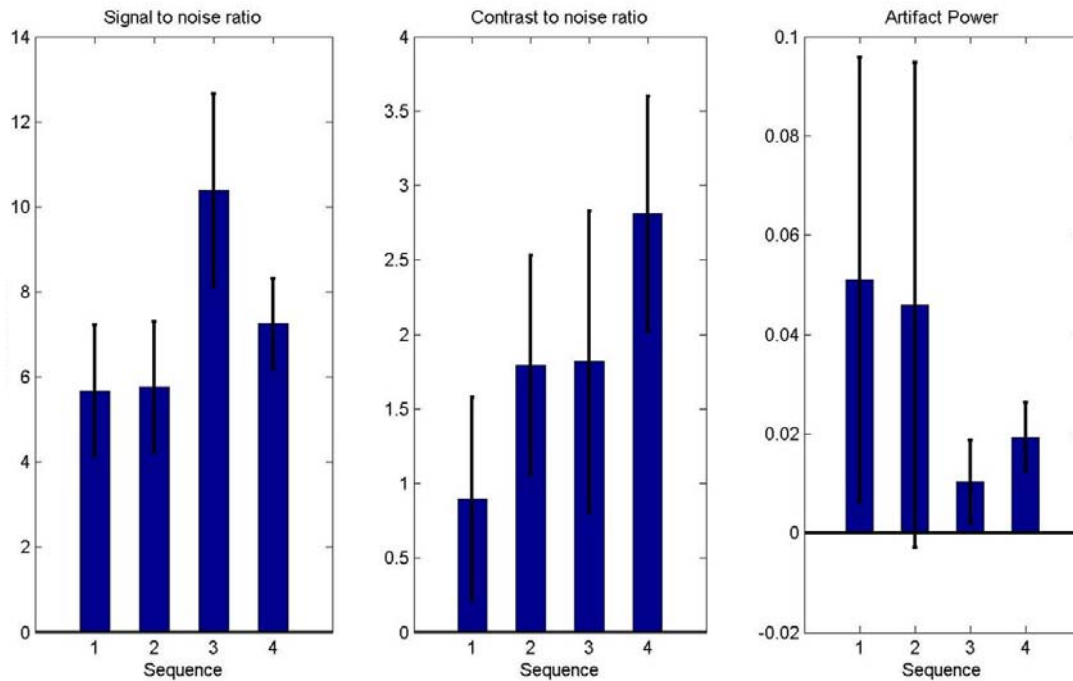


Figure 3-33 Measured SNR (left), liver-muscle CNR (middle) and AP (right) in mouse body imaged in-vivo at 9.4T using four acquisition methods: 1. ssFSE, 2. msFSE, 3. msFSE with respiratory triggering & 4. FSE-PROPELLER.

Data reconstructed with PROPELLER and PETALS as in Figure 3-34 and Figure 3-35 show higher CNR ($p=4.5e-6$) and lower SNR ($p=2.4e-3$) in the latter, consistent with simulations. AP was not increased in PETALS ($p=0.21$). While there was relatively large inter-subject variability in AP measurements, this did not increase using PETALS.

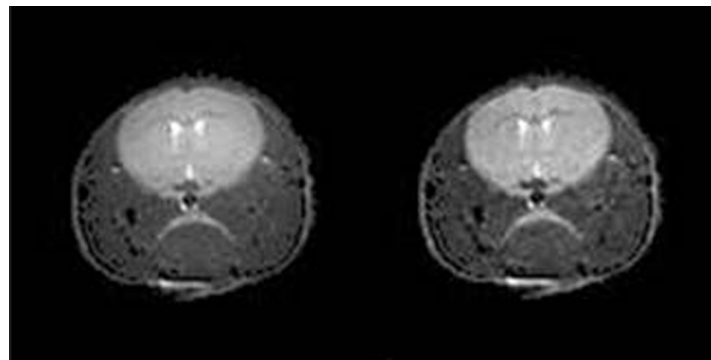


Figure 3-34 In-vivo mouse brain images at 9.4T reconstructed with PROPELLER (left) and PETALS (right) in a single slice. Acquisition matrix = 128 x 16 x 16. Note improvement in GM-WM contrast in the latter.

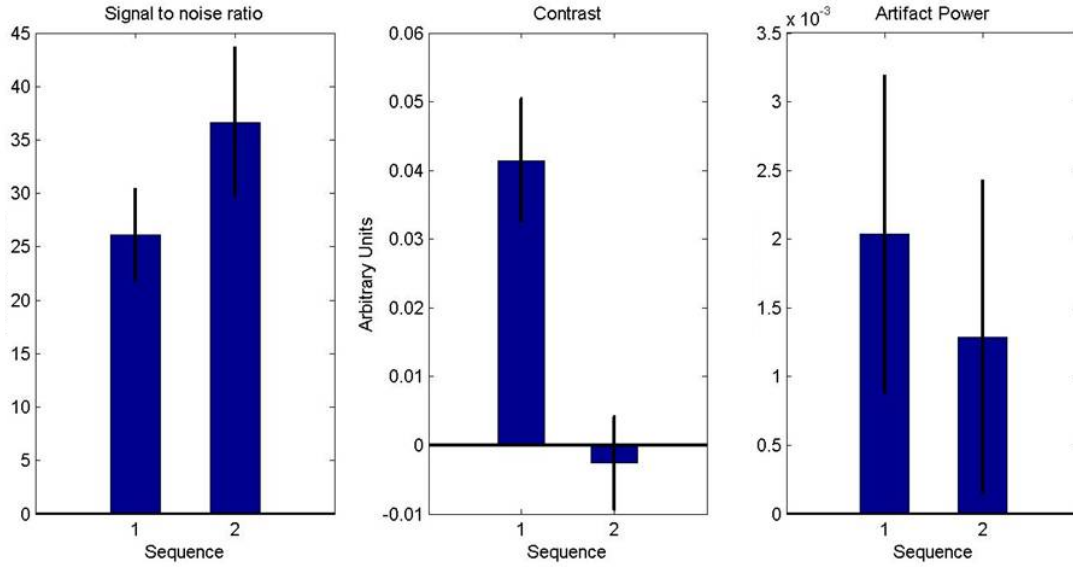


Figure 3-35 Measured SNR (left), GM-WM contrast (middle) and AP (right) in mouse brain in-vivo at 9.4T using two reconstruction methods: 1. PETALS and 2. PROPELLER.

3.3.3 Human Studies

Figure 3-36 illustrates volunteer brain data acquired at 3T using single-shot, multi-shot, EPI, FSE, Cartesian and PROPELLER methods. The EPI images demonstrate that geometric distortion due to off-resonance effects was less severe at 3T than at 9.4T. It also reflects the automatic and effective prescan calibration, phase correction and eddy current compensation implemented on a clinical scanner. However, susceptibility, chemical shift and blurring due to T_2^* remained which were more prominent in the ssEPI than msEPI. The ssFSE data were free from distortion but blurred due to T_2 , while the msFSE and FSE-PROPELLER images looked almost identical.

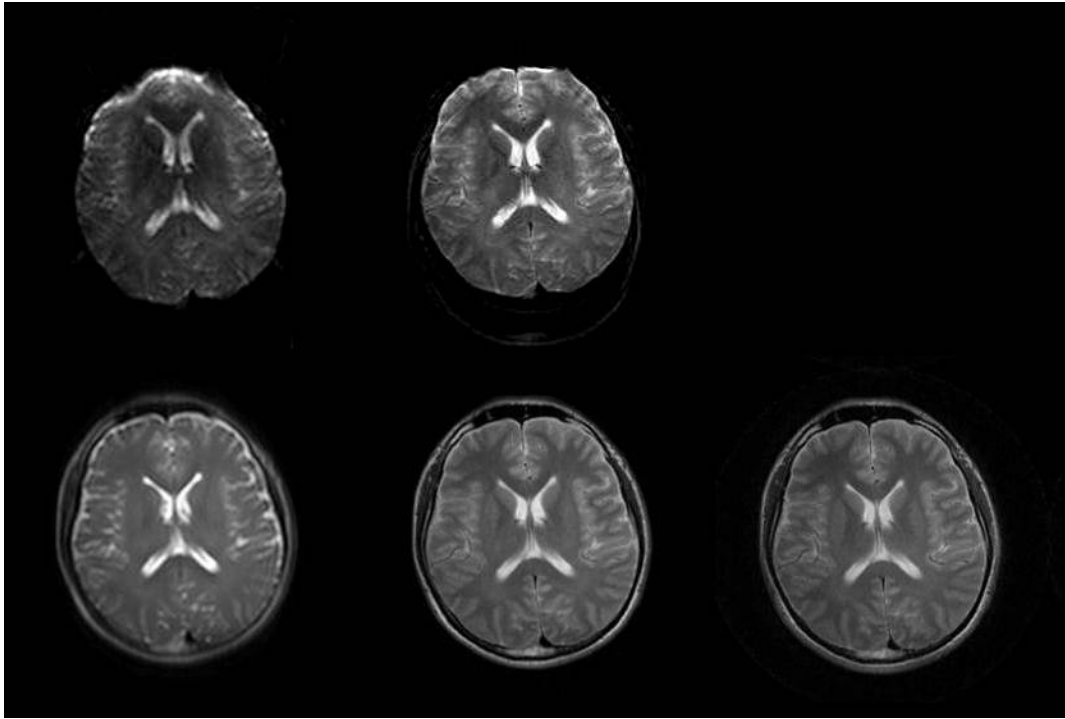


Figure 3-36 In-vivo human brain images at 3T acquired in the absence of motion with ssEPI (top left), msEPI (top middle), ssFSE (bottom left), msFSE (bottom middle) and FSE-PROPELLER (bottom right). EPI-PROPELLER was not acquired due to software constraints.

Figure 3-37 illustrates human brain SNR, CNR and AP of msEPI, msFSE and FSE-PROPELLER data. Despite the lower field, larger coil geometry and 25% shorter scan times, SNR here was generally higher than that in animal experiments due to the larger nominal voxel size of 4.4mm^3 compared to 0.01mm^3 . CNR was correspondingly higher, and AP was lower in general.

As before, EPI methods suffered from distortion and thus had lower CNR and higher AP. Multi-shot FSE showed improvement in all three parameters over msEPI. It did not perform significantly better than FSE-PROPELLER with $p_{\text{SNR}}=0.15$, $p_{\text{CNR}}=0.59$ and $p_{\text{AP}}=0.24$. This was consistent with simulations in Figure 3-24 & Figure 3-26 that showed similar contrast and AP for msFSE and FSE-PROPELLER at 3T.

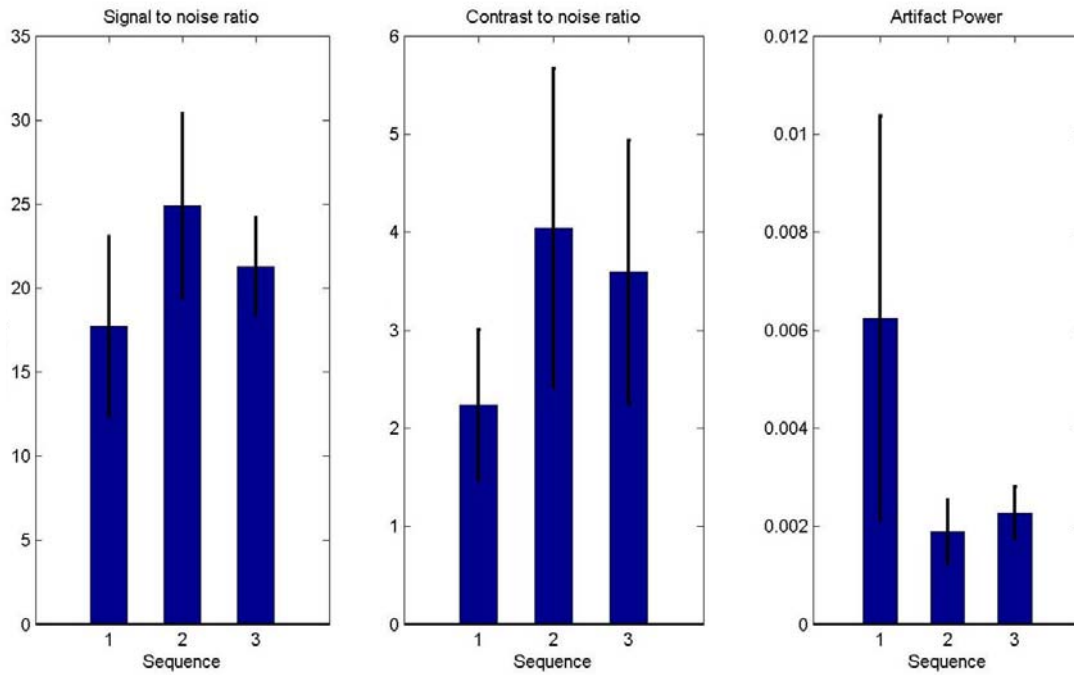


Figure 3-37 Measured SNR (left), GM-WM CNR (middle) and AP (right) in human brains imaged in-vivo at 3T using three sequences: 1. msEPI, 2. msFSE & 3. FSE-PROPELLER.

The lack of improvement using FSE-PROPELLER indicates that msFSE methods may be preferable in imaging cooperative subjects at 3T given the shorter reconstruction times. However, Figure 3-38 shows that in the presence of motion, strong motion artifacts can be seen in msFSE along the phase encoding direction. This was largely ameliorated in FSE-PROPELLER where resolution and contrast were preserved. Multi-shot EPI showed similar ghosting artifacts, while single-shot methods were robust to motion.

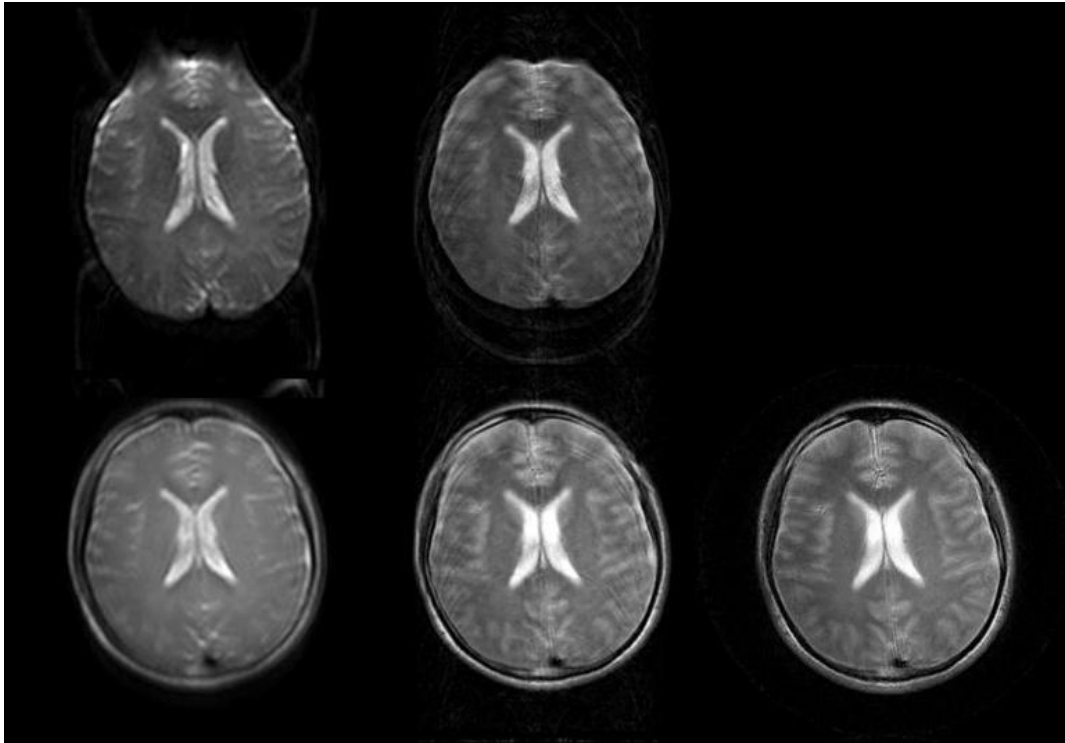


Figure 3-38 In-vivo human brain images at 3T acquired in the presence of motion with ssEPI (top left), msEPI (top middle), ssFSE (bottom left), msFSE (bottom middle) and FSE-PROPELLER (bottom right).

PETALS reconstruction in pilot human data showed reduced SNR ($p=0.024$) and worse AP ($p=2.2e-3$). Contrast however was not improved ($p=0.34$) (See Figure 3-39 & Figure 3-40). The lack of observable improvement compared to what was seen at 9.4T was consistent with simulations that found that improvement in contrast (See Figure 3-19) using PETALS was dependent on field strength.

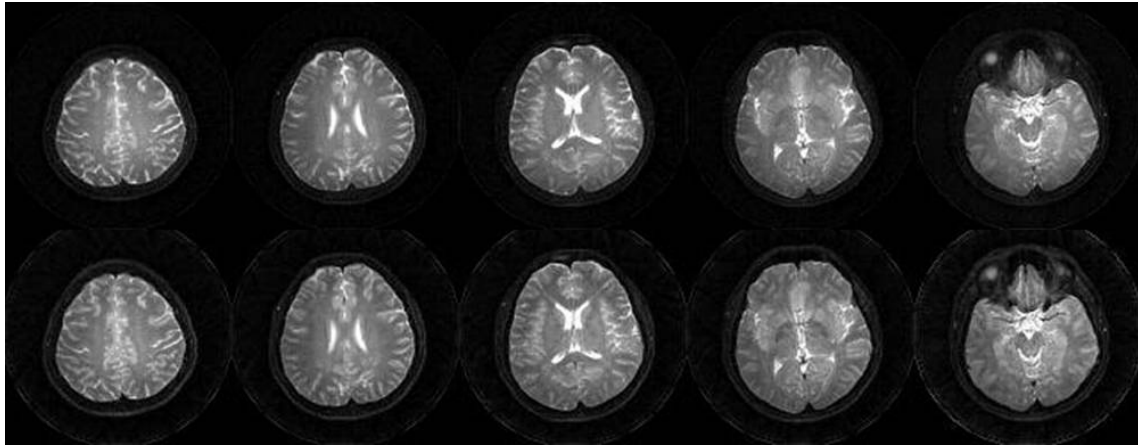


Figure 3-39 In-vivo human brain images at 3T reconstructed with PROPELLER (top row) and PETALS (bottom row) in 5 transverse slices. Acquisition matrix = 128 x 24 x 10.

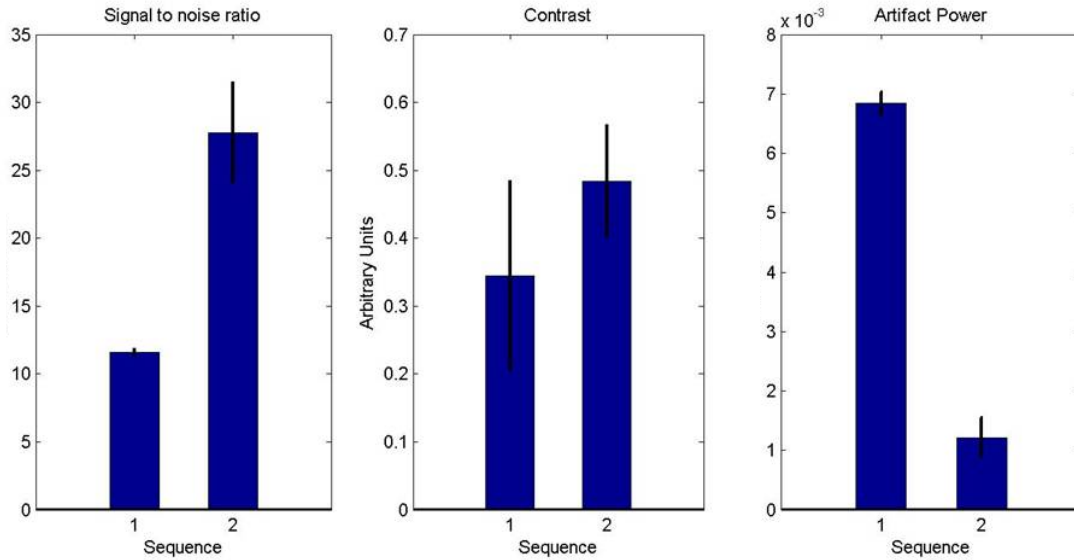


Figure 3-40 Measured SNR (left), GM-WM contrast (middle) and AP (right) in human brain in-vivo at 3T using two reconstruction methods: 1. PETALS and 2. PROPELLER.

3.4 Conclusion

High resolution imaging at high field strength presents a challenge in terms of enhanced T_2 , T_2^* , and geometric distortions due to B_0 inhomogeneity, susceptibility and chemical shift. Single-shot methods are highly time-SNR efficient but suffer from severe distortion and blurring, and are better suited to rapid lower resolution applications. EPI methods are often used for fast imaging and to generate T_2^* contrast, but require high performance gradient systems and are generally prone to greater geometric distortion and T_2^* . This may be

tolerable at 3T, but becomes a significant hurdle particularly at 9.4T and in regions outside the brain. FSE methods are much more robust to geometric distortions although the repeated refocusing pulses may result in SAR limits in imaging humans. However, a number of SAR reducing strategies exist, including using variable flip angles as in hyperecho-FSE imaging (102), using variable-rate selective excitation or VERSE RF pulses (103), and increasing the TR. Cartesian k-space acquisition methods are usually used in the acquisition of MR images, due to their efficiency in filling k-space and their rapid reconstruction using the FFT. When acquired in multiple shots however, they become prone to artifacts arising mainly from motion in between shots. This was less of an issue in imaging cooperative subjects or mouse brains which can be firmly secured, but presented a major challenge in other regions and subjects.

FSE-PROPELLER multiply samples the centre of k-space allowing for self navigation. In our data, motion artifacts were significantly reduced at both 3T and 9.4T, while SNR and CNR were increased in imaging at 9.4T compared to Cartesian scans. A modest blurring of the point spread function in the order of 1-2% would have decreased the actual resolution obtained using FSE-PROPELLER thereby enhancing apparent SNR. This however would not account for the 40% improvement in SNR in imaging mouse brain at 9.4T which was attributed to the multiple sampling of the centre of k-space. The sequence was highly compatible with T_2 -weighted imaging for ETL=8 and 16, and simulations and data showed that it performed better than Cartesian sampling at 9.4T. It is recommended as a substitute for standard FSE Cartesian sampling in T_2 -weighted imaging at 9.4T regardless of the presence of motion. At lower fields, the main utility of PROPELLER remains its ability to correct for motion.

A mixing of TEs at the central part of k-space led to a loss of contrast in FSE-PROPELLER with TE=6.38ms. PETALS was introduced as a postprocessing method to improve contrast at the expense of SNR. Simulations showed that it improved contrast at 3T at ETL=32, and at 9.4T for ETL=16 to 64. Contrast was improved in mouse brain at 9.4T but not in human brain at 3T. The contrast arising with PETALS depends on the degree of truncation of k-space, particularly the width of the remaining blades at the centre of k-space. A detailed study with varying degrees of truncation was not performed, and parameters used here were chosen after visual assessment of various reconstructed data. It was observed that the improvement in contrast in PETALS over PROPELLER was dependent on field strength.

The main drawback of PROPELLER is up to a 50% lengthening of time taken to fully sample k-space. However, all the time-normalised data at 9.4T showed that PROPELLER had higher SNR, CNR and lower AP than Cartesian sampling. Nonetheless, acquisition times for multi-shot scans such as PROPELLER remain substantially longer than single-shot methods. The next chapter will present work on k-space undersampling in PROPELLER as a method for reducing acquisition times. The time savings are measured against image fidelity at a range of field strengths.

4 Optimal Strategies for PROPELLER Undersampling at High Field Strength

4.1 Introduction

PROPELLER increases the acquisition time of a comparable standard Cartesian FSE acquisition by about 50%, due to the inherent oversampling of the center of k-space. The number of blades needed to fully sample k-space was defined in Section 3.2.1. This prompted the investigation of methods to reduce the acquisition time.

PROPELLER has been combined with rapid sequences like EPI (64) and Gradient and spin echo (GRASE) (104) in an effort to acquire more data in each TR, thereby widening the PROPELLER blades and reducing the number of blades needed. However, these methods introduce susceptibility-induced geometric distortions that scale with EPI train length and field strength. Combination of distorted blades can give rise to severe blurring and artifacts. In contrast, FSE methods were shown in Chapter 3 to be inherently robust to susceptibility and B_0 inhomogeneity effects.

An increasingly popular method to reduce the acquisition time is the use of k-space undersampling. Undersampling most often aims to reduce the acquisition time, and this can be achieved in the context of PROPELLER by reducing either the number of blades used or expanding the space in between consecutive phase encoding steps and acquiring correspondingly fewer blades (See Figure 4-1) (105). This leads to the violation of the Nyquist criterion and may result in severe artifacts depending on the degree of undersampling and the manner in which blades or phase encodes were removed. Undersampling in Cartesian sampling methods either leads to blurring or artifacts depending on which k-space data are not acquired. The advantage of combining undersampling with PROPELLER is that only the edges of k-space are undersampled. As the centre is always massively oversampled, PROPELLER is expected to be able to tolerate undersampling in a way that Cartesian methods cannot.

Arfanakis, et al. studied various methods of undersampling using regridding and an undersampling factor of 2, ie. acquiring half the data that is needed for full sampling of k-space (105). They found that excluding alternate blades led to reconstructed images without significant artifacts, whereas doubling the spacing between successive phase encodes and halving the number of blades acquired led to significant artifacts. The study did not however

present a quantitative measure of contrast or error, and did not assess the effects of motion or varying degrees of undersampling.

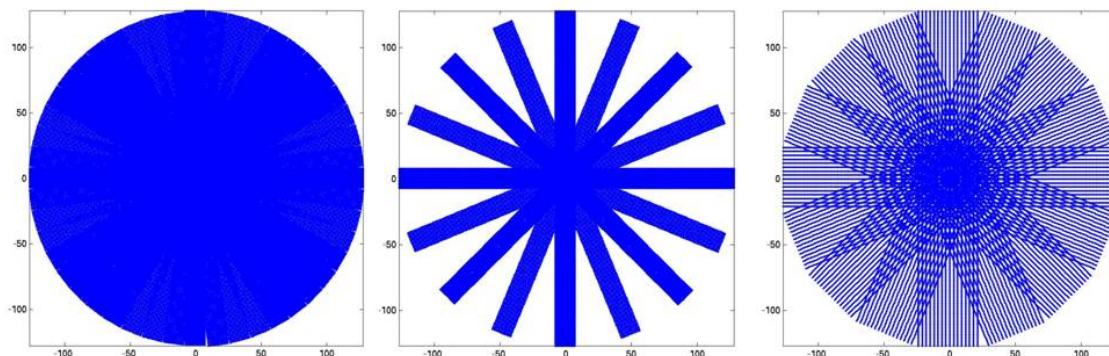


Figure 4-1 Representative k-space that illustrate two methods of undersampling as intended to reduce acquisition time. Fully sampled PROPELLER (left), 3x undersampled by blades (middle) and 3x undersampled by spacing between phase encoding steps (right). Matrix sizes are 256 x 16 x 24, 256 x 16 x 8 and 256 x 16 x 8 respectively. The examples of undersampled PROPELLER here can be acquired in a third of the time taken to acquire fully sampled data.

Different groups have taken advantage of parallel imaging methods to synthesize missing k-space data. In so doing, blades could be widened and fewer blades could be acquired. Such methods include using sensitivity encoding (SENSE) (17,64), anti-aliasing partially parallel encoded acquisition reconstruction (APPEAR) (106), mutual calibration with split blade approach (107), generalised autocalibrating partially parallel acquisitions (GRAPPA) (108-110), and fast reduced encoding imaging by generalised series reconstruction (RIGR) (111). The wider blades thus generated by parallel imaging have also been used to reduce T_2 blurring and improve motion correction (112). However, the RF coil used in imaging at 9.4T was a single channel transmit-receive volume coil and thus parallel imaging was not considered due to hardware limitations. Although it was not implemented here, it is expected that parallel imaging where available, would be compatible with k-space undersampling methods.

Iterative reconstruction methods may be used to regenerate missing k-space data by interpolation, extrapolation or regularization. These were described in Section 3.2.1 and offer significant savings in acquisition time at the expense of image quality and postprocessing requirements.

In Chapter 3, NUFFT was identified as an efficient and effective interpolation method that outperformed regridding methods. Tamhane, et al. combined NUFFT (80) with PROPELLER and showed that the reconstructed image quality using NUFFT was superior to using standard regridding (113). This was consistent with my observations as illustrated in Figure 3-4. They proceeded to quantify the error based on the degree of undersampling (114). However, undersampling here was achieved by varying the spacing between phase encoding steps. The choice of undersampling method appeared to conflict with their earlier observation that undersampling by blades (USB) resulted in fewer artifacts than undersampling by phase encodes (USP). Further, these measurements were made only in simulated data.

The attractiveness of undersampled PROPELLER lies in its rotational symmetry and compatibility with various parallel imaging and non-cartesian reconstruction methods. These impart flexibility and allow for the determination of a suitable balance between degree of undersampling and desired image quality. Studies investigating the effects of undersampling have not previously been conducted at field strengths beyond 3T. At 9.4T, severe T_2 may dictate one method of undersampling over another. Of these studies, few have quantitatively measured the quality of data at different degrees of undersampling (114).

In this chapter, the relationship between image quality and methods of undersampling, degree of undersampling, field strength and blade configuration are investigated using both simulations and experiments. The aim of which is to identify an optimal strategy for undersampling in PROPELLER at 9.4T that is resistant to artifacts. Simulation data that examine SNR, CNR, PSF and AP behaviour for different blade configurations and field strengths using USB are first presented. This is subsequently compared against USP for a suitable blade configuration. The effects of motion are investigated using both USB and USP. To separate motion effects from undersampling effects, in-vivo data in healthy mouse brains were acquired where motion was minimised. These were undersampled to varying degrees using various sampling configurations. Preliminary human volunteer studies suggest that undersampling techniques can also be used in the presence of motion. The potential and limitations of undersampling techniques are discussed.

4.2 Materials & Methods

4.2.1 Simulations

Shepp-Logan simulations were generated using PROPELLER k-space sampling, in the manner as described in Section 3.2.2. They contain the same geometries, noise, and simulated tissue properties of PD and T_2 as described therein. In all cases, the reconstructed matrix size was 256×256 , and linear phase encoding with $TE_{\text{eff}}=51.0\text{ms}$ and $ESP=6.38\text{ms}$ were used. At 9.4T , $T_{2,\text{brain}} \sim 40\text{ms}$. In order to obtain T_2 -weighted images using linear phase encoding and to limit T_2 decay, blade widths were limited to 16. Motion was first neglected.

First, reference images with T_2 at various field strengths (no T_2 , 3T and 9.4T) without noise were generated to illustrate the effect of T_2 on contrast. These would subsequently be used in measurements of AP.

Next, simulation data were generated by under and oversampling k-space by blades, with T_2 at the various field strengths given above, and for blade sizes = 256×8 and 256×16 . These would require 50 and 25 blades respectively for full k-space sampling. In both cases, data using blade numbers from 4 to 48 at intervals of 4 were computed. This meant that data with blade sizes of 256×8 were twice undersampled compared to data with blade sizes of 256×16 at equal blade numbers. This facilitated the direct comparison of blade configurations with equal acquisition times. USB data were generated by uniformly distributing the blades in a rotational fashion about the origin. Simulations were repeated five times in each case to investigate the data consistency over multiple acquisitions.

The images, MTFs and PSFs in a subset of these data were displayed to illustrate the artifacts, k-space sampling trajectory and blurring associated with varying degrees of undersampling. Difference images were also obtained by normalizing the mean of the reconstructed image data to the mean of the ideal simulation data, then finding the absolute difference between this normalised reconstructed image data and the ideal simulation data.

By identifying ROIs in the simulated brain, WM and GM as described in Figure 3-6, measures of image quality were obtained to compare the image fidelity using the various sampling methods. These were SNR, CNR, FWHM of the PSF and AP, as described in Section 3.2.2. These metrics were plotted against blade number, in an effort to better understand the impact of under and oversampling by blades.

Since blade numbers of 48 and 24 were more easily factored than 50 and 25, the former pair was used as a reference 'fully sampled' k-space for blade sizes = 256 x 8 and 256 x 16 respectively. These values represented 95% k-space sampling based on Eqn 3.1. The graphs above were reformatted to express the given metrics in terms of a percentage of their values at 95% k-space sampling. The x-axis was similarly reformatted to reflect the blade number as a percentage of the number of blades required for 95% k-space sampling. Rather than comparing data of different blade sizes at equal acquisition times, these graphs plot the behaviour of SNR, CNR, PSF and AP as a function of degree of undersampling.

Having identified a 256 x 16 as a suitable blade size (See Section 4.3.1), the behaviour of using USB versus USP was compared to determine which approach if either was more suitable. Using a blade size of 256 x 16, simulations of USB and USP PROPELLER data were constructed with 5 repetitions, across a range of blade numbers from 4 to 48, and in intervals of 4. USP data were generated by varying the spacing between the phase encoding steps such that the number of blades required for full k-space sampling, assuming the region of k-space within each blade was fully sampled, was as desired using Eqn 3.1. This meant that for blade numbers = [4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48] the corresponding distance

$$\text{between phase encoding steps} = \frac{1}{FOV} \times [6, 3, 2, 1.5, 1.2, 1, 0.857, 0.75, 0.667, 0.6, 0.545, 0.5],$$

using 95% sampling as the nominal full k-space sampling. The comparison between USB and USP methods was repeated in the presence of a random $\pm 5^\circ$ rotation to simulate motion in-vivo.

4.2.2 Animal Studies

T₂-weighted PROPELLER data were obtained by adaptation of a conventional 2D-FSE sequence, using the 9.4T MRI scanner (Varian, Palo Alto, CA), gradient coil and RF coil setup as described in Chapter 3. 7 healthy wildtype C57/Bl6 mouse datasets were acquired in-vivo, in accordance to local IACUC guidelines. Experiments were performed at the Lab of Molecular Imaging, Singapore Bioimaging Consortium, Singapore. Since the focus was to investigate the effects of undersampling, brain data were acquired with animals secured with a nosecone and bitebar, in order to minimize motion. Anaesthesia was induced with 3.5% isoflurane and maintained at 1-1.5% isoflurane in a 55%:45% mixture of N₂:O₂. Respiration was monitored using an air pillow transducer and controlled between 60-80 breaths/min. Animals were free breathing. Body temperature was measured using a rectal probe and maintained at 36.5°C by circulating warm air.

Each animal was scanned using FSE-PROPELLER. TR=4000ms, TE=51ms, ESP=6.38ms, ETL=16, FOV=25.6 x 25.6mm, reconstructed matrix=256 x 256, matrix=256 x 16 x 48, thickness=1mm, gap=0.5mm, slices=5, phase encoding=linear, slice order=interleaved, orientation=axial, readout bandwidth=208kHz and acquisition time=3m 24s. The configuration of blade width and blade numbers meant that data were twice oversampled. By excluding interleaved blades in postprocessing, effective blade numbers, $N_b=6, 8, 12, 16, 24$ & 48 were generated. Values of N_b were necessarily factors of the 48 blades acquired so that the undersampled blades could be uniformly angularly distributed. This encompassed a sampling percentage of 24% to 191% for blade size=256 x 16. In addition, the edges of each blade were cropped to produce blade sizes of 256 x 8 and 256 x 12, and these were also examined over the range of effective blade numbers from 6 to 48.

All experiments were repeated to obtain SNR, CNR and AP information based on manually drawn ROIs for each subject (See Figure 3-10). Of interest were $SNR_{\text{whole brain}}$, GM-WM contrast, and $AP_{\text{whole brain}}$. These were calculated with Eqns 3.3, 3.4 & 3.5 respectively.

In order to calculate AP, a reference image had to be identified. Despite the fact that the data acquired with nPE=16 and $N_b=48$ had the highest SNR and minimal artifacts by inspection (See Figure 4-20), it was not used as the reference image. Since the intention of the study was to investigate undersampling, the 95% sampled data with the least artifacts by inspection was chosen as the reference image. This was obtained with nPE=16 and $N_b=24$. The choice was further supported by the simulation data that showed that this blade configuration resulted in the lowest AP at 9.4T (See Figure 4-8).

4.2.3 Human Studies

Since motion was well restrained in the mouse brain, data from human volunteers were used to investigate the robustness of undersampled PROPELLER in the presence of motion. Multi-shot FSE and FSE-PROPELLER data were extracted from volunteer data acquired in Section 3.2.4. Alternate blades were excluded in the FSE-PROPELLER data to generate a USB dataset with acquired matrix=256 x 20 x 12 with half the nominal acquisition time. Volunteers were asked to keep still in one set of experiments and to rotate their heads from side to side during another.

To recap, each volunteer was scanned using a msFSE and FSE-PROPELLER sequence with the following parameters: TR=2000ms, TE=80ms, ESP=7.6ms, ETL=20, FOV=240 x

240mm, reconstructed matrix=256 x 256, thickness=5mm, gap=1mm, slices=14, slice order=interleaved, orientation=transverse and acquisition time=1m 44s. Parameters specific to msFSE were acquired matrix=256 x 240, averages=2; and parameters specific to FSE-PROPELLER were acquired matrix=256 x 20 x 24, averages=1. Work was carried out on a 3T Achieva scanner (Philips, Best, Netherlands) in accordance to the sequence development protocol under local IRB guidelines.

4.3 Results & Discussion

T_2 associated with different field strengths give rise to a range of contrasts. These are illustrated in Figure 4-2 without T_2 , at 3T and at 9.4T. These reference images were used in calculations of AP in the simulation data at various field strengths.

4.3.1 Simulations



Figure 4-2 Shepp-Logan reference magnitude images depicting contrast without T_2 (left), T_2 at 3T (middle) and T_2 and 9.4T (right). Motion and noise were neglected.

Figure 4-3 illustrates magnitude images, MTFs, PSFs and difference images for progressively undersampled PROPELLER data at 9.4T where blade size=256 x 8. Undersampling by blades gave rise to artifacts that generally increased with degree of undersampling. These manifested primarily as a loss in resolution in the direction parallel to the removed blades, and in streaking artifacts particularly at regions with sudden changes in geometry and contrast. These were due to inadequate sampling especially at the periphery of k-space, and resultant interpolation errors. Even 95% sampling where $N_b=48$ resulted in ringing artifacts due to the errors in the PSF. At each value of undersampling, the observed undulating intensities in the PSF resulted in various degrees of ringing and streaking artifacts, while the broadening of the PSF gave rise to blurring. In the extreme case where $N_b=8$, the rotational modulation of the PSF that coincided with the sampled blades, was

severe and led to marked streaking artifacts and angular discontinuities in the image. The MTF reflects the sampling density and weighting functions arising from the NUFFT algorithm, and radial signal variations were observed particularly at $N_b=48$. Difference images also highlighted the streaking and ringing artifacts that were particularly prominent at $N_b=8$ and $N_b=48$ respectively.

The same data with blade size=256 x 16 are displayed in Figure 4-4. Despite the longer ETL, images were generally more consistent, with fewer artifacts than the equivalent image at blade size=256 x 8. This was due to the more complete sampling of k-space. PSFs behaved similarly to the previous case, with rotational signal oscillations coincident with blades. However, the radial oscillations (ie. ringing artifacts) doubled in frequency, and overall signal variations were lower. Artifacts were correspondingly more dispersed and less intense.

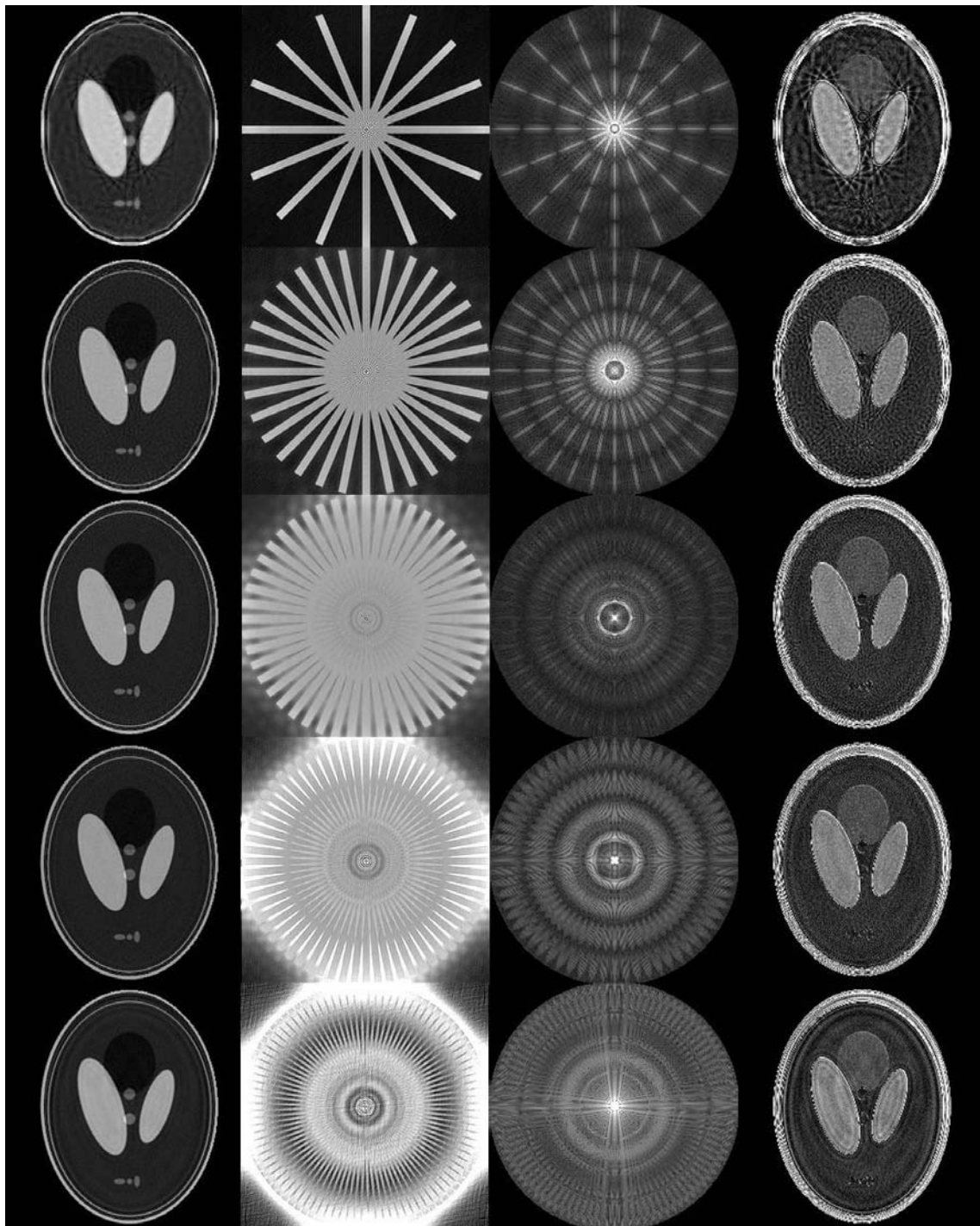


Figure 4-3 Shepp-Logan simulations under/oversampling by blades. Features magnitude images (leftmost column), MTFs (second column), PSFs (third column) and difference images (rightmost column) over a range of blade numbers = [8, 16, 24, 32 and 48] (from top to bottom row). Blade size=256 x 8. For display purposes, images were normalized to noise, MTFs and difference images were multiplied by a fixed scaling factor, PSFs were raised to the $1/3$ power to highlight the intensities away from the centre.

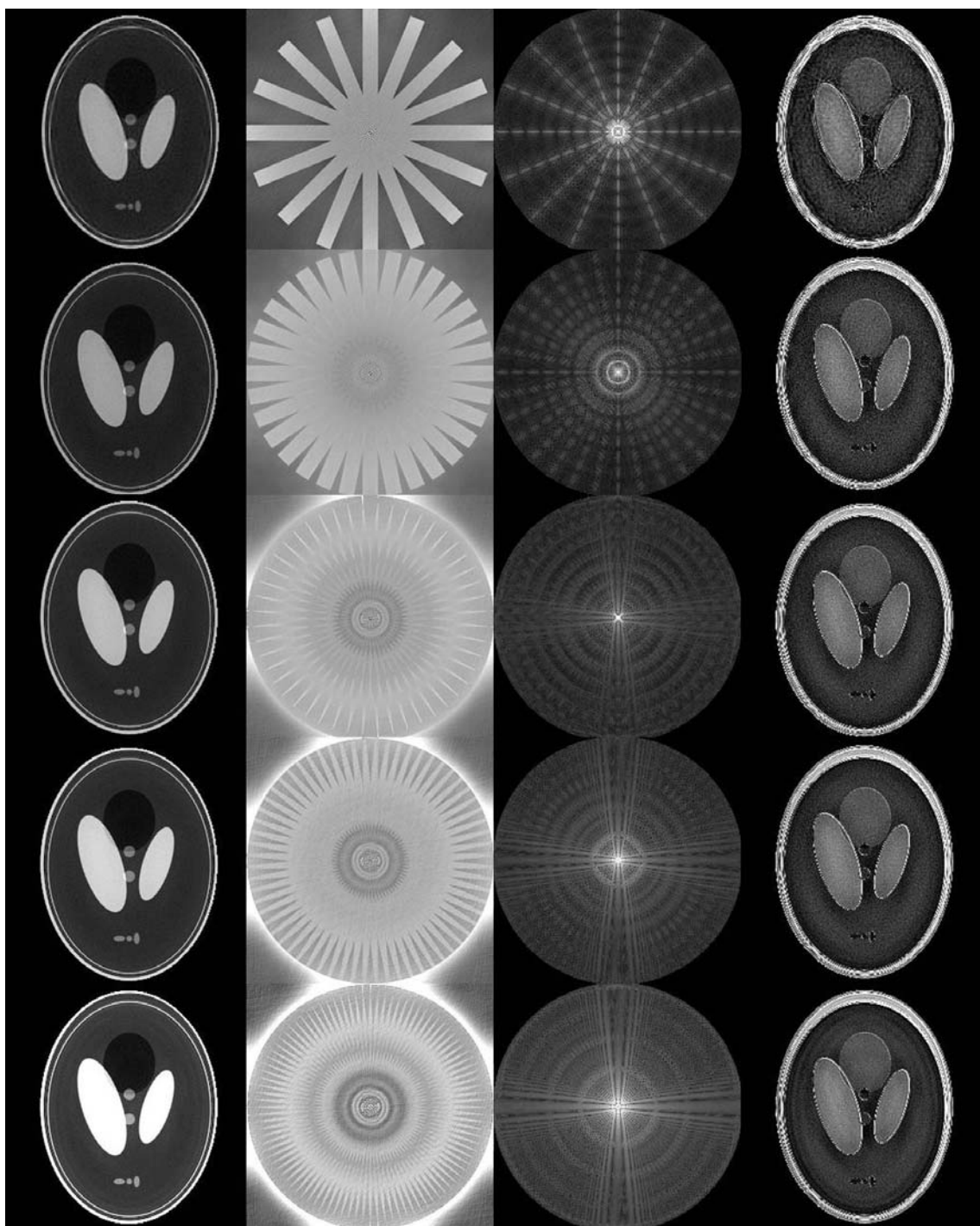


Figure 4-4 Shepp-Logan simulations under/oversampling by blades. Features magnitude images (leftmost column), MTFs (second column), PSFs (third column) and difference images (rightmost column) over a range of blade numbers = [8, 16, 24, 32 and 48] (from top to bottom row). Blade size=256 x 16. For display purposes, images were normalized to noise, MTFs and difference images were multiplied by a fixed scaling factor, PSFs were raised to the $^{1/3}$ power to highlight the intensities away from the centre.

SNR data for blade size=256 x 8 & 256 x 16 without T_2 , at 3T and at 9.4T are given in Figure 4-5 across a range of under and oversampling by blades. In general, SNR increased with blade number as would be expected by the multiple sampling of the centre of k-space, and decreased with field strength due to shortening T_2 . At 3T and 9.4T, SNR was higher at $N_b \geq 20$ using nPE=16 due to wider k-space coverage. Although SNR using nPE=8 was higher at $N_b < 20$, this corresponded to an undersampling factor of 3, and in this range, artifacts were visually severe. Where T_2 was neglected, the disparity between nPE=8 and nPE=16 was less obvious, due to the lack of T_2 signal modulation and more consistent data at the centre of k-space. As a reference point, 95% k-space sampling for blades size of 256 x 8 and 256 x 16 were achieved with $N_b=48$ and $N_b=24$ respectively.

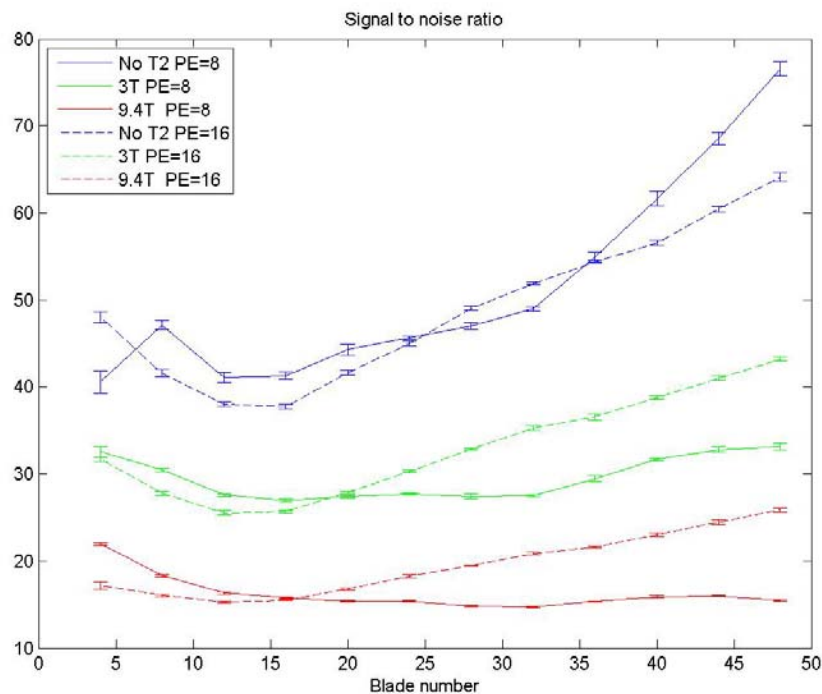


Figure 4-5 SNR of Shepp-Logan simulation data with under/oversampling by blades. Data were reconstructed using different numbers of blades, blade widths and T_2 . Blade readout=256.

GM-WM CNR data are presented in Figure 4-6. It shows that CNR generally improved with blade number, except for $N_b < 16$ due mainly to signal modulations in the PSF and associated artifacts. For this range, nPE=16 demonstrated better CNR than nPE=8 at 3T and 9.4T. Overall, the CNR data were closely related to the SNR data. The main difference was that the CNR at 3T was generally higher than that neglecting T_2 . This was indicative of the better contrast that could be obtained using T_2 -weighting as opposed to PD-weighting. CNR

however dropped precipitously at 9.4T due to severe rotational signal intensity modulation and mixing of k-space of more widely varying intensities. The diminished contrast highlights one significant challenge of PROPELLER imaging at high field.

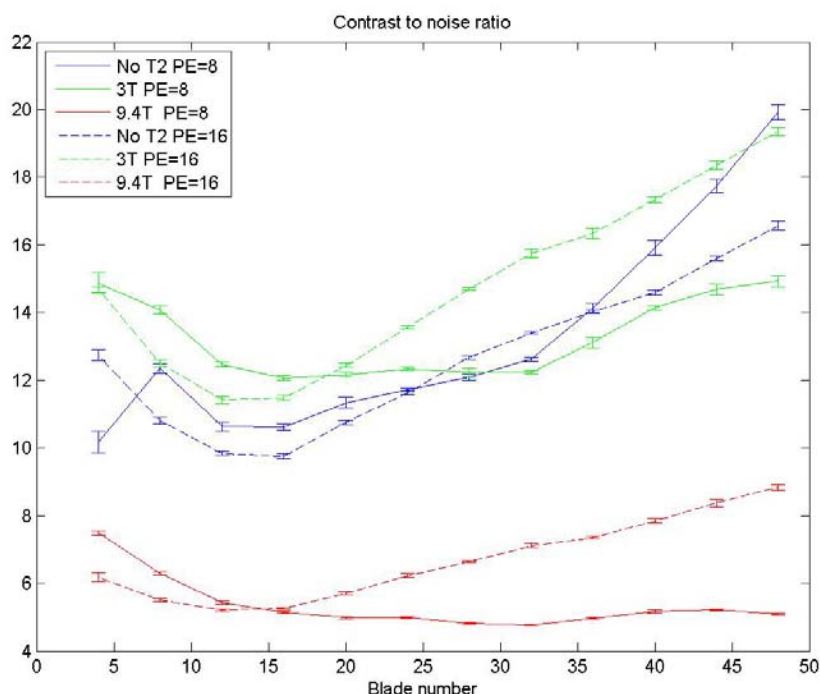


Figure 4-6 CNR of Shepp-Logan simulation data with under/oversampling by blades. Data were reconstructed using different numbers of blades, blade widths and T_2 . Blade readout=256.

As an indicator of the degree of blurring, the mean of the FWHM of the PSF was measured in each case and is given in Figure 4-7. It was found that at $nPE=8$ and $nPE=16$, T_2 decay was low enough that the PSF was the same across field strengths. The PSF was dominated here by the sampling method. The mean FWHM increased with higher degrees of undersampling and was higher using $nPE=8$ compared to $nPE=16$. This was mainly due to the lower k-space coverage in the former. Comparing values of $nPE=16$ at N_b blades with $nPE=8$ at $2N_b$ blades (ie. equivalent k-space percentage sampling instead of acquisition time), shows much closer agreement where $N_b \geq 16$. This means that blurring for data that is $\leq 36\%$ undersampled was similar for $nPE=8$ and $nPE=16$.

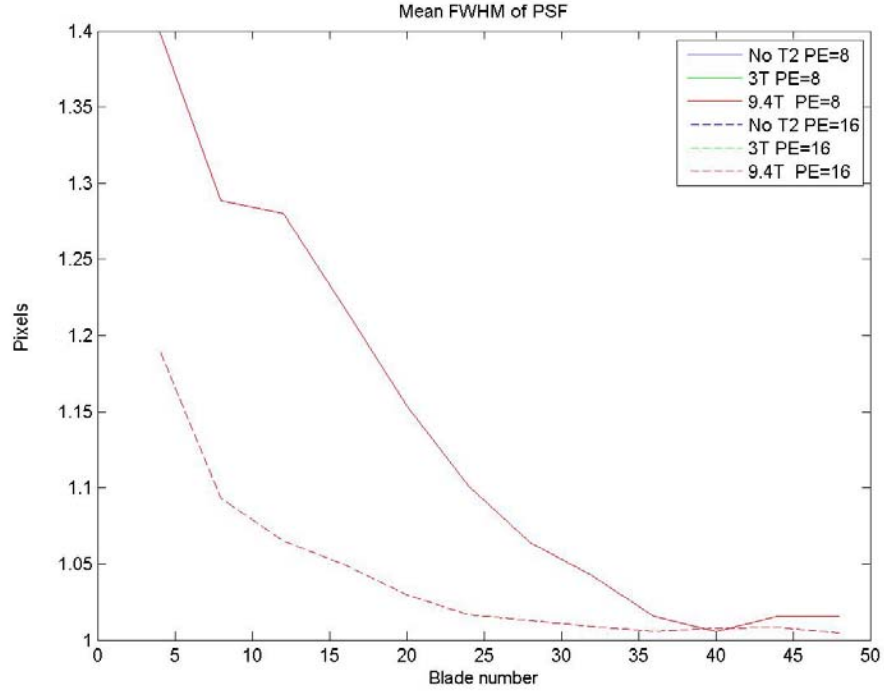


Figure 4-7 PSF FWHM of Shepp-Logan simulation data with under/oversampling by blades. Data were reconstructed using different numbers of blades, blade widths and T_2 . Blade readout=256. Data at different field strengths were collinear.

AP was directly related to field strength as shown in Figure 4-8, and remained relatively constant over the range of blade numbers used, with the exception of gross undersampling at $N_b=4$. When T_2 was neglected, $nPE=16$ consistently had lower AP than $nPE=8$. This improvement was further enhanced at higher field strengths where $N_b \leq 32$. At higher blade numbers, differences between $nPE=8$ and $nPE=16$ became less apparent. This suggested that NUFFT performed better when data was not oversampled.

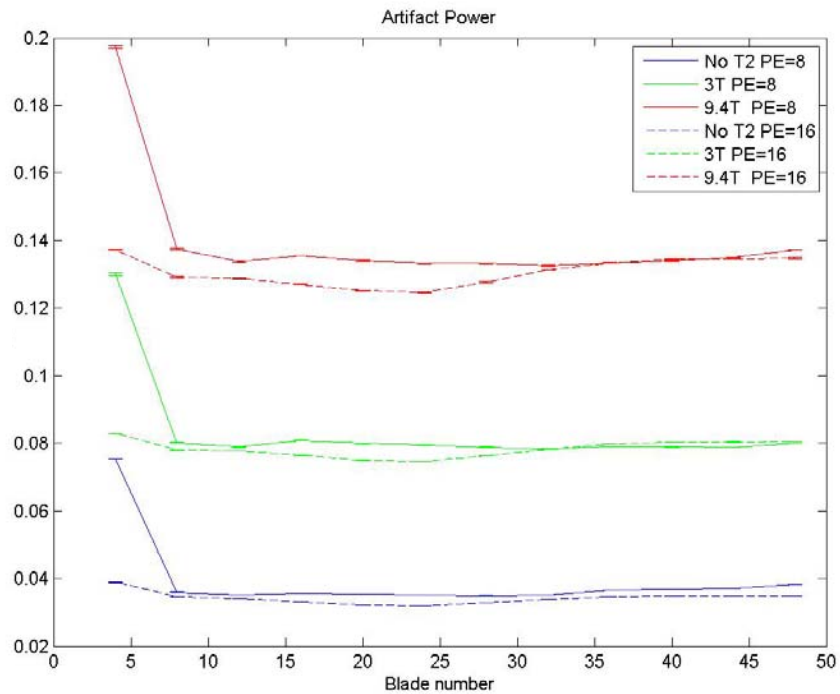


Figure 4-8 AP of Shepp-Logan simulation data with under/oversampling by blades. Data were reconstructed using different numbers of blades, blade widths and T_2 . Blade readout=256.

Figure 4-9 to Figure 4-12 express the same data found in the previous four figures, as normalized to the respective values at 95% k-space sampling (ie. $N_b=24$ & 48 for $nPE=16$ & 8 respectively). Data is shown for sampling percentages ranging from 20% to 95%. Note that comparisons of data at $nPE=8$ and $nPE=16$ using these graphs should take into account that at the same percentage of k-space sampling, the acquisition time for $nPE=8$ was double that for $nPE=16$. In addition, percentages described here are taken with respect to the reference value at a particular field strength and blade width, and are independent of absolute values across field strengths and blade widths.

Figure 4-9 shows that SNR varied greatly with undersampling when $nPE=8$ was used. The relative drop in SNR with degree of undersampling was most prominent without T_2 , and diminished greatly at 9.4T. This was probably due to noise and T_2 mixing at the k-space centre that limited coherent addition of the signal in the latter case even when fully sampled. Removing blades thus did not result in the same relative drop in SNR. Using $nPE=16$ led to SNR measurements that were less dependent on field strength, and this was likely due to the broader coverage of the centre of k-space with each blade. While SNR generally increased with k-space sampling, an increase was also observed at sampling <48%. The latter increase

however was attributed to a loss in resolution and convergence in reconstructed data owing to excessive undersampling. This was accompanied by an increase in PSF line broadening and AP.

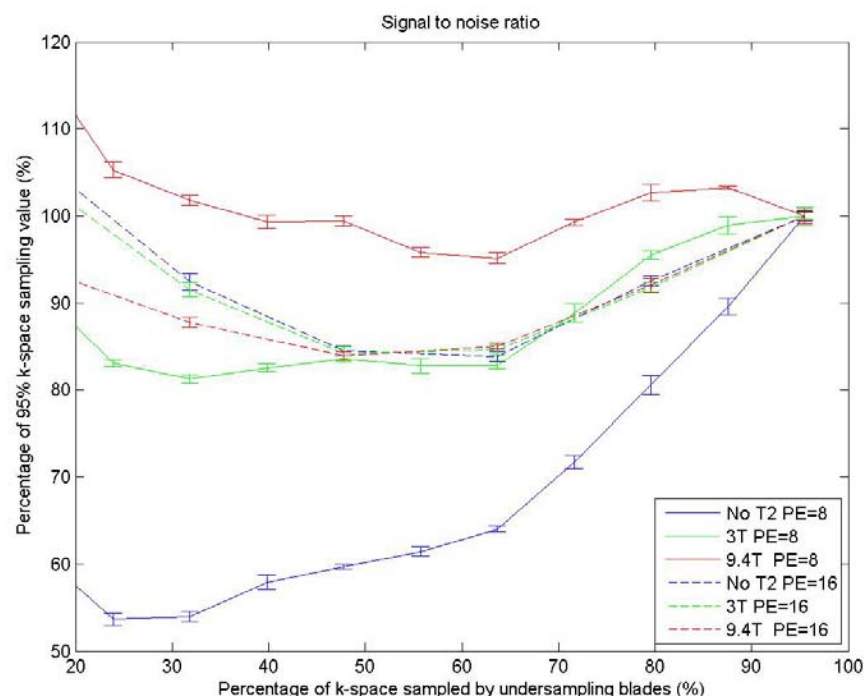


Figure 4-9 SNR of Shepp-Logan simulation with undersampling by blades. Data presented is a subset of Figure 4-5, expressed as a percentage of the value of data at 95% k-space sampling.

GM-WM CNR behaved in a similar manner to SNR as seen in Figure 4-10, and showed that CNR was dominated by noise levels rather than changes in absolute contrast.

Figure 4-11 describes the increase in PSF line broadening with degree of undersampling. At sampling >60%, there is less relative line broadening where $nPE=8$, while at lower sampling, there is less relative line broadening where $nPE=16$. This could be due to the more severe and rapid rotational modulation of k-space with narrower blade widths.

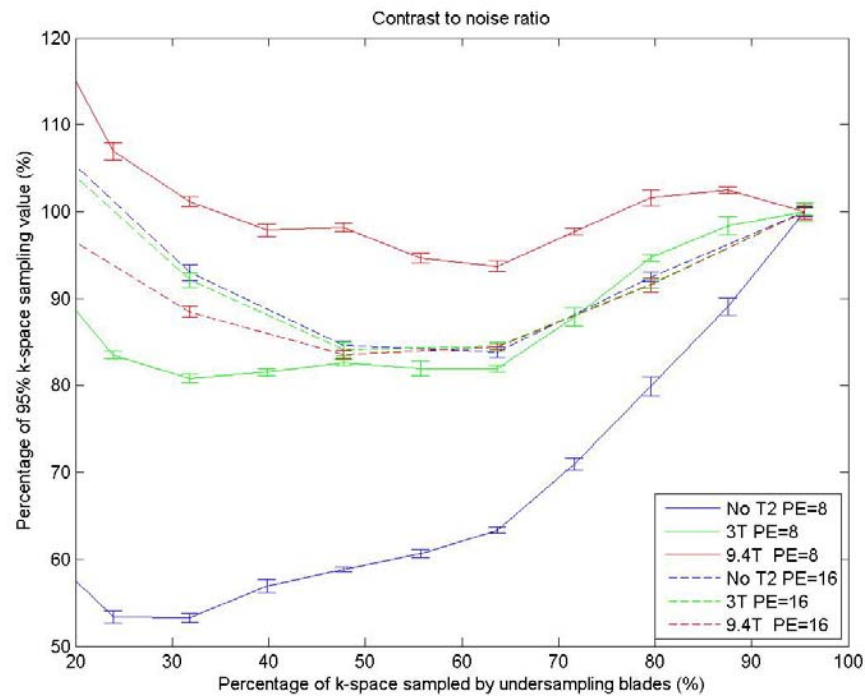


Figure 4-10 CNR of Shepp-Logan simulation with undersampling by blades. Data presented is a subset of Figure 4-6, expressed as a percentage of the value of data at 95% k-space sampling.

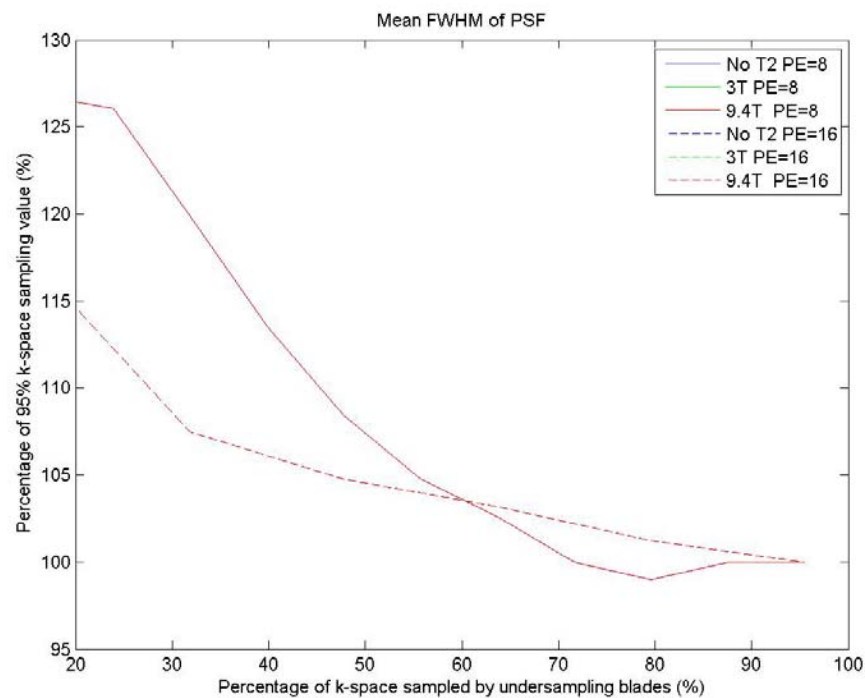


Figure 4-11 PSF FWHM of Shepp-Logan simulation with undersampling by blades. Data presented is a subset of Figure 4-7, expressed as a percentage of the value of data at 95% k-space sampling. Data at different field strengths were collinear.

AP data presented in Figure 4-12 show that at nPE=16, relative AP increased with degree of undersampling, and this increase was less severe at higher field strengths. Surprisingly, relative AP decreased when data were undersampled using nPE=8, particularly without T₂. This was due to the fact that at blade widths as narrow as nPE=8, inconsistencies in the PSF and MTF resulted in image artifacts even when k-space was fully sampled. Reducing the blade numbers led to more consistent PSF and MTF, and hence lower AP.

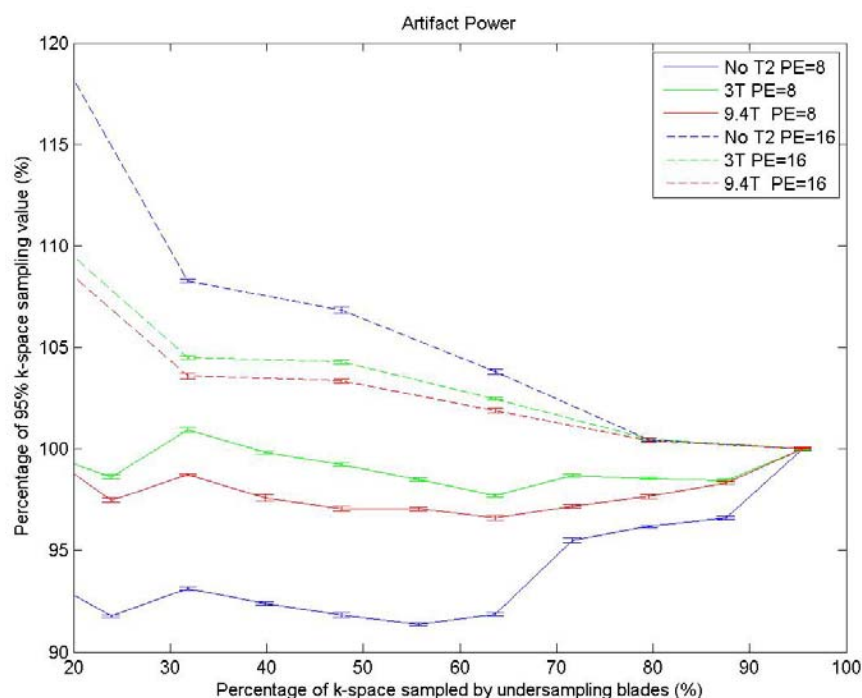


Figure 4-12 AP of Shepp-Logan simulation with undersampling by blades. Data presented is a subset of Figure 4-8, expressed as a percentage of the value of data at 95% k-space sampling.

The simulation data show that for a given acquisition time, using nPE=16 produced data that were more resistant to blurring and artifacts than using nPE=8, for a practical range of undersampling with blade numbers from 8 to 24. Additionally, the improvement in resistance to artifacts was greater at 9.4T than at lower field strengths. SNR and CNR were more variable and depended on the specific blade number. This was due to the increased SNR at high degrees of undersampling, which in turn arose from reconstruction artifacts associated with insufficient data. At such levels, blurring and image artifacts were prominent. As a result, at these blade numbers, it may be suggested that the SNR and CNR with nPE=8 were more greatly overestimated than with nPE=16.

The improved resistance to blurring and artifacts, particularly at 9.4T, motivated the comparison of USB and USP using $nPE=16$. USP data using the same range of blade numbers as before are presented in Figure 4-13. While image SNR increased with N_b , it appeared to drop when oversampled with 48 blades. This was likely due to the increased variation in the MTF and PSF compared to using fewer blades. With a high degree of undersampling where $N_b=8$, severe local maxima in the PSF lead to considerable artifacts in the reconstructed and difference images. In addition, there appears to be ringing artifacts in the MTF that were not present in the USB data in Figure 4-4.

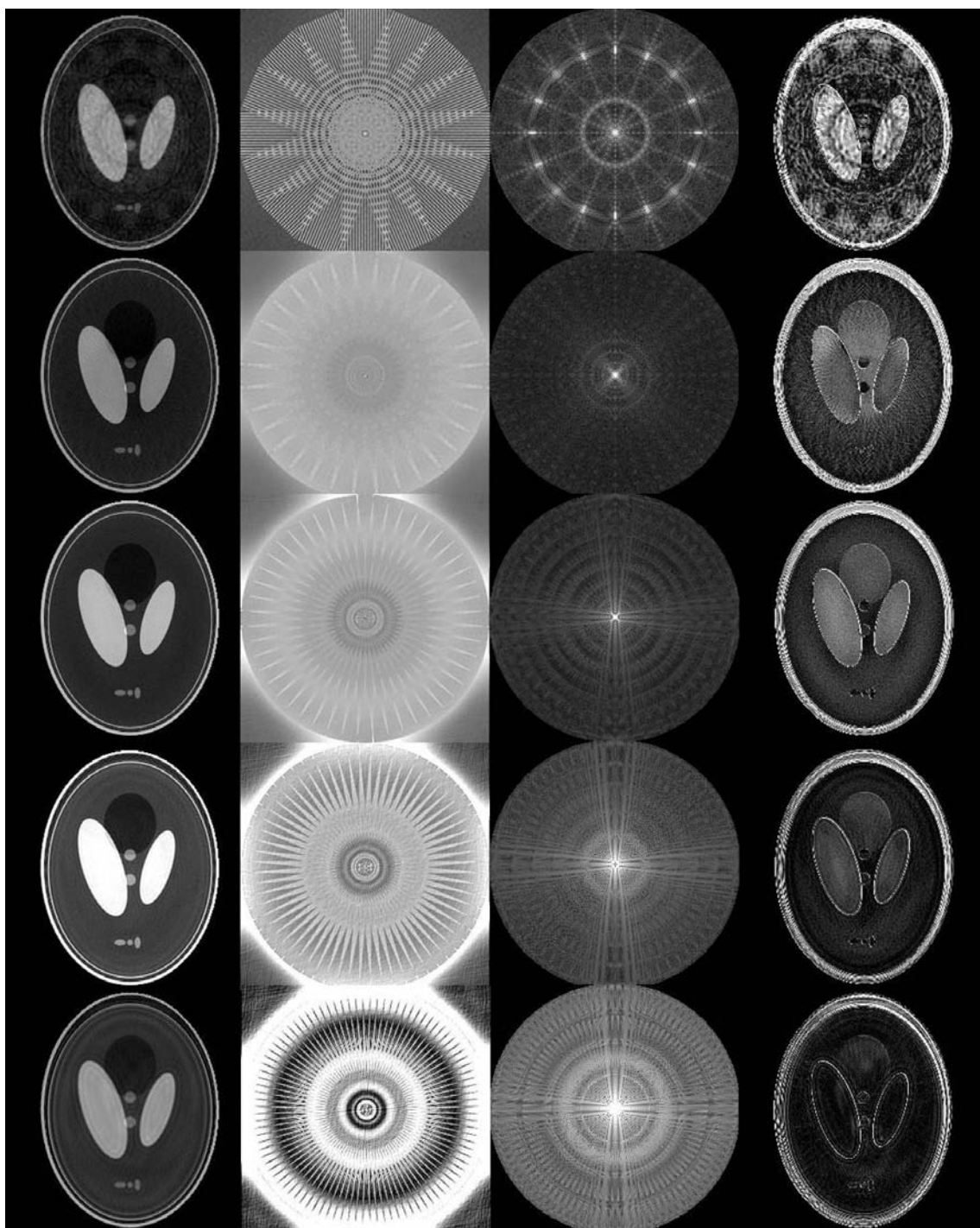


Figure 4-13 Shepp-Logan simulations under/oversampling by spacing between phase encoding steps. Features magnitude images (leftmost column), MTFs (second column), PSFs (third column) and difference images (rightmost column) over a range of evenly spaced phase encoding steps such that blade numbers = [8, 16, 24, 32 and 48] (from top to bottom row). Blade size=256 x 16. For display purposes, images were normalized to noise, MTFs and difference images were multiplied by a fixed scaling factor, PSFs were raised to the $1/3$ power to highlight the intensities away from the centre.

SNR were measured for $n_{PE}=16$ using USP at the various field strengths. These were compared to the earlier USB data and given in Figure 4-14. As before, the SNR using USP increased with blade number due to the multiple sampling of the centre of k-space. However, since this overlap was denser closer to the centre of kspace when k-space was oversampled, the result was an increase in SNR over that of USB, up to a point at $N_b=44$ where artifacts due to damage to the MTF and PSF started to dominate. The converse was true as undersampling increased. In this range, sampling at the centre was more sparse using USP, and this led to lower measured SNR. SNR reached a minimum at about $N_b=12$ or 50% sampling before rising further. It is expected that the increase in SNR here was due to reconstruction error and inadequate k-space sampling. USB consistently exhibited higher SNR across the range of undersampled values.

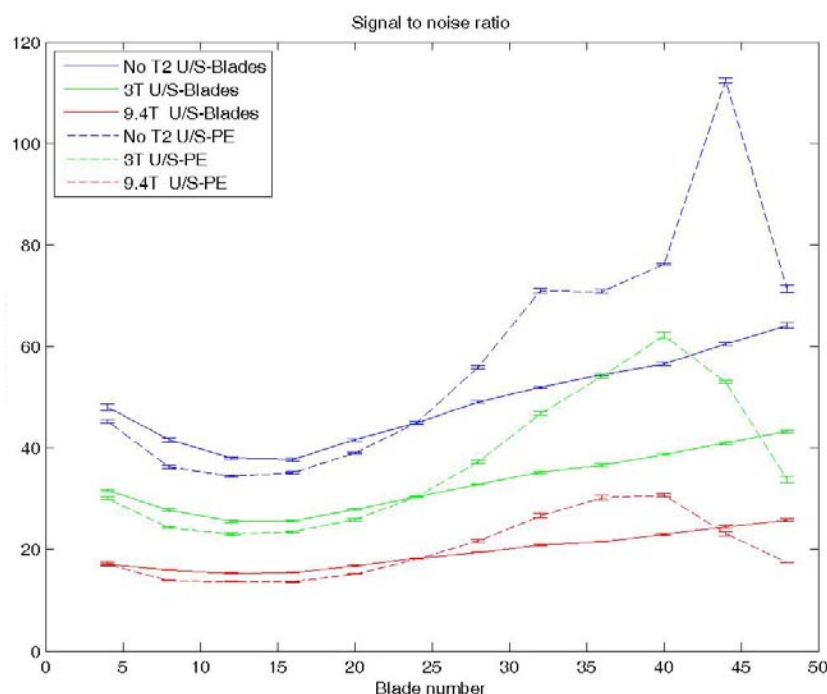


Figure 4-14 SNR of Shepp-Logan simulation data comparing under/oversampling by blades and spacing between phase encoding steps. Data were reconstructed using different numbers of blades and T_2 . Blade size=256 x 16.

Similar trends of increasing CNR with blade numbers were made using USP. Again, this elevated the CNR above that of USB up to $N_b=44$ for 3T & 9.4T, after which CNR dropped due to artifacts. With undersampling, instead of increasing at very low blade numbers, CNR continued to decrease due to increasingly severe artifacts. At $N_b \leq 12$, USB exhibited higher CNR than USP. At $N_b=16$ & 20, the reverse was true, particularly at lower field strengths. At

9.4T, however, the CNR using USP was only marginally better by up to 5%. As before, CNR at 3T was higher than without T_2 , underscoring the better contrast with T_2 -weighting compared to PD-weighting. T_2 -weighted contrast at 9.4T however was compromised.

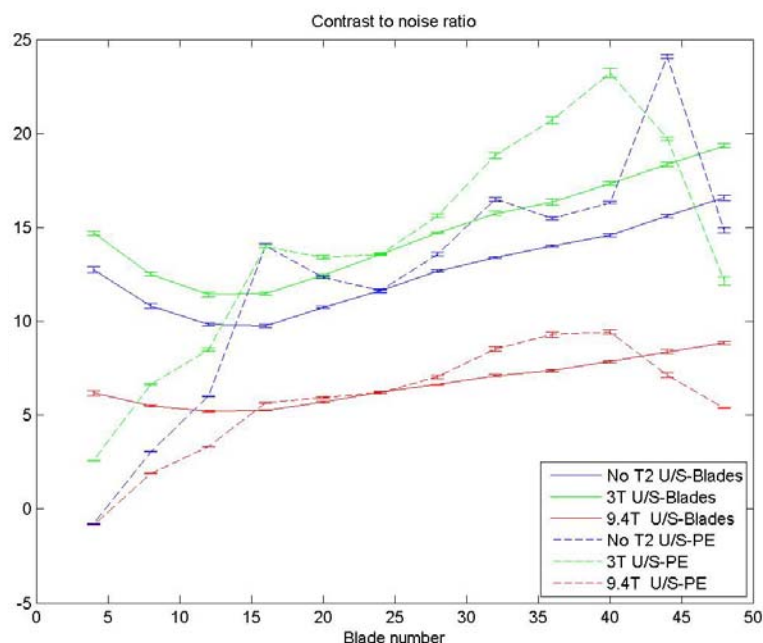


Figure 4-15 CNR of Shepp-Logan simulation data comparing under/oversampling by blades and spacing between phase encoding steps. Data were reconstructed using different numbers of blades and T_2 . Blade size=256 x 16.

Blurring was variably better or worse with USP compared to USB depending on N_b (See Figure 4-16). At high $N_b \geq 36$, blurring progressively increased in USP due to reconstruction artifacts. With undersampling, USB maintained equal or less blurring for $N_b \leq 12$. However, USP resulted in less blurring at $N_b = 16$ & 20.

Most significant were AP data as shown in Figure 4-17. It shows a considerable variation in AP with blade number using USP. While USP led to lower levels of artifacts compared to USB when data were oversampled, undersampling led to a consistently elevated AP. This increased with the degree of undersampling. Further, these variations in AP were enhanced at higher field strengths. At 9.4T and $N_b = 20$ for example, AP_{USP} exceeded AP_{USB} by over 20%. Interestingly, the variation in AP with USP was much more discrete than USB. This applied across all other parameters as well, and was related to the contributions of the specific combination of spacing between phase encoding steps, numbers of blades and blade overlap, to the MTF and PSF.

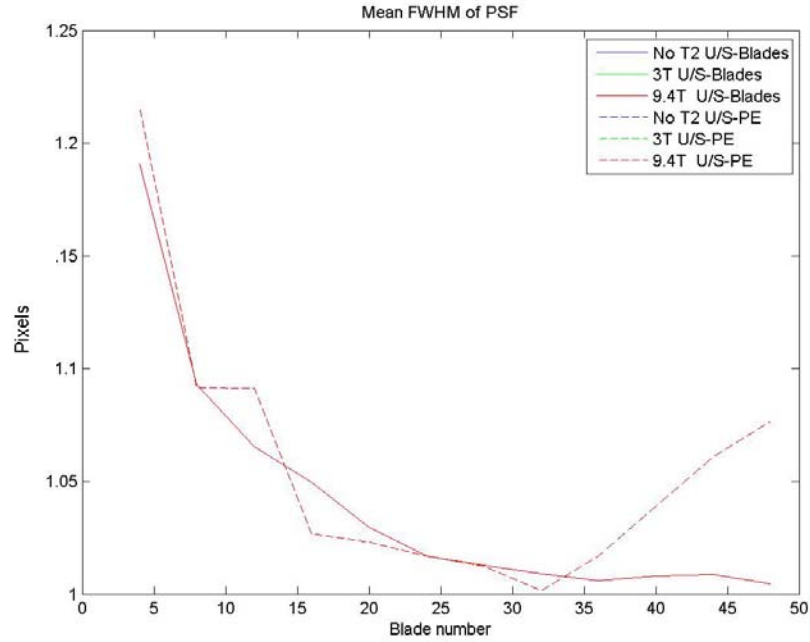


Figure 4-16 PSF FWHM of Shepp-Logan simulation data comparing under/oversampling by blades and spacing between phase encoding steps. Data were reconstructed using different numbers of blades and T_2 . Blade size=256 x 16. Data at different field strengths were collinear.

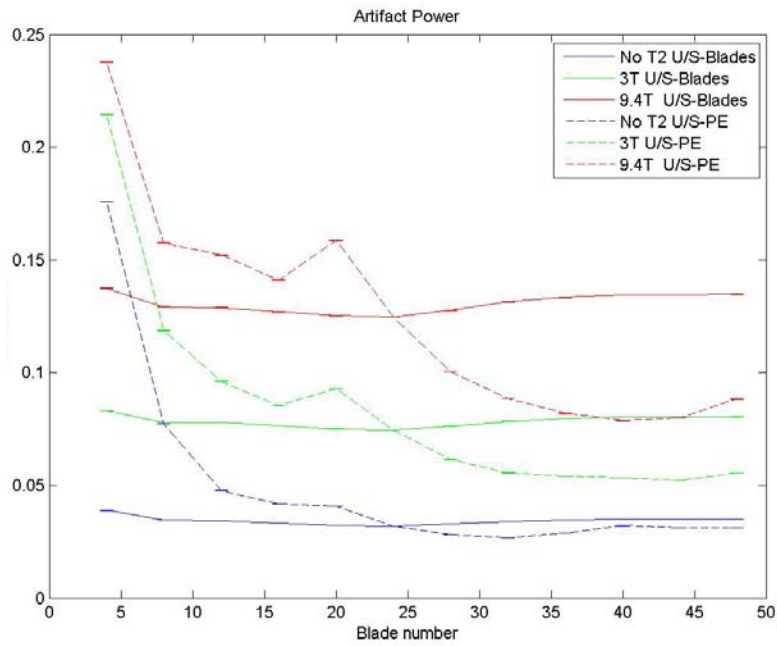


Figure 4-17 AP of Shepp-Logan simulation data comparing under/oversampling by blades and spacing between phase encoding steps. Data were reconstructed using different numbers of blades and T_2 . Blade size=256 x 16.

The USB & USP data at 9.4T and varying degrees of undersampling were examined in terms of percentages of the corresponding values at 95% sampling as done previously, and summarized in Table 4.1. Since USB & USP at 95% sampling were identical, the relative change in parameters between the two methods were directly comparable.

Number of blades, N_b		4	8	12	16	20	24
% K-space sampling		16	32	48	64	80	95
Mean SNR (%)	USB	94.1	87.8	84.0	85.0	92.0	100
	USP	94.4	76.6	75.8	75.3	83.7	100
Mean CNR (%)	USB	99.2	88.5	83.6	84.4	91.6	100
	USP	-13.8	30.7	53.7	91.4	95.8	100
Mean FWHM of PSF (%)	USB	117.1	107.5	104.8	103.2	101.2	100
	USP	119.6	107.4	107.3	101.0	100.6	100
Mean AP (%)	USB	110.2	103.6	103.3	101.9	100.4	100
	USP	190.6	126.3	122.1	113.2	127.2	100

Table 4.1 Summary of mean values of SNR, CNR, FWHM of the PSF and AP as percentage values of 95% k-space sampling, for USB and USP methods. Data presented are at 9.4T, and all differences between USB and corresponding USP values were significant. Of interest were the feasible range of undersampling values between 48% and <95%. Other values were greyed out. Parameters where USB performed better than USP were highlighted in blue, while those instances where USP outperformed USB were highlighted in red.

Based on my findings that undersampling by greater than 2x leads to visually significant image artifacts and artificially raised SNR and CNR, this was identified as the maximum undersampling limit that may be tolerated using NUFFT as a reconstruction method. For the range of k-space sampling between 48% and 95%, it was observed that as sampling decreased, SNR and CNR decreased while the FWHM of the PSF and AP increased. At $N_b=16$ & 20, it was found that CNR was higher and line broadening was lower with USP compared to with USB. In all other cases however, USB performed better than USP, with higher SNR and CNR, and lower levels of line broadening and artifacts. Of overriding importance was how AP increased by up to 3.3% in USB for sampling values of 48%. The same acquisition time using USP yielded an increase in AP of 22.1% or 6.7 times that of USB. The difference in levels of artifacts was clearly observed in the images.

The impact of motion on USB and USP methods was investigated and data are presented in Figure 4-18. Although small errors may be detected in the USB data arising from the limited blade width and imperfect motion correction, these were fairly consistent across the range of degrees of undersampling. In contrast, the USP data showed distinct artifacts that increased as the spacing between phase encoding steps departed from $1/FOV$. Aliasing from inadequate FOV were clearly visible in the undersampled zero-filled single blade images in

the rightmost column. The k-space blade illustrated here was the vertical blade, parallel to the long axis of the simulated image. Foldover artifacts were seen in the inadequately sampled left-right direction. Non-undersampled data exhibited increased blurring with reduced k-space coverage and aliasing arising from the sharp discontinuities in the phase encoding direction in k-space.



Figure 4-18 Under/oversampled Shepp-Logan simulations comparing USB and USP methods in the presence of a random $\pm 5^\circ$ rotation and linear phase encoding at 9.4T. Features USB magnitude images (leftmost column), USB difference images (second column), USP magnitude images (third column) and USP difference images (fourth column) over blade numbers = [8, 16, 24, 32 and 48] (from top to bottom row). Images were normalized to noise and difference images were multiplied by a fixed scaling factor. The rightmost column illustrates one blade from the corresponding USP data. The corresponding k-space were zero-filled to 256 x 256.

Examination of corresponding AP values as in Figure 4-19 showed that motion increased the levels of artifact and their variability across all data. AP in USB data remained fairly consistent across all levels of under and oversampling. This was because in all cases,

motion estimation was based on maximizing the correlation of central k-space data of the same dimensions. Reducing blade numbers should not affect the quality of motion correction, but only the ability to exclude blades that have been badly corrupted by motion. Excluding such blades in already undersampled data may lead to insufficient data and excessive blurring in the directions of the missing blades. AP in USP data increased with degree of undersampling. Unlike the case without motion, oversampled USP data did not lead to any reductions in AP with respect to USB data. In USP, blade widths expanded as blade numbers were reduced. The possible improvement in motion estimation from the use of wider blades was overshadowed by the effect of aliasing due to inadequate FOV. When USP data were oversampled, motion estimation was compromised due to the use of narrower blades.

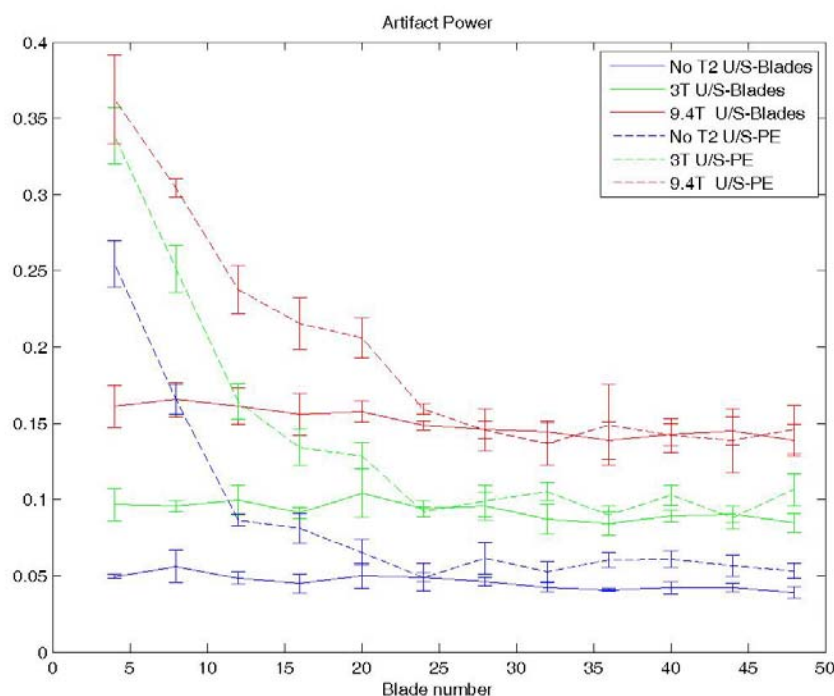


Figure 4-19 AP of Shepp-Logan simulation data comparing USB and USP methods in the presence of motion. Data were reconstructed using different numbers of blades and T_2 . Blade size=256 x 16.

From the simulations, it was found that USB with $nPE=16$ led to better image fidelity than using either USP or $nPE=8$. USP led to aliasing arising from inadequate FOV, and variable sizes in the region of central k-space overlap that had a negative impact on SNR, AP and motion correction when data were undersampled. $nPE=8$ required double the acquisition time of $nPE=16$ for the same degree of k-space sampling. Further, AP was higher even when

data were 95% sampled. For the same acquisition time, $nPE=16$ exhibited lower levels of blurring and artifacts. Due to short T_2 at 9.4T, blade sizes were necessarily limited due to SNR and CNR considerations. Using linear phase encoding, $TE_{eff}=51.0ms$ and $ESP=6.38ms$, the maximum blade width achievable was 16. Hence, USB with $nPE=16$ was identified as the best strategy for undersampling at 9.4T using available sequence parameters.

4.3.2 Animal Studies

In-vivo data in one healthy mouse brain is presented in Figure 4-20. The images depict a series of images with varying degrees of USB under and oversampling for blade sizes=256 x 8, 256 x 12 and 256 x 16. Each horizontal row represents data acquired with the same number of blades. Each blade width required different numbers of blades to fully sample k-space. For the three blade sizes, 95% sampling required $N_b=48$, 32 (not shown) and 24 respectively. Examining these two images revealed edge artifacts that were more prominent in $nPE=8$ than at $nPE=16$. This was consistent with the simulation data. In general, increasing undersampling decreased SNR and increased artifact levels while oversampling increased SNR.

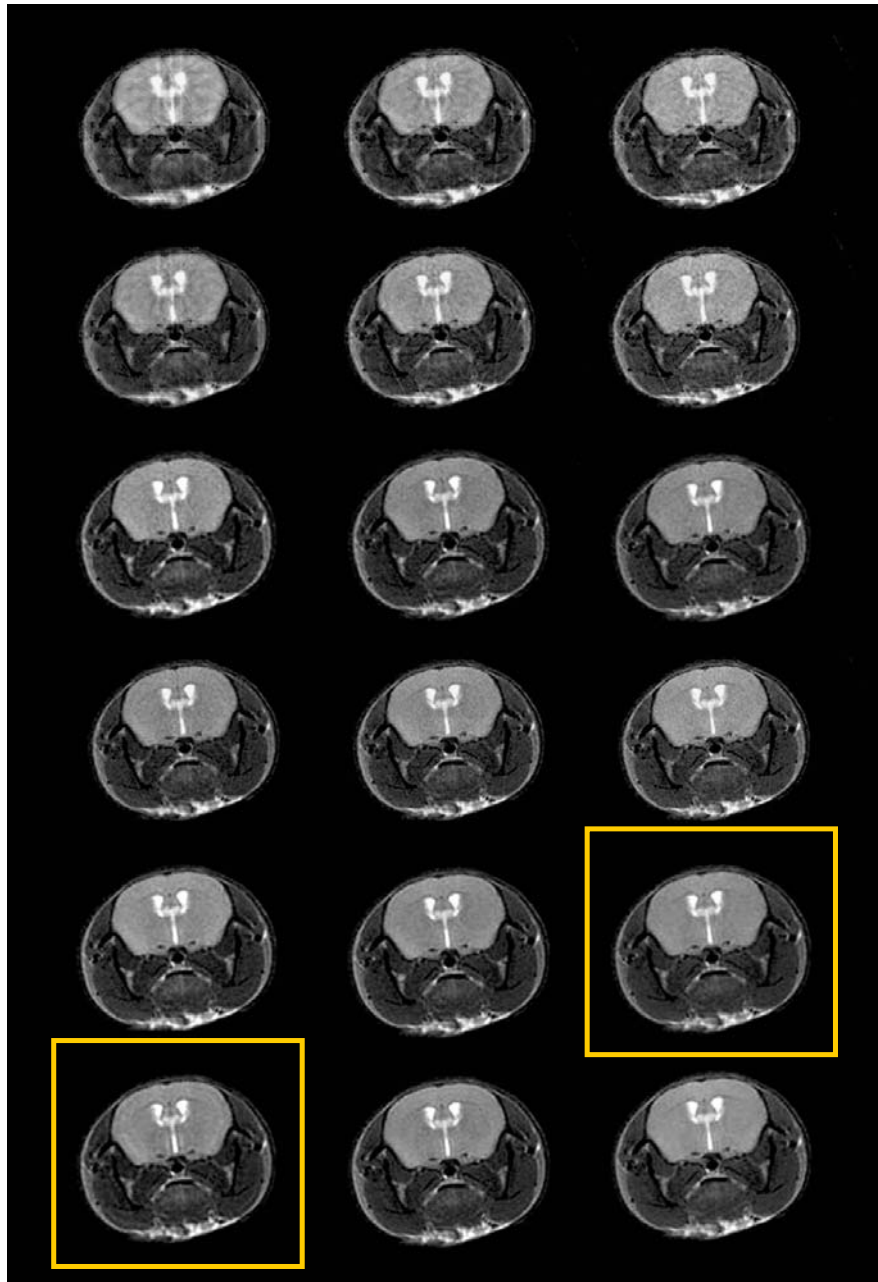


Figure 4-20 Mouse brain images acquired in-vivo at 9.4T using FSE-PROPELLER with varying degrees of under/oversampling by blades. Blade size=256 x 8 (left column), 256 x 12 (middle column) and 256 x 16 (right column) and blade numbers, $N_b = [6, 8, 12, 16, 24, 48]$ (top to bottom). 95% sampled data are highlighted. Oversampled data with $nPE=16$ and $N_b = 48$ were acquired (bottom right). All other images were generated by subsampling this dataset during postprocessing.

SNR as measured in the mouse brains were plotted in Figure 4-21 over a range of blade numbers from 8 to 48. The results demonstrated close agreement with the corresponding simulation data given in Figure 4-5. That is, a general increase in SNR was observed as blade numbers increased and the centre of k-space was sampled increasingly. This increase was higher in nPE=16 than at nPE=8. Similarly, high degrees of undersampling yielded increases in SNR that were due to reconstruction artifacts, in particular, the broadening of the PSF. The local minimum observed was attained at various blade numbers depending on the blade size, and corresponded to about 50% k-space sampling. This suggests a lower limit for undersampling. nPE=12 resulted in data that were intermediate to the other two nPE values.

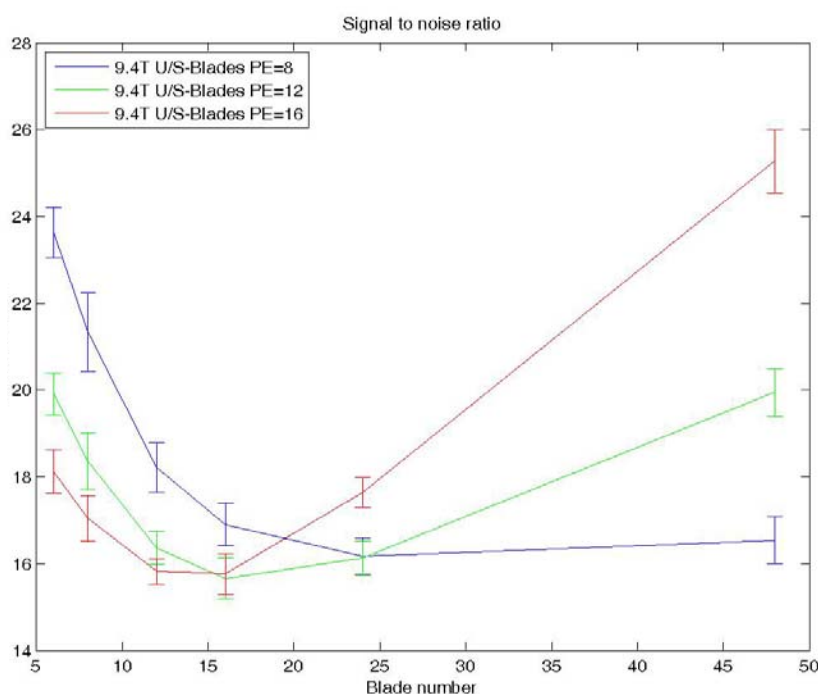


Figure 4-21 SNR measured in the in-vivo mouse brain at 9.4T reconstructed with a range of blade numbers and at blade widths of 8, 12 and 16.

Figure 4-22 showed that differences in GM-WM CNR were much harder to determine. There was a general upward trend in CNR with blade number, although large error prevented any significant finding. There was little difference as well across various blade sizes. The reasons for the large errors were likely due to partial voluming and difficulty in accurate manual selection of a small ROI like the corpus callosum.

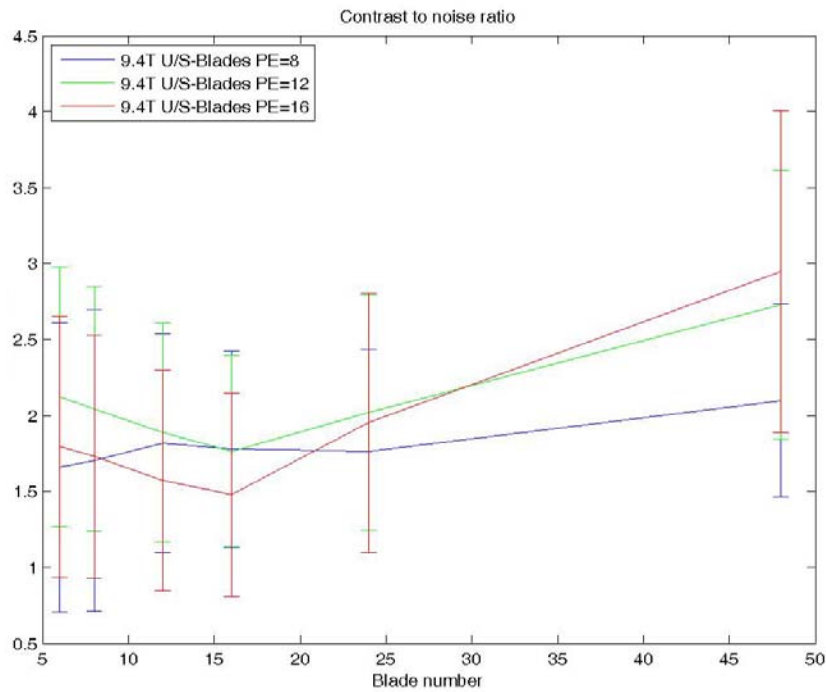


Figure 4-22 CNR measured in the in-vivo mouse brain at 9.4T reconstructed with a range of blade numbers and at blade widths of 8, 12 and 16.

Using data acquired with $nPE=16$ and $N_b=24$ as the reference image, AP was calculated in the mouse brains and given in Figure 4-23. The result was that wider blades consistently exhibited lower AP than narrower blades at all values of N_b . There was also a general decrease in AP with increasing N_b . Interestingly, there was a local maximum at $N_b=16$. This could have been due to the fact that the blades at $N_b=6$ & 12 were differently angulated from blades at $N_b=8$ & 16, as opposed to being subsets of each other like $N_b=8$ was a subset of $N_b=16$, 24 & 48. These differences in blade angulations led to differently oriented blurring and artifacts, and hence could have increased values of AP. The result was also dissimilar to the simulation data as an ideal reference image did not exist. The real image reference chosen had some level of noise and artifacts. In addition, the nature of the subject had more complex structure than the simulation data.

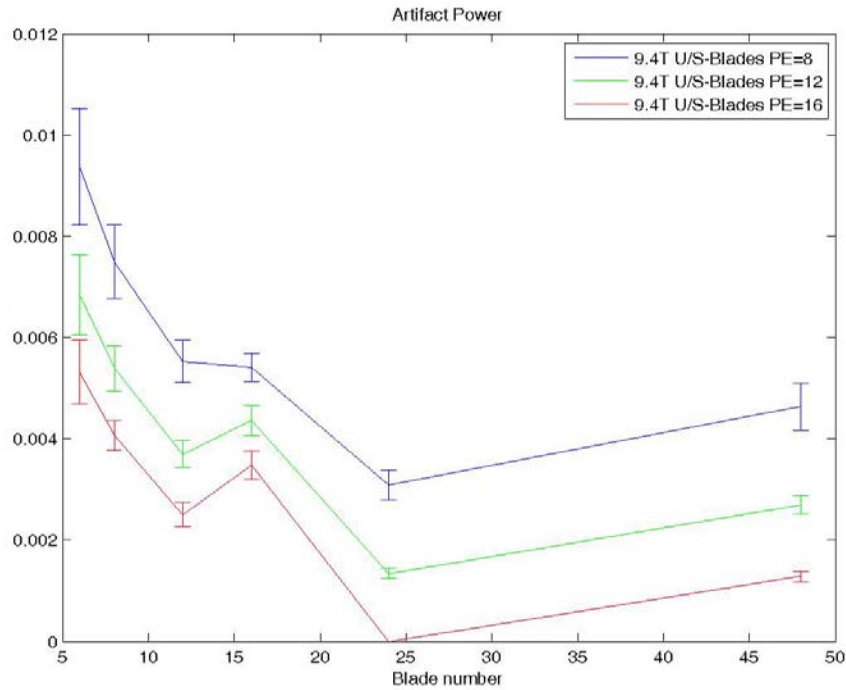


Figure 4-23 AP measured in the in-vivo mouse brain at 9.4T reconstructed with a range of blade numbers and at blade widths of 8, 12 and 16. Data with nPE=16 and $N_b=24$ (ie. 95% sampled) were used as a reference image.

Table 4.2 summarizes the mean and standard deviations of the SNR, CNR and AP in the in-vivo mouse brain data at varying degrees of undersampling. P-values were determined by comparing nPE=8 and nPE=12 data against nPE=16 data at a given blade number. This indicated if a significant difference was observed using the three blade widths for a given acquisition time. It was found that nPE=8 and nPE=12 result in significantly higher SNR than nPE=16 for $N_b \leq 12$. However, these were likely due to artificial broadening of the PSF and lower effective resolution (See Figure 4-7). At $N_b=16$, nPE=16 had significantly higher SNR than nPE=8 but not nPE=12. Higher N_b led to uniformly higher SNR in nPE=16 compared to nPE=8 and nPE=12. This was caused by increased errors in the MTF and PSF when k-space were highly oversampled.

It was found that in all cases, CNR did not exhibit any significant difference across blade widths. However, a significant improvement in AP was observed in nPE=16 over both nPE=8 and nPE=12, over the range of $N_b=8$ to 24.

		nPE=8				nPE=12				nPE=16			
No. of blades		8	12	16	24	8	12	16	24	8	12	16	24
SNR	Mean	21.3	18.2	16.9	16.2	18.4	16.4	15.7	16.1	17.0	15.8	15.8	17.6
	SD	0.905	0.572	0.486	0.419	0.661	0.381	0.473	0.388	0.520	0.297	0.472	0.343
	p	1.4e-7	4.1e-7	8.0e-4	1.1e-5	1.4e-3	0.012	.70	5.1e-6	1	1	1	1
CNR	Mean	1.70	1.82	1.78	1.77	2.04	1.89	1.76	2.02	1.73	1.57	1.48	1.95
	SD	0.995	0.720	0.644	0.669	0.804	0.721	0.634	0.774	0.798	0.726	0.667	0.853
	p	0.96	0.54	0.41	0.66	0.48	0.43	0.43	0.88	1	1	1	1
AP	Mean (x10 ⁻³)	7.49	5.53	5.41	3.08	5.39	3.70	4.36	1.34	4.06	2.50	3.48	0
	SD (x10 ⁻³)	0.729	0.412	0.282	0.291	0.446	0.264	0.294	0.103	0.294	0.233	0.273	0
	p	7.4e-8	9.7e-10	1.9e-8	2.6e-12	2.7e-5	1.2e-6	8.0e-5	2.2e-13	1	1	1	1

Table 4.2 Summary of in-vivo mouse brain data with various degrees of under/oversampling using various blade configurations. Significant improvements in nPE=8 & nPE=12 parameters over corresponding nPE=16 are highlighted in blue. Significantly poorer results are highlighted in red.

4.3.3 Human Studies

Preliminary studies in human volunteers using undersampling by blades showed that k-space undersampling by up to a factor of 2 led to minimal artifacts when volunteers kept still (See Figure 4-24). The loss of resolution in specific directions was of sufficiently high angular frequency that artifacts were incoherent and appeared as noise. When volunteers were asked to rotate their heads, Cartesian sampling led to coherent phase errors and significant ghosting artifacts. FSE-PROPELLER images were much more robust to motion. FSE-PROPELLER with USB data was likewise more robust to motion, but streaking artifacts were observed at regions of high edge contrast.

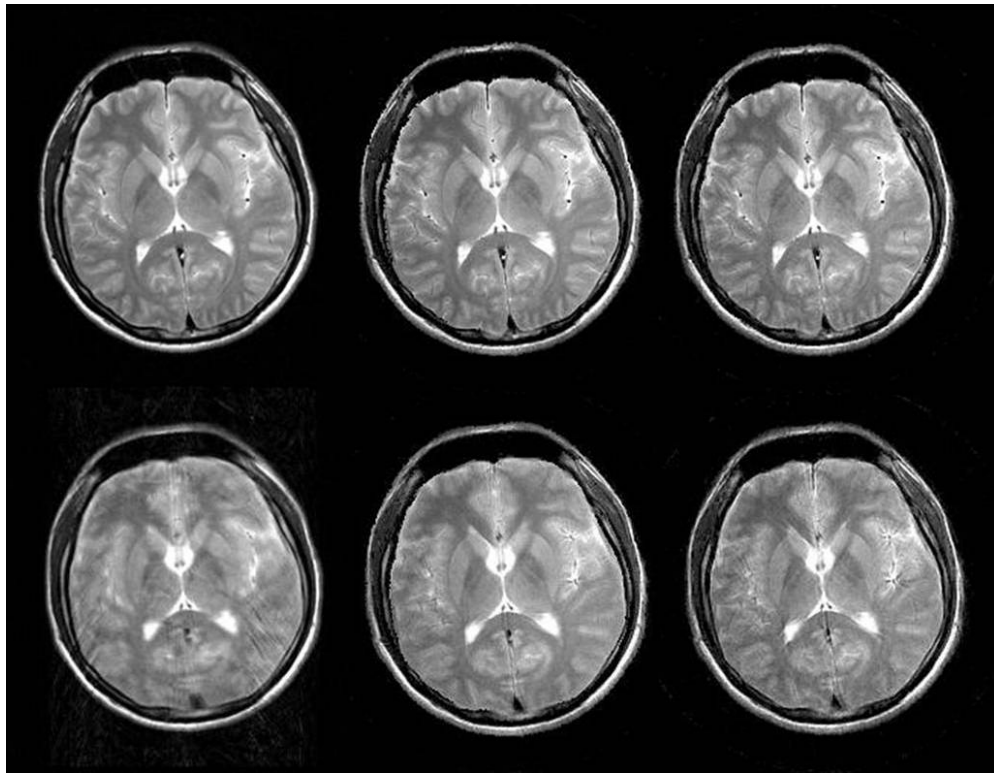


Figure 4-24 Human volunteer in-vivo brain data at 3T without motion (top row) and with motion (bottom row). Sequences used were msFSE (left column), FSE-PROPELLER (middle column) and FSE-PROPELLER with 2x undersampling by blades (right column).

4.4 Conclusion

Undersampling of PROPELLER k-space trades image fidelity for reduced acquisition time. Finding a suitable combination of blade configuration, and degree and method of undersampling given physiological and scanner restrictions posed a practical challenge that had not previously been explored at high field strength.

The simulation data showed that using USB and for a given acquisition time, SNR and CNR increased while PSF line broadening decreased with blade number, as a result of multiple sampling of the centre of k-space. AP decreased as data approached full sampling, but increased with oversampling, suggesting that NUFFT was ill-suited to the reconstruction of oversampled k-space. Instead of acquiring additional blades, a better method of improving SNR would be to combine multiple PROPELLER images with fully sampled k-space.

Predictably, T_2 at 9.4T resulted in a severe compromise in SNR, CNR and AP. This arose from the mixing of different T_2 near the centre of k-space and presents a challenge for

PROPELLER imaging at high field. To mitigate this, ESP should be reduced to the minimum possible. Although reducing the ETL could also reduce the variation in T_2 , this also results in narrower blades which were shown to have detrimental effects on blurring and artifacts. A likely method that has been employed by others at lower fields, would be to use parallel imaging to reduce the ETL without compromising blade width (112). This would potentially allow blade widths of wider than 16 phase encodes and improve robustness to motion.

Having identified $nPE=16$ as less blurring and error prone than $nPE=8$, data quality using USB was measured against USP. It was found that over a practical range of undersampling from 48% to <95% sampling, USB consistently yielded higher SNR, lower AP and better motion correction. Images with more severe undersampling suffered from high levels of artifacts due to errors in reconstruction.

SNR data in the in-vivo mouse brain agreed closely with the simulation results. However there were no clear differences in the CNR. Acquiring higher resolution data and improving ROI selection may reduce the error in the CNR measurements. As with the simulations, AP was consistently lower using wider blades. At low levels of undersampling, artifacts could not be discerned from noise. At higher levels, they tended to manifest as streaking artifacts near edges and regions of sudden changes in contrast. This resulted from interpolation errors particularly at the edges of k-space.

Human data with motion showed that USB introduced a degree of streaking artifacts as a result of the missing k-space data. Exclusion of blades reduces the redundancy of blades and the option of removing blades that have been overly corrupted by motion. In-vivo, this increases the risk of either including bad data or excluding too many blades. Care should be exercised in undersampling k-space based on the degree and nature of the expected subject motion. In the case of extreme motion, undersampling may not be advised.

Overall, T_2 decay at 9.4T presents specific challenges to undersampling in PROPELLER. This restricts our choice of parameters based on the desired contrast and tissues of interest. USB with $nPE=16$ was found to be an optimal approach for T_2 -weighted imaging in the brain. This could reduce acquisition times by up to two-fold while minimizing reconstruction errors. In Chapter 5, diffusion-weighted imaging at high field is examined. Simulations demonstrate that undersampling can also reduce acquisition times in DW-PROPELLER imaging, without compromising the accuracy of measured ADC values.

5 Diffusion Weighted Imaging at High Field Strength

5.1 Introduction

Chapter 2 introduced the basic concepts and applications of DWI in animals and humans. From Chapter 3, EPI sequences were seen to suffer from severe geometric distortion due to susceptibility and off-resonance effects. These are exacerbated with high field strength, long echo trains and eddy currents induced by large diffusion gradients. Reducing the echo train length reduces these artifacts, but introduces the problem of motion in between shots. Single-shot EPI and FSE methods were robust to motion but shown to suffer from major distortion and blurring respectively. They were unsuitable for high resolution imaging at high fields without implementing more sophisticated techniques to reduce the echo train length. Multi-shot FSE methods were effective in non-DW imaging, however, the unknown starting phase of the magnetization caused by the DW preparation violates the CPMG condition (See Chapter 1). The resultant echo phases alternate in polarity, resulting in signal dropout and artifacts due to phase cancellation. A number of methods to mitigate the alternating phase include using phase cycling (59), variable crushers (115), separating the odd-even echoes (59), separating the spin echo and stimulated echoes with imbalanced readout gradients (116,117), and acquiring only the MG component of the magnetization (118).

DWI is sensitive to subvoxel microscopic diffusion of water and is correspondingly highly sensitive to bulk motion. While most motion in the animal brain can be minimized by securing the animal, respiratory, cardiac and gastrointestinal motion contaminate the signal in other regions. In human patients, motion may occur in uncooperative subjects. Moreover, immobilization cannot completely remove effects from pulsatile brain motion and respiratory motion (119). To correct for this, others have used 2D navigator schemes (120,121), radial sampling methods (58,122,123) and PROPELLER at 1.5 and 3T (59,104,116,124-127).

The standard PGSE DW method potentially gives rise to artifacts from diffusion gradient-induced eddy currents, error in b-value estimation due to imaging gradients and cross-terms, a variation of effective b-value at each echo, motion-induced phase errors, signal dropout and phase oscillations due to unknown phase of the magnetization at the end of the diffusion preparation and imperfect refocusing pulses.

Several methods exist to improve the consistency of DW-FSE data. Schick developed the split acquisition of fast spin echo signals for diffusion imaging (SPLICE) (117). The sequence used a unipolar DW stimulated echo preparation to generate echo trains comprising spin

echoes (E1) and stimulated echoes (E2). These were acquired with an extended readout gradient window and magnitude images that were formed separately from E1 and E2 were combined in image space. Like other stimulated echo sequences (128-130), SPLICE was less sensitive to T_2 which would be advantageous at high field strengths. To minimize motion, a single-shot approach was used. This was subsequently combined with PROPELLER to take advantage of its robustness to motion (116). However, SPLICE suffered an increase in interecho spacing of 15-30% and the SNR was $\sqrt{2}$ lower than the equivalent DW-FSE acquisition. This was due to the $\sqrt{2}$ increase in noise as the same available signal was acquired in two separate windows and the data subsequently combined.

A phase insensitive approach for single-shot DW-FSE was implemented by Alsop (118). The method was based on the observation that the magnetizations of the MG and non-MG components were determined by their phase at $TE/2$ before the first refocusing pulse. By applying a 90° pulse with the same phase as the refocusing pulses at this time, the non-MG component can be rotated into the longitudinal axis and effectively removed. The drawbacks of this method are the lengthening of TE due to insertion of the 90° pulse and a loss of half the available SNR from the removed component.

The displaced ultrafast low angle rapid acquisition and relaxation enhancement (U-FLARE) method suggested by Norris, et al. acquired only even echoes by adding an additional gradient immediately prior to the readout gradient (131). This also extended the ESP and reduced SNR by half.

In order to improve multi-shot DW-FSE acquisitions and obtain better resolution, Mori and van Zijl proposed a method that monitored intra- and inter-echo phase errors using twin navigators in each echo train (120). By acquiring a non-phase encoded odd and even echo, the phase of both spin echo and stimulated echo pathways can be determined and corrected for, resolving for both motion and non-CPMG effects. This was applicable to SPLICE and methods that crushed the non-MG components, and suffered SNR losses accordingly. In addition, echo trains are lengthened due to the acquisition of two navigators.

The consistent theme about the methods proposed above are that they were implemented at lower field strengths ($<7T$) with the exception of the twin navigator echo method that was implemented only in ex-vivo subjects. The other consistent theme was the drop in SNR by $\sqrt{2}$ or half, and the extension of the echo train using longer readout windows, additional RF

pulses or navigator echoes. While these were tolerable at lower fields, strong T_2 and small voxel sizes (i.e. low SNR) in mouse imaging conspire against these methods at high fields.

A summary of papers of DWI in rodents performed at high field strengths ($\geq 7T$) is presented in Table 5.1. It shows that applications were mainly limited to brain and spine, where T_2 was less severe and motion, at least in the brain, could be well restrained. In fact, there have been very few DW-FSE studies involving live rodents at high field. One example was the use of DW-FSE with PGSE DW preparation and multiple averaging in in-vivo mouse embryo imaging in-utero (132). Despite issues with motion, DW-PGSE and msDW-EPI methods remain popular, with navigators included in some cases to correct for motion. ssDW-EPI was applied in two studies but only for low resolution 64×32 data (133,134). DWI with stimulated echo acquisition mode (STEAM) has also been used to reduce the sensitivity to T_2 . Ex-vivo methods, for example those using the twin navigator method, were in general not comparable due to the lack of motion and acquisition times extending to hours.

		Field Strength				Subject					Pulse Sequence			
		7T	9.4T	11.7T	14.1T	In-vivo	Ex-vivo	Rat	Mouse	ROI	DW-PGSE	DW-EPI	DW-STEAM	DW-FSE
Bockhorst, et al. (135)	2008	✓				✓		✓		Brain		✓ ^a		
Chahboune, et al. (136)	2007		✓			✓			✓	Brain	✓			
Boretius, et al. (130)	2007	✓				✓			✓	Brain			✓	
Larvaron, et al. (137)	2006		✓			✓			✓	Brain	✓			
Deo, et al. (138)	2006	✓				✓		✓		Spine		✓ ^a		
Nair, et al. (129)	2005		✓			✓			✓	Brain			✓	
Bilgen, et al. (139)	2005		✓			✓			✓	Spine	✓			
Madi, et al. (140)	2005	✓				✓	✓	✓		Spine		✓ ^a		
Barber, et al. (141)	2005		✓			✓			✓	Brain	✓			
Vonarbourg, et al. (128)	2004	✓				✓		✓		Brain			✓	
Moffat, et al. (142)	2004	✓				✓		✓		Brain	✓			
Guilfoyle, et al. (143)	2003	✓				✓	✓		✓	Brain	✓			
Lee, et al. (134)	2002		✓			✓		✓		Brain		✓ ^b		
Hogers, et al. (132)	2000	✓				✓			✓	Embryo	✓			✓
Lee, et al. (133)	1999		✓			✓		✓		Brain		✓ ^{a,b}		
Wang, et al. (144)	2006			✓			✓		✓	Brain				✓ ^c
Shepherd, et al. (145)	2006				✓		✓	✓		Brain	✓			
Zhang, et al. (146)	2005		✓				✓		✓	Brain				✓ ^c
Zhang, et al. (147)	2003		✓				✓		✓	Brain				✓ ^c
Zhang, et al. (148)	2002		✓				✓		✓	Brain				✓ ^c
Mori, et al. (56)	2001		✓				✓		✓	Brain	✓			

Table 5.1 Summary of papers of diffusion in rodents at 7T and above. In-vivo results are presented before ex-vivo and sorted by date of publication. ^aMulti-shot DW-EPI, ^bsingle-shot DW-EPI, ^cDW-FSE with twin echo navigators.

Pipe, et al. showed that a phase cycling acquisition scheme that alternated the phase of the refocusing pulses in an x-y-x-y-... fashion could minimize signal loss for up to 16 echoes provided the refocusing flip angles were close to 180° (59). Incorporated into the strategy were the use of PROPELLER for motion and phase correction, and the separation of odd and even echoes by collecting the more stable even echoes towards the centre of each k-space blade. The proposed phase encoding scheme was implemented and tested on the Varian 9.4T scanner but failed to improve contrast and resolution in the images over linear phase encoding. Linear phase encoding was used due to its ubiquitous implementation on MRI scanners.

Other methods to improve the consistency of data collection include methods to reduce the impact of eddy currents due to the DW gradients such as the use of twice refocused spin

echo (51) and shaped DW gradients (115), flow compensation using gradient moment nulling (149), methods to reduce cross-terms with bipolar gradients (150), methods to improve echo train stability like the use of customized, non-uniform RF flip angles (151) and methods to mitigate the non-MG magnetization using variable crusher gradients (115).

Beaulieu, et al. showed that in the absence of imaging gradients, the b-value along an FSE train with PGSE DW preparation is independent of echo number (115). However, in the presence of readout gradients, phase encoding gradients and crushers, the b-value at the nth echo can be expressed as the Eqn 5.1 and varies according to the echo position. In practice, he reported no significant differences in effective b-value for ETLs of up to 16 echoes using a PGSE DW preparation with FSE acquisition.

$$b(nTE) = \gamma^2 \int_0^{nTE} \left[\int_t^{nTE} G(t'') dt'' \right]^2 dt' \quad 5.1$$

Where γ is the gyromagnetic ratio, G is the gradient amplitude and nTE is the echo time at the nth echo.

ADC measurements have been widely used in the clinic as well, as an early biomarker in the onset and progression of stroke (19,30,152). The early diagnosis of which may help identify salvageable regions as specified by the ischemic penumbra (153). The progression of the ADC with stage of the disease has been well characterized (154). The standard imaging protocol used in the clinic to measure the ADC is ssDW-EPI due to its rapid acquisition and robustness to motion. Often it is combined with techniques like partial Fourier and parallel imaging to reduce the echo train and corresponding distortions. However, in regions near the sinuses and the brain stem, susceptibility and signal pileup artifacts remain, degrading the ability to make useful diagnoses in these regions. DW-FSE-PROPELLER trades geometric distortion with increased acquisition time. It has been used successfully in the clinic at 1.5T (125) to improve diagnoses in patients with acute stroke in areas prone to susceptibility, and its potential application at 3T is investigated.

In this chapter, DW-FSE-PROPELLER is presented as an effective method for acquiring in-vivo DW data at 9.4T. The choice of pulse sequence is outlined in the context of various other multi-shot DW-FSE sequences available. To better understand if using PROPELLER has an effect on the measured ADC, simulations were constructed to examine the dependence of the ADC on PROPELLER parameters and tissue properties. In-vivo data

were acquired in healthy mouse brain and liver at 9.4T and it is shown that DW-FSE-PROPELLER produced more consistent data than other sequences based on single-shot, EPI and Cartesian techniques. Pilot data at 3T in human stroke patients demonstrated good contrast and an exclusion of the geometric distortions found using standard single-shot EPI methods. It is hypothesized that data acquired using DW-FSE-PROPELLER will be more resistant to geometric distortion than EPI methods and more robust to motion than other multi-shot methods.

5.2 Materials & Methods

To address the challenges of motion, non-CPMG condition, small voxel size and severe T_2 decay, a strategy was chosen that maximised SNR and minimized TE and the echo train length. PROPELLER was implemented together with the DW-FSE pulse sequence on the 9.4T Varian scanner (Varian Inc, Palo Alto, CA). The DW-FSE sequence used a 90° excitation pulse followed by a PGSE DW preparation (34) comprising a set of two unipolar trapezoidal gradients about the first 180° refocusing pulse, and an FSE acquisition, with nominally 180° refocusing pulses and crushers about the first refocusing pulse (See Figure 5-1). The 180° refocusing pulses, crushers and modest ETL of 8 were used to limit and reduce non-MG coherence pathways. Signal was acquired from the first spin echo and the echo train kept short to maintain good SNR and minimize TE. Built-in generic gradient pre-emphasis reduced eddy current effects by correcting the applied gradient waveforms. Nominal b-values were specified for the diffusion weighting. Finally, PROPELLER allowed for motion and phase correction without lengthening the effective TE or echo train, while potentially improving the SNR through the multiple sampling of the centre of k-space (See Chapter 3).

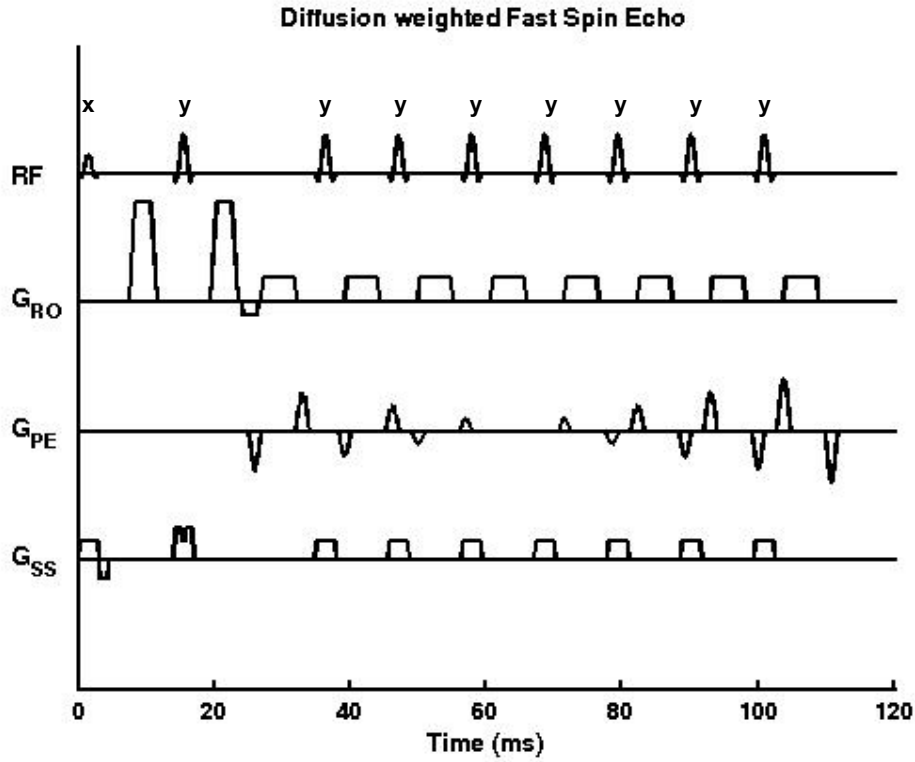


Figure 5-1 Diffusion weighted fast spin echo sequence used on the Varian 9.4T scanner. The sequence features PGSE diffusion preparation, nominal 180° refocusing pulses, ETL=8 and linear phase encoding.

5.2.1 B-value simulations

B-value variation across the echo train was expected to be minimal (115). This was verified by simulating $\mathbf{b}$ at the various echo times for the pulse sequence as described. DW was applied in 3 orthogonal directions and Eqn 5.2 was used to calculate both on-diagonal and off-diagonal b-terms. Since $\mathbf{b}$ was a 3 x 3 symmetric matrix, 6 unique values were used to define $\mathbf{b}$.

$$\text{b-value, } b_{i,j} = \gamma^2 \int_0^{\tau} F_{ij}^2 d\tau = \gamma^2 \int_0^{\tau} \left(\int_0^t G_i(t') dt' \right) \left(\int_0^t G_j(t') dt' \right) d\tau \quad 5.2$$

For diffusion directions i and j , b is the scalar b-value, γ is the gyromagnetic ratio, F is the effective field gradient, $G(t')$ is the gradient strength as a function of time, and τ is the time to the spin echo.

5.2.2 Simulations

Previous work had investigated the effects of parameters like SNR (47), DTI sampling scheme (155), number of b-values measured (156) on the measured mean ADC in Cartesian sampling. Others had explored the effects of blade configuration (100), undersampling (105) and noise (157) on image fidelity in PROPELLER MRI. Here, the effects of blade configuration, tissue geometry, tissue anisotropy, T_2 and FA on the measured ADC in PROPELLER are examined. This would allow for a better assessment of the data from in-vivo imaging and help optimize the choice of PROPELLER parameters in order to obtain the least biased ADC.

Because of the highly anisotropic resolution in a single blade in PROPELLER, it is expected that the direction along which the DW gradients are applied will have a significant impact on the final images. To explore this, a phantom with high levels of anisotropy combined with highly varying spatial frequency content is needed.

A simulation was constructed to assess the effects of blade parameters and tissue FA on the measured ADC. In a manner similar to that found in Section 3.2.2, ellipsoidal ROIs with different geometry and tissue properties were expressed analytically in k-space along a specified PROPELLER sampling trajectory and summed. The result was transformed to image space by FFT. The intention was to focus on the tissue properties and k-space sampling methods, hence motion and noise were neglected. The simulations included PD, T_2 , ADC and FA parameters as measured by generally more accurate spin echo DWI as given in Table 5.2. It should be noted that while spin echo methods could be more accurate, they require ETL times longer to acquire and require excellent motion minimization. This requires a good setup for immobilization, increases the animal preparation time, may place the animal at increased risk of injury or death, and is not applicable in regions outside the brain due to physiologic motion. Tumour T_2 , ADC and FA values were cited from studies that implanted U87 gliomas, 9L gliomas and 9L gliosarcomas respectively in the rodent brain.

Subject	Parameters	WM	GM	Tumour
Rodent	PD	0.617 ⁽⁸³⁾	0.745 ⁽⁸³⁾	0.95 ⁽⁸³⁾
	T ₂ (ms)	35.4 ⁽⁸⁸⁾	40.3 ⁽⁸⁸⁾	62 ⁽⁸⁹⁾
	ADC (x10 ⁻³ mm ² /s)	0.61 ⁽¹³⁷⁾	0.59 ⁽¹³⁷⁾	0.85 ⁽¹²⁸⁾
	FA	0.79 ⁽¹³⁷⁾	0.38 ⁽¹³⁷⁾	0.38 ⁽¹⁵⁸⁾

Table 5.2 Simulated tissue properties in a selection of tissue types. Relaxation and diffusion parameter values cited were from rodent data $\geq 7T$.

Since the cited ADC values for WM and GM were similar, the simulation specified was that of multiple tumours of various sizes and shapes embedded in a region of GM. This would be further relevant in our study of a mouse model of spontaneous melanoma in Chapter 6. The object is illustrated in Figure 5-2. Specific ROIs 1-4 are highlighted and represent four possible tissue geometries in-vivo.

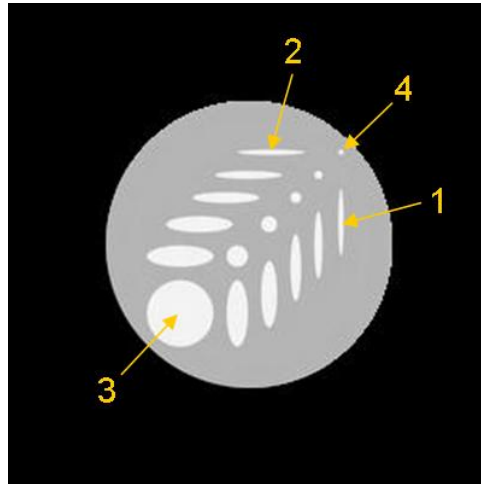


Figure 5-2 Simulated object comprising tumour regions of different shapes and sizes embedded in GM. Regions 1-4 represent the tumour lesions and have identical tissue properties as given in Table 5.2. The direction of principal diffusion in tumours was oriented left-right. The direction of principal diffusion in the surrounding GM was oriented in-out of the page.

All simulations included a b_0 image and 3 images at $b=800\text{s/mm}^2$ with DW in orthogonal directions, ie. readout (RO), phase encoding (PE) and slice select (SS) directions. Mean ADC maps were calculated from these data according to Eqn 2.8. Masks were created based on the four ROIs specified and the peripheral pixels of these masks were eroded to

reduce high frequency artifacts arising from finite k-space sampling. Mean ADC values in these ROIs using different ranges of acquisition and reconstruction parameters were reported across a range of FA from 0 to 1. Reconstructed matrix size was 256 x 256.

The first simulation looks at the effect of tissue geometry and blade configuration on the measured ADC. ADC values from the four ROIs in images reconstructed with practical PROPELLER sampling configurations of 256 x 8 x 48, 256 x 16 x 24, 256 x 24 x 16 and 256 x 32 x 12 were obtained. Due to the uniform direction and magnitude of the applied diffusion weighting across each k-space blade within each image, and the orthogonal diffusion weighting scheme, geometry effects are expected to be minimal. As T_2 was neglected here, the data between blades should be consistent and minor variations to the measured ADC may come from the point spread function specific to each blade configuration.

This was repeated in the presence of T_2 with effective $TE=28\text{ms}$ and $ESP=5.38\text{ms}$ corresponding to in-vivo experiments at 9.4T, using a centric phase encoding. Also tested was a linear phase encoding scheme with the same ESP, but with TE adjusted to the minimum for that ETL, ie. Effective $TE= 44.1, 65.7, 87.2 \text{ \& } 109\text{ms}$ for $ETL=8, 16, 24 \text{ \& } 32$ respectively. T_2 will result in a rotational modulation of k-space whose frequency and magnitude is determined by the blade width. This will degrade the point spread function and should be more severe at wider blade widths.

Since PROPELLER rotates blades of k-space in-plane, the effects of the direction of tissue anisotropy with respect to the imaging plane, neglecting T_2 , are investigated. Since the diffusion weighting directions are fixed to the object and not the rotating blades, and data are acquired with DW in three orthogonal directions, the ADC is expected to be dependent again on the reconstruction process. This was repeated with the anisotropy of the GM changed to the left-right orientation in order to check if the differences in directions of anisotropy between different tissues affected the measured ADC.

A final set of simulations including T_2 were constructed using a suitable blade configuration and phase encoding as determined by the above simulations. As a follow-up to Chapter 4, undersampled PROPELLER was tested with DWI to examine if undersampling had an effect on the measured ADC. Undersampled DW-PROPELLER data were acquired by reducing the number of blades sampled. The loss in resolution in the directions of the missing blades increases the error in reconstruction and may give rise to wider deviations in ADC with greater degrees of undersampling.

5.2.3 Simulating the Diffusion Tensor

To generate the diffusion-weighted images, the b-value tensor, $\mathbf{b}$ and the diffusion tensor, $\mathbf{D}$ need to be calculated. Assuming cylindrical symmetry as in nerve fibres such as the corpus callosum (159), Hasan and Narayana derived Eqn 5.3 & Eqn 5.4 to solve for principal eigenvalues $\lambda_{\parallel}$ and $\lambda_{\perp}$ (160). Mean ADC and FA was specified, allowing $\mathbf{D}$ to be defined as in Eqn 5.5, which was rotated in 3D so that $\lambda_{\parallel}$ aligned with the principal diffusion direction. Eqn 5.6 lists the rotation matrices. Fixing the DW direction with respect to the object meant rotating the DW with respect to each PROPELLER blade. The in-plane component of the b-value was thus rotated in 2D about the slice select axis as in Eqn 5.7. The resultant signal decay due to diffusion was calculated with Eqn 2.4 neglecting T_1 .

$$\text{Eigenvalue ratio, } x = \frac{\lambda_{\parallel}}{\lambda_{\perp}} = \frac{1 + \sqrt{1 + (2FA^2 - 1)(1 - FA^2)}}{(1 - FA^2)} \quad 5.3$$

Where $\lambda_{\parallel}$ and $\lambda_{\perp}$ are the principal eigenvalues, and FA is the fractional anisotropy.

$$\text{Eigenvalue, } \lambda_{\parallel} = \frac{3xD_{av}}{2 + x} \text{ and eigenvalue, } \lambda_{\perp} = \frac{3D_{av}}{2 + x} \quad 5.4$$

Where D_{av} is the mean ADC and x is the eigenvalue ratio.

$$\text{Diffusion tensor, } \mathbf{D} = \mathbf{R}' \times \begin{bmatrix} \lambda_{\parallel} & 0 & 0 \\ 0 & \lambda_{\perp} & 0 \\ 0 & 0 & \lambda_{\perp} \end{bmatrix} \times \mathbf{R} \quad 5.5$$

Where $\lambda_{\parallel}$ and $\lambda_{\perp}$ are the principal eigenvalues and $\mathbf{R}$ is the appropriate 3D rotation matrix given in Eqn 5.6.

$$\mathbf{R}_x = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos \theta & -\sin \theta \\ 0 & \sin \theta & \cos \theta \end{bmatrix}, \mathbf{R}_y = \begin{bmatrix} \cos \theta & 0 & \sin \theta \\ 0 & 1 & 0 \\ -\sin \theta & 0 & \cos \theta \end{bmatrix}, \mathbf{R}_z = \begin{bmatrix} \cos \theta & -\sin \theta & 0 \\ \sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad 5.6$$

Where $\mathbf{R}_x$, $\mathbf{R}_y$ and $\mathbf{R}_z$ are rotation matrices about the x, y and z axes and θ is the angle of rotation. In these simulations, tissue anisotropy was orthogonal and hence $\theta = \pi/2$ rad.

$$\mathbf{b} = \mathbf{R}_z' \times \begin{bmatrix} b_{ro} & 0 & 0 \\ 0 & b_{pe} & 0 \\ 0 & 0 & b_{ss} \end{bmatrix} \times \mathbf{R}_z \quad 5.7$$

Where b_{ro} , b_{pe} and b_{ss} are specified b-values in the respective directions. Blades are always rotated about the slice select axis.

5.2.4 Animal Studies

PROPELLER sampling was combined with the DW-FSE sequence and implemented on the 9.4T MRI scanner (Varian, Palo Alto, CA) with the gradient coil and RF coil setup as described in Chapter 3. 8 healthy wildtype C57/Bl6 mouse datasets were acquired in-vivo, in accordance to local IACUC guidelines. Experiments were performed at the Lab of Molecular Imaging, Singapore Bioimaging Consortium, Singapore. Due to the high sensitivity of DWI to motion, brain data were acquired with animals secured with a nosecone and bitebar. The animals were also imaged in the liver with DWI. They were secured with tape, however significant respiratory motion remained. Anaesthesia was induced with 3.5% isoflurane and maintained at 1-1.5% isoflurane in a 55%:45% mixture of $N_2:O_2$. Respiration was monitored using an air pillow transducer and controlled between 60-80 breaths/min. Animals were free breathing. Body temperature was measured using a rectal probe and maintained at 36.5°C by circulating warm air.

In the brain, each animal was scanned using the following sequences: ssDW-EPI, msDW-EPI, DW-EPI-PROPELLER, ssDW-FSE, msDW-FSE and DW-FSE-PROPELLER. All sequences used TR=4000ms, TE=44ms, FOV=25.6 x 25.6mm, reconstructed matrix=128 x 128, thickness=1mm, gap=0.5mm, slices=5, slice order=interleaved, orientation=axial, DW directions=3, $b=800s/mm^2$. Note that readout bandwidths were 208kHz and 156kHz for FSE and EPI acquisitions respectively, and this would enhance the relative SNR of the EPI data at the expense of added chemical shift.

Acquisition times for multi-shot sequences were largely equalized to facilitate comparison, while single-shot sequences were much more rapid. One reference scan for each average was collected for phase correction in EPI acquisitions. In single-shot EPI, partial Fourier and zero-filling was used to maintain a reasonable TE. Acquisition times were calculated according to Eqn 5.8, neglecting dummy scans, and scan parameters are given in Table 5.3.

$$\text{Acquisition Time, AT} = \text{TR} * \text{Shots} * [\text{Ref} + \text{Ave} * (\text{N}(\text{b}_0) + \text{N}(\text{b}_{800}))] \quad 5.8$$

Where TR=4s, Shots is the number of shots or blades required, Ref is the number of reference scans, Ave is the number of averages, and N(b₀) and N(b₈₀₀) is the number of images acquired at b=0 s/mm² and b=800 s/mm² respectively.

	ETL	Shots	Ref	Ave	N(b ₀)	N(b ₈₀₀)	Scan time
ssDW-EPI	24	1	1	1	1	3	20s
msDW-EPI	16	8	3	3	1	3	8m
DW-EPI-PROPELLER	8	26	1	1	1	3	8m 40s
ssDW-FSE	128	1	0	2	1	3	32s
msDW-FSE	8	16	0	2	1	3	8m 32s
DW-FSE-PROPELLER	8	32	0	1	1	3	8m 32s

Table 5.3 Scan parameters for in-vivo mouse brain imaging at 9.4T. Multi-shot sequences were selected so that scan times were similar, while single-shot sequences were significantly faster.

Due to severe distortion using EPI acquisition methods, as seen earlier (Figure 3-11), DW-EPI data were excluded in liver scans. The other sequences were repeated in the liver with an additional msDW-FSE scan with respiratory triggering. This was to compare the effectiveness of triggering vs PROPELLER in reducing motion artifacts. All sequences used TR=4000ms, TE=28ms, FOV=25.6 x 25.6mm, reconstructed matrix=96 x 96, thickness=1mm, gap=0.5mm, slices=5, slice order=interleaved, orientation=axial, DW directions=3, b=800s/mm². Readout bandwidths were 208kHz and 156kHz for FSE and EPI acquisitions respectively. Multi-shot scans were time-normalised as well and other parameters are given in Table 5.4. A 90° spectrally selective fat saturation pulse was applied in the preparation phase to minimize off-resonance effects due to fat.

	ETL	Shots	Ref	Ave	N(b ₀)	N(b ₈₀₀)	Scan time
ssDW-FSE	96	1	0	4	1	3	1m 4s
msDW-FSE	8	12	0	4	1	3	12m 48s
msDW-FSE	8	48	0	1	1	3	12m 48s ⁺⁺
DW-FSE-PROPELLER	8	1	0	4	1	3	12m 48s

Table 5.4 Scan parameters for in-vivo mouse liver imaging at 9.4T. Multi-shot sequences were selected so that scan times were similar, while the single-shot sequence was significantly faster. ⁺⁺Triggering led to variable extensions of the nominal scan time.

From these experiments, the mean ADC was measured in ROIs in WM, GM, liver and muscle. ROIs were manually drawn for each subject, in a manner described in Section 3.2.3.

All experiments were repeated to obtain SNR and AP of the ADC measurements to quantify the consistency of such data. SNR and AP were calculated according to Eqn 3.3 & Eqn 3.5 respectively. P-values were cited using one way ANOVA and $p < 0.05$ was used to determine if a result was significant.

5.2.5 Human Studies

Pilot human data were acquired in a cooperative 81 year old, male patient exhibiting acute stroke. Clinical symptoms were drowsiness and a slowness in answering questions. This work was carried out on a 3T Achieva scanner (Philips, Best, Netherlands) using a whole body transmit coil and an 8-Ch birdcage receive coil. Studies were conducted at the National Neuroscience Institute, Singapore, in accordance to the sequence development protocol under local IRB guidelines.

The patient was scanned using a standard single-shot DW-EPI sequence and a DW-FSE-PROPELLER sequence. As DWI was not normally available in combination with MultiVane, this was enabled manually by pulse programming. Due to timing restrictions in the code, RF refocusing pulses used were Gaussian instead of longer pulses with better slice profiles. Figure 5-3 illustrates the pulse sequence used (118). The pulse sequence comprised a 90° slice selective excitation, followed by a PGSE DW preparation scheme about the first 180° refocusing pulse, a 90° pulse to separate MG and non-MG components of the magnetization and an FSE readout with decreasing flip angles to reduce SAR.

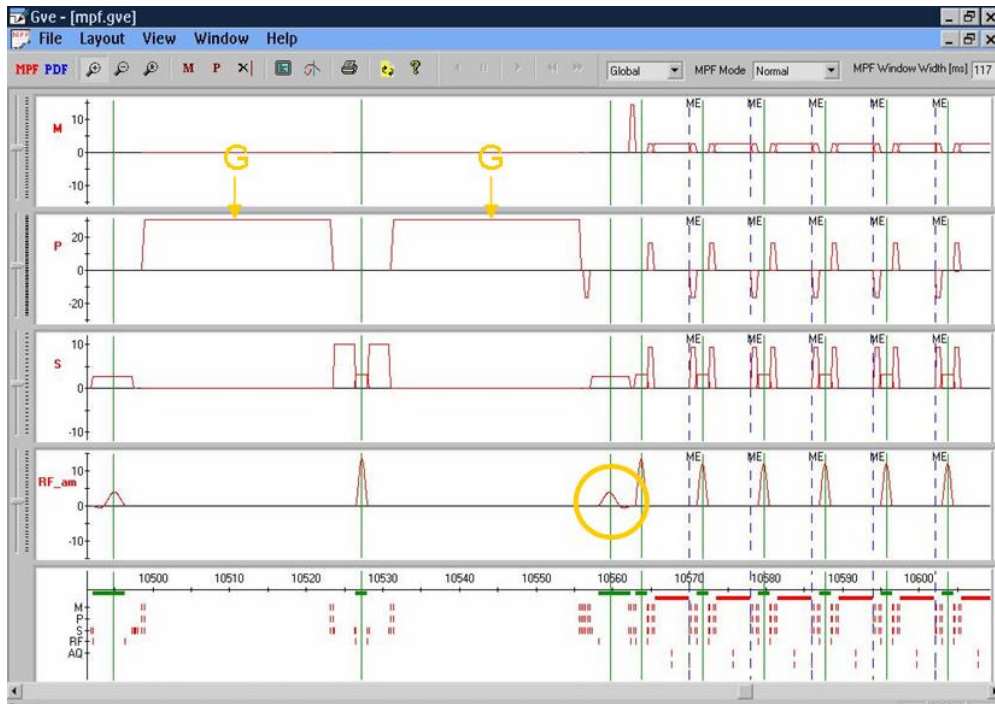


Figure 5-3 Diffusion weighted pulse sequence on the Philips 3T scanner. Key features are added to a conventional FSE sequence, including large diffusion gradients, G and a 90° RF pulse that separates MG & non-MG components of the magnetization.

Experimental parameters were TR=4000ms, FOV=240 x 240mm, Matrix=128 x 24 x 8, DW directions=3, $b=1000\text{s/mm}^2$, thickness=4mm, gap=1mm, slice=transverse, number of slices=17, $AT_{ssEPI} = 25\text{s}$, $AT_{PROPELLER} = 4\text{m } 32\text{s}$. SENSE factor=2 was used in the EPI acquisition.

5.3 Results & Discussion

5.3.1 B-value simulations

Table 5.5 shows the contribution of the imaging gradients to the effective b-value due to additional dephasing effects. DW was applied in orthogonal directions and b-values calculated at respective echo times. They increased the actual on-diagonal b-values at the first echo by up to 3% of the nominal b-values. Off-diagonal terms at the first echo similarly increased by up to 1.4% of the nominal b-values. These small but measurable effects may be taken into consideration to improve the accuracy of ADC and anisotropy estimations.

As anticipated, while imaging gradients progressively added to the b-values, their variation down the echo train was minimal. A maximum of a 1% increase in on-diagonal b-values

along the echo train was observed with DW along the readout direction. As a result, the b-values used in calculating diffusion data ignored echo train dependent effects and were based on the nominal b-value at the first echo. Where these have been ignored here, contributions to b-value due to off-resonance, motion, eddy currents and imperfect gradient linearity in-vivo may cause significant perturbations in the b-values that are much harder to account for.

	DW along readout direction								DW along phase encoding direction								DW along slice select direction							
Echo	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
b _{xx}	824	825	826	828	829	830	831	833	1	2	4	5	7	8	9	11	1	2	4	5	7	8	9	11
b _{yy}	1	1	1	1	1	1	1	1	824	824	824	824	824	824	824	824	1	1	1	1	1	1	1	1
b _{zz}	2	2	2	3	3	3	3	3	2	2	2	3	3	3	3	3	820	821	820	821	821	822	822	822
b _{xy}	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	1	1	1	1	1	1	1	1
b _{xz}	9	9	10	10	10	10	11	11	1	2	2	2	2	3	3	3	11	11	12	12	12	12	13	13
b _{yz}	1	1	1	1	1	1	1	1	9	9	9	9	9	9	9	9	11	11	11	11	11	11	11	11

Table 5.5 Simulated b-values across echoes 1-8 for orthogonal DW directions. B-values were rounded to the nearest integer and presented in units of (s/mm²).

5.3.2 Simulations

A sample set of DW data is shown in Figure 5-4 including the b₀ image, 3 images with diffusion weighting in orthogonal directions and the mean ADC map. The images illustrate the signal drop experienced when diffusion is applied along the principal diffusion direction. For example, the principal diffusion direction in the simulated tumours was oriented left-right. In the third image from left, this corresponded with the diffusion weighting that was in the phase encoding direction, resulting in a marked drop in lesion signal. The loss of signal in GM was greatest in the rightmost image, where the applied DW was aligned to the GM anisotropy which was in-out of the page. Other variations in intensity, such as the slight hyperintensity in GM in the third image compared to the second image from left are indicative of minor variations (<2%) in DW signal due to the PROPELLER reconstruction, magnified in display due to the lack of noise. Of key interest however, were the mean ADC measurements as depicted in Figure 5-5.

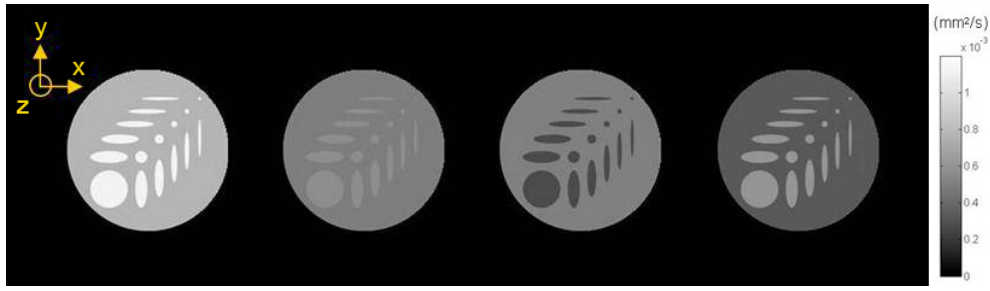


Figure 5-4 DW-PROPELLER simulated data of tumour lesions embedded in GM (Refer to Section 5.2.2). Matrix=256 x 16 x 24. The images given from left to right are: b_0 , $b=800\text{s/mm}^2$ (y), $b=800\text{s/mm}^2$ (x) and $b=800\text{s/mm}^2$ (z). Units are absolute signal intensities.

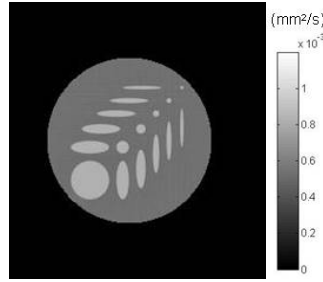


Figure 5-5 Corresponding mean ADC image reconstructed from DW images in Figure 5-4.

Figure 5-6 plots the relationship between mean ADC, blade width and FA in the absence of motion, noise and T_2 . With the exception of ROI 4 at $n\text{PE}=8$, it was observed that the measured ADC was largely independent of blade configuration. ROI 4 was a particularly small circular ROI with nominal diameter of 0.4mm, and this may have been affected by the damaged PSF at $\text{ETL}=8$ as pointed out in Figure 3-17. The ADC was however dependent on the geometry of the tumour regions (Refer to Figure 5-2 for ROI definitions). There was a general overestimation of the ADC as measured that decreased with tumour size and increased with FA. This is reflected in the images in Figure 5-7. Due to the slight blurring inherent to PROPELLER as discussed in Chapter 3, smaller lesions were more susceptible to greater changes in signal intensity hence the geometry dependence. Small errors occur during the interpolation and reconstruction process depending on the data. The signal differences in the lesions between images with DW applied in different directions increased as anisotropy increased. This lent to increasing differences in errors in reconstruction that led to an enhanced deviation in the measured ADC.

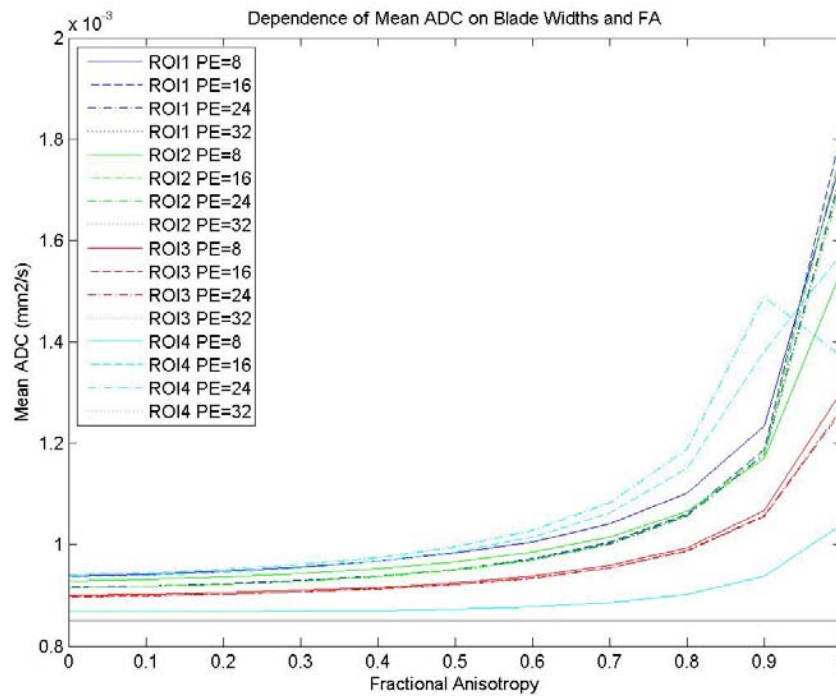


Figure 5-6 Dependence of Mean ADC on PROPELLER blade width and tissue FA. Matrix sizes were 256 x 8 x 48, 256 x 16 x 24, 256 x 24 x 16 and 256 x 32 x 12. T_2 was neglected.

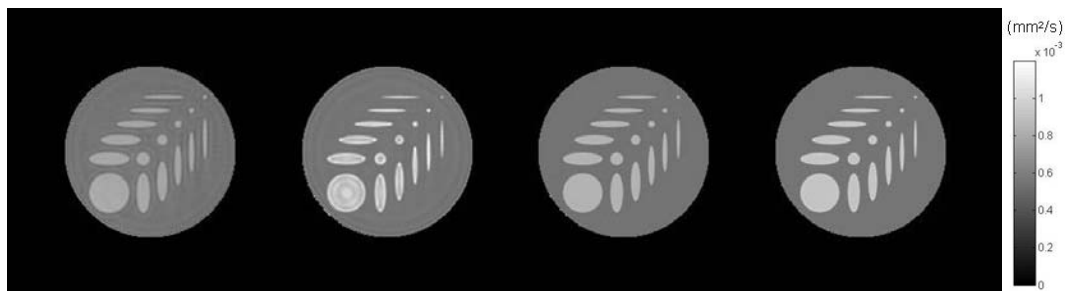


Figure 5-7 Mean ADC maps of simulations without T_2 . From left to right: (i) Matrix=256 x 8 x 48, FA=0, (ii) Matrix=256 x 8 x 48, FA=0.8, (iii) Matrix=256 x 32 x 12, FA=0 and (iv) Matrix=256 x 32 x 12, FA=0.8.

In the presence of T_2 and centric phase encoding, the trend of increasing ADC with FA was reversed in all cases with blade width ≥ 16 (See Figure 5-8). For clarity, only ROIs 1 & 2 were plotted. This was due to the broadening of the point spread function and mixed T_2 contrast where blades overlapped. This depended on blade width. As FA increased, the mixed contrast resulted in an artificially raised signal in lesions in DW images. This affected regions with low intensity due to the DW relatively more so than others with less DW signal

loss. This reduced the measured ADC as a function of FA. This can be seen in Figure 5-9. At ETL=8 however, TE modulation across the blade was not as significant, and resulted in a reduction in ADC that partially compensated for the raised ADC seen in Figure 5-6. As before, smaller lesions were more greatly affected by reconstruction errors, blurring and mixed contrast, and tend to deviate more greatly from the nominal ADC.

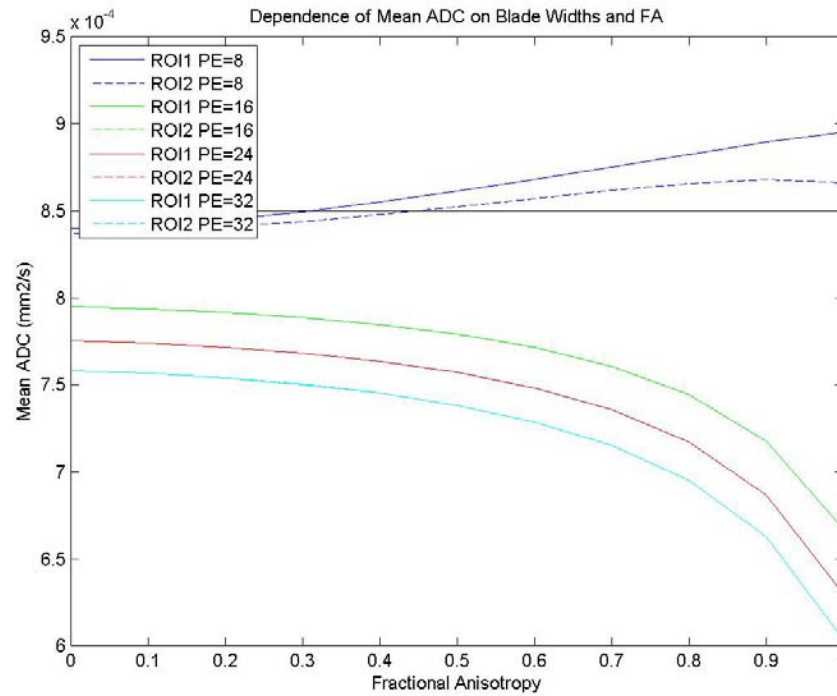


Figure 5-8 Dependence of Mean ADC on PROPELLER blade width and tissue FA, with T_2 at 9.4T and centric phase encoding. Matrix sizes were 256 x 8 x 48, 256 x 16 x 24, 256 x 24 x 16 and 256 x 32 x 12 and TE=28ms.

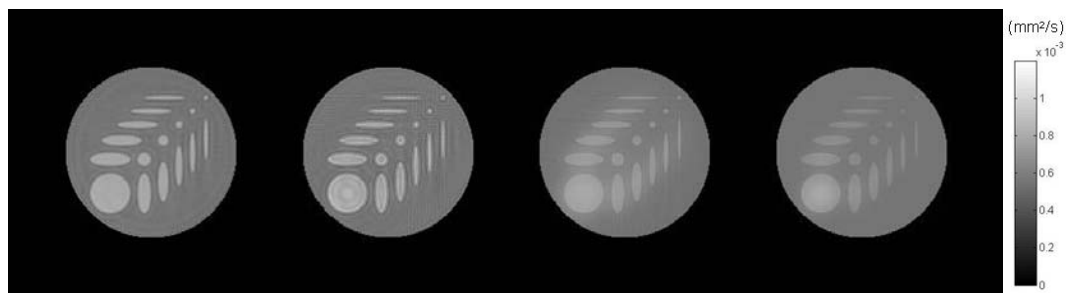


Figure 5-9 Mean ADC maps of simulations with T_2 at 9.4T and centric phase encoding. From left to right: (i) Matrix=256 x 8 x 48, FA=0, (ii) Matrix=256 x 8 x 48, FA=0.8, (iii) Matrix=256 x 32 x 12, FA=0 and (iv) Matrix=256 x 32 x 12, FA=0.8.

Chapter 3 reported that using linear phase encoding, as opposed to centric, produced T_2 contrast and improved image fidelity in non-DW data for $ETL \leq 16$. In DWI, longer minimum effective TE in linear phase encoding is compounded by the diffusion preparation period leading to severe T_2 effects. Figure 5-10 shows overestimations of mean ADC with FA, wider blades and longer effective TEs. Aside from mixed T_2 contrast, the dominant source of error here was the long effective TE. At $nPE=32$ and $T_{2, \text{tumour}}=65\text{ms}$ for instance, a drop in signal of 81% at $k=0$ may be expected. This rotational modulation of k-space leads to edge artifacts as the periphery of k-space is effectively undersampled. This can be seen in Figure 5-11 and would be intolerable with limited SNR in-vivo.

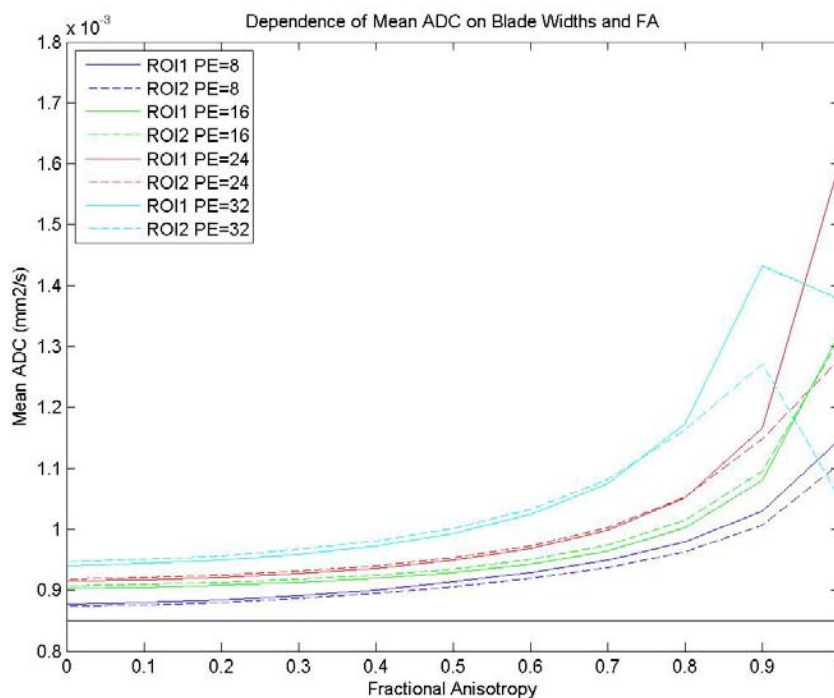


Figure 5-10 Dependence of Mean ADC on PROPELLER blade width and tissue FA, with T_2 at 9.4T and linear phase encoding. Matrix sizes were $256 \times 8 \times 48$, $256 \times 16 \times 24$, $256 \times 24 \times 16$ and $256 \times 32 \times 12$ and $TE = [44.1, 65.7, 87.2, 109]\text{ms}$ respectively.

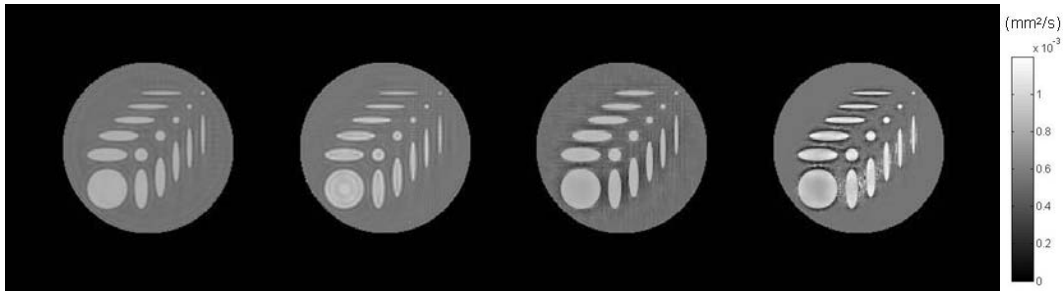


Figure 5-11 Mean ADC maps of simulations with T_2 at 9.4T and linear phase encoding. From left to right: (i) Matrix=256 x 8 x 48, FA=0, (ii) Matrix=256 x 8 x 48, FA=0.8, (iii) Matrix=256 x 32 x 12, FA=0 and (iv) Matrix=256 x 32 x 12, FA=0.8.

In practice, the choice of blade width would be strongly governed by the SNR achievable with the available time and hardware. Based on the above simulations, an ETL of 8 with linear phase encoding was chosen for further simulations and in-vivo acquisitions. This narrow blade width may give rise to some artifacts due to the PSF, but this may be mitigated by the nature of the real data containing less object symmetry and lower high spatial frequency content compared to the simulation. At lower fields, T_2 has been shown in Chapter 3 to be a much less restrictive factor, and wider blades may be used to reduce acquisition time with lesser penalty in accuracy of ADC estimation.

The data from simulations examining the effect of the relationship between (i) orientation of tumour principal diffusivity and (ii) PROPELLER imaging plane orientation on the ADC are given in Figure 5-12. It shows that the mean ADC was overestimated more when the tumour anisotropy was oriented in the imaging plane. In this case, GM anisotropy was oriented normal to this plane. It made no difference whether the tumour anisotropy was in the RO or PE direction.

In Figure 5-13, GM anisotropy was oriented in the PE direction, and the experiment was repeated. The results were reversed, with the mean ADC being overestimated more when tumour anisotropy was normal to the imaging plane. ADC measurements were identical when tumour anisotropy was aligned to the RO and SS directions.

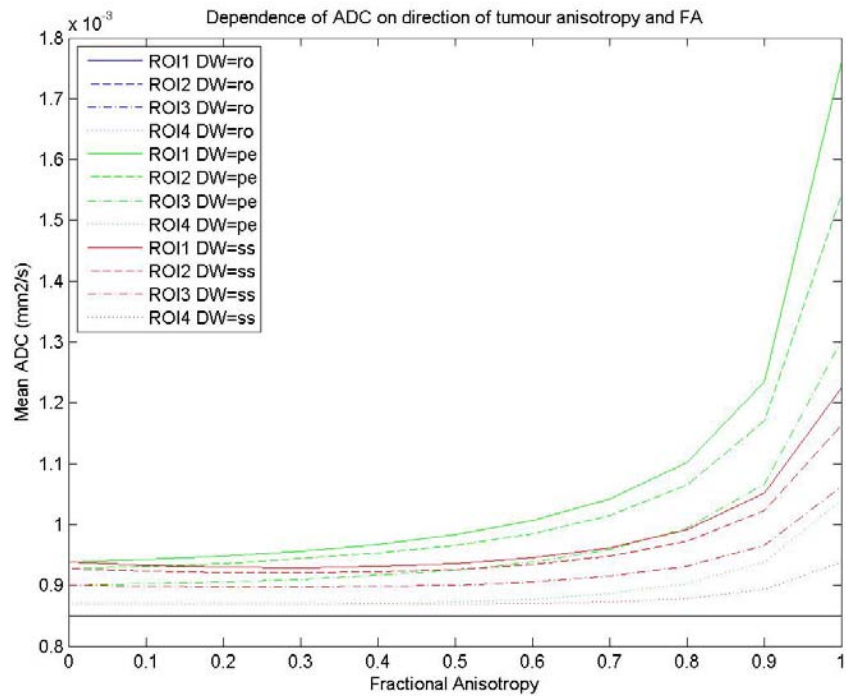


Figure 5-12 Dependence of mean ADC on direction of lesion anisotropy and tissue FA in the absence of T_2 . Directions were RO, PE & SS respectively. GM anisotropy was oriented along the SS direction. Blue & green lines overlapped.

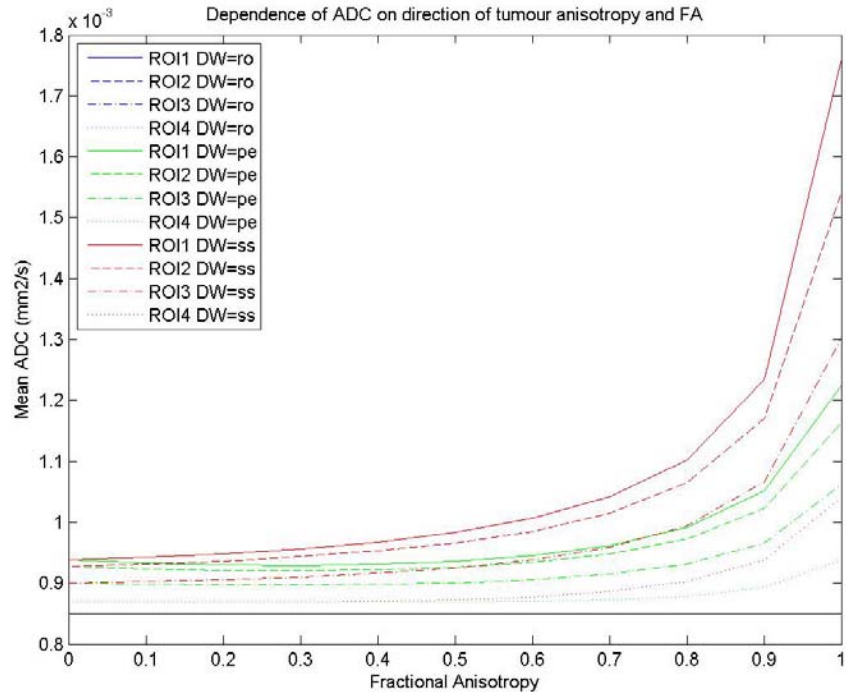


Figure 5-13 As per Figure 5-12, but with GM anisotropy was oriented along the PE direction. Blue & red lines overlapped.

This indicated that rather than depending on absolute orientations of tissue principal diffusivity with respect to the imaging plane, the measured ADC was dependent on the relative orientations of principal diffusivities between different tissues. The data show that errors in ADC measurement were minimized when the directions of principal diffusivity of different tissues were collinear. This could result from blurring and interpolation errors that increase when tissue principal diffusivities are orthogonal. This implies that errors in ADC measurement are directly related to FA and the complexity of tissue, in terms of comprising adjacent tissues with multiple orientations of principal diffusivities.

A simulation using varying degrees of k-space undersampling (See Chapter 4) showed that k-space undersampling had little effect on the measured ADC across the typical range of FA values found in GM, WM and tumours (See Figure 5-14) when linear phase encoding was used. Centric phase encoding led to an overestimation of the mean ADC by up to 15% at FA=0.8. This supported the use of k-space undersampling methods with linear phase encoding schemes in reducing acquisition times without introducing significant additional errors in the measured ADC.

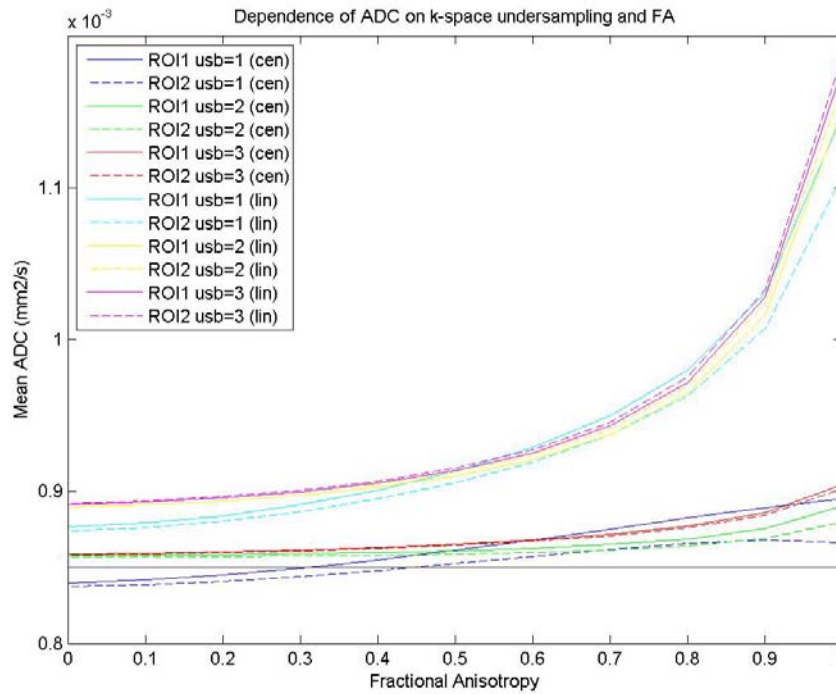


Figure 5-14 Dependence of mean ADC on degree of k-space undersampling and tissue FA with T_2 at 9.4T, $TE=44.1ms$ using centric (cen) and linear (lin) phase encoding. Undersampling was achieved by reducing the number of blades by a factor of USB. USB=1 referred to fully sampled PROPELLER where Matrix=256 x 8 x 48. USB=2 and 3 referred to data comprising 24 and 16 blades respectively.

The deviations from the nominal mean ADC due to the various factors explored dictate a careful choice of imaging parameters. In the presence of T_2 , unknown geometry in pathology, and physiologic values of FA and directions of anisotropy, the simulations supported the choice of ETL=8. This produced less error than using wider blades. For FA values ranging from 0 to 0.8, the corresponding overestimation of ADC was 2.9% to 15% with linear phase encoding, and -1.8% to 3.5% with centric phase encoding.

5.3.3 Animal Studies

In-vivo mouse data were acquired and images from a sample slice from one mouse acquired using six different methods are presented in Figure 5-15. The images include the b_0 image, 3 images with $b=800s/mm^2$ and DW in orthogonal directions, and the mean ADC map. Due to susceptibility, off-resonance effects and inadequate alignment of odd-even echoes as described in Section 3.3.2, the EPI data generally suffered from significant geometric distortions. Due to inadequate k-space sampling and T_2^* , single-shot DW-EPI data were

particularly degraded. Multi-shot DW-EPI performed much better due to the shorter echo trains, however motion artifact can be observed in the DW image with diffusion in the phase encoding direction. While DW-EPI-PROPELLER could potentially resolve this, suitable distortion correction methods were not implemented due to software constraints. As a result, the DW-EPI-PROPELLER exhibited substantial streaking artifacts due to rotationally varying distortions between blades.

Fast spin echo data were generally resistant to geometric distortions due to off-resonance effects. The single-shot DW-FSE data were blurred considerably in the phase encoding direction due to T_2 , and motion artifacts were observed possibly due to intrashot motion during the relatively long echo train. Multi-shot DW-FSE produced less blurring due to the shorter echo train, but suffered from intershot motion as evidenced in the ghosting and signal dropout in the DW images. On the other hand, DW-FSE-PROPELLER produced images that were more consistent, robust to motion and retained an apparent contrast and resolution comparable to that of the Cartesian acquisition.

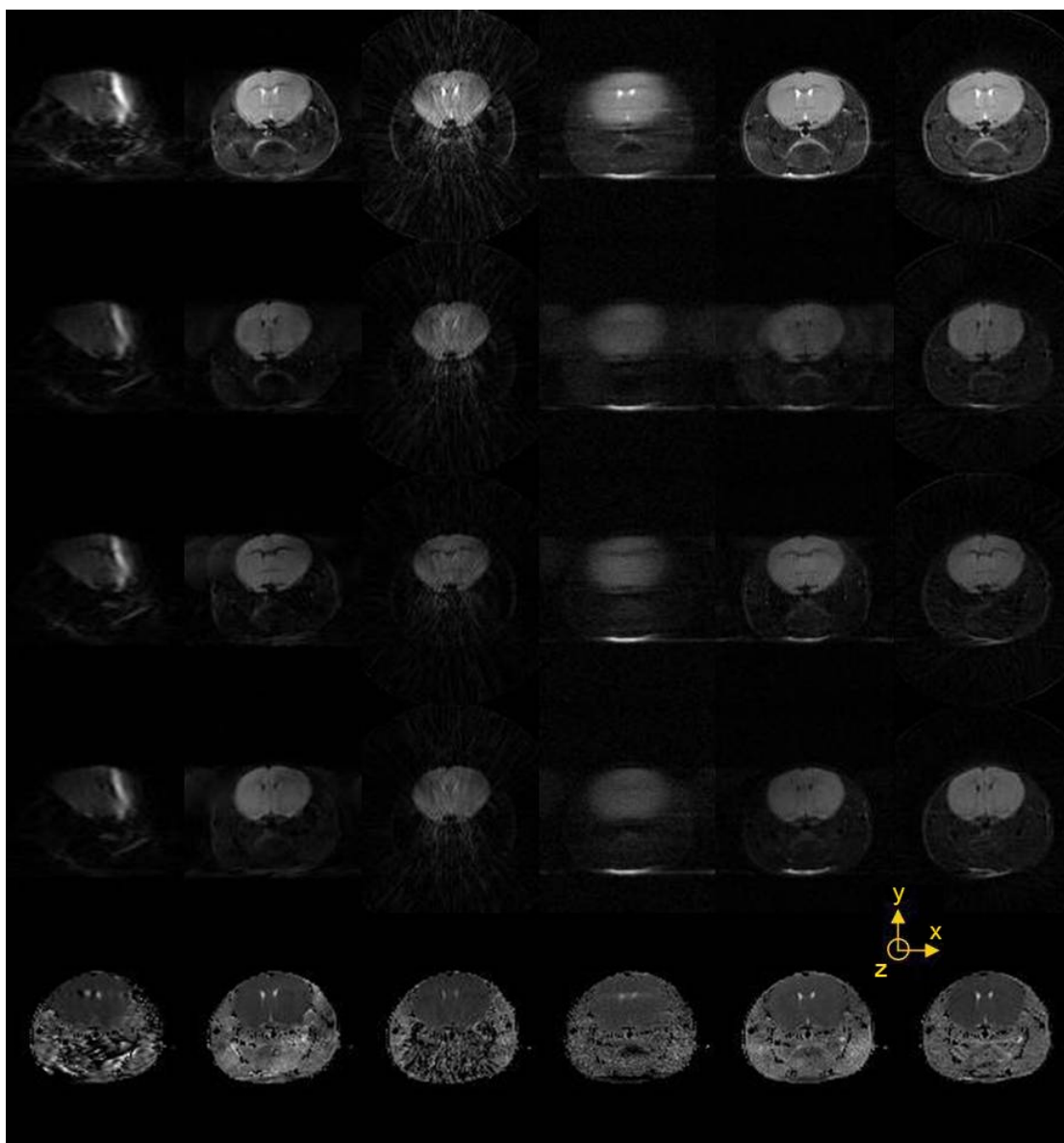


Figure 5-15 Diffusion weighted imaging of free-breathing mouse brain in-vivo at 9.4T using six pulse sequences. From left to right are ssDW-EPI, msDW-EPI, DW-EPI-PROPELLER, ssDW-FSE, msDW-FSE & DW-FSE-PROPELLER. From top to bottom are $b=0$, $b=800\text{s/mm}^2$ (y), $b=800\text{s/mm}^2$ (x), $b=800\text{s/mm}^2$ (z) images & mean ADC maps. Nominal resolution = 128×128 and a single slice is displayed.

The mean ADC was measured in grey matter and white matter across the 8 subjects, and these are given in Figure 5-16 & Figure 5-17 respectively. Despite the distortions, the EPI data were found to more closely match values of mean ADC as cited in the literature using PGSE and DW-STEAM methods (128,137). In fact the mean ADC map in the brain using ssDW-EPI looks significantly less distorted than the corresponding DW images. This was due to the relative homogenous nature of the ADC in the mouse brain and the EPI-related

distortions affecting the b_0 image as well as the DW images in a similar manner. Outside the brain, tissue is more heterogeneous with greater susceptibility effects, and ADC quality is severely degraded.

In contrast, the DW-FSE data tended to give a higher mean ADC and lesser distortion. The former could be due to residual non-CPMG effects and phase cancellation from non-MG magnetization that was not fully crushed. Single-shot DW-FSE data exhibited a 130% overestimation arising from signal dropout due to the combination of blurring and intrashot motion. Reduced blurring reduced the measured ADC in msDW-FSE and DW-FSE-PROPELLER. The mean ADC however was not significantly different using these two sequences.

The lack of significance despite the consistent better apparent image quality in the latter could be due to sampling at only 2 b-values. The resultant exponential fit to obtain the ADC did not assess the quality of fit. Acquiring data at a greater number of b-values would allow a better assessment of the fitting error. Discarding those data beyond a certain threshold, should reduce the ADC variation and improve the significance of our findings. According to the simulations, the ADC would have been overestimated by some 5.9% - 15% using PROPELLER, this possibly contributed to the higher value than those reported in the literature. In general, the single-shot DW-EPI and DW-PROPELLER methods showed the least inter-subject variation, while the other methods show greater variation, mainly due to motion artifacts.

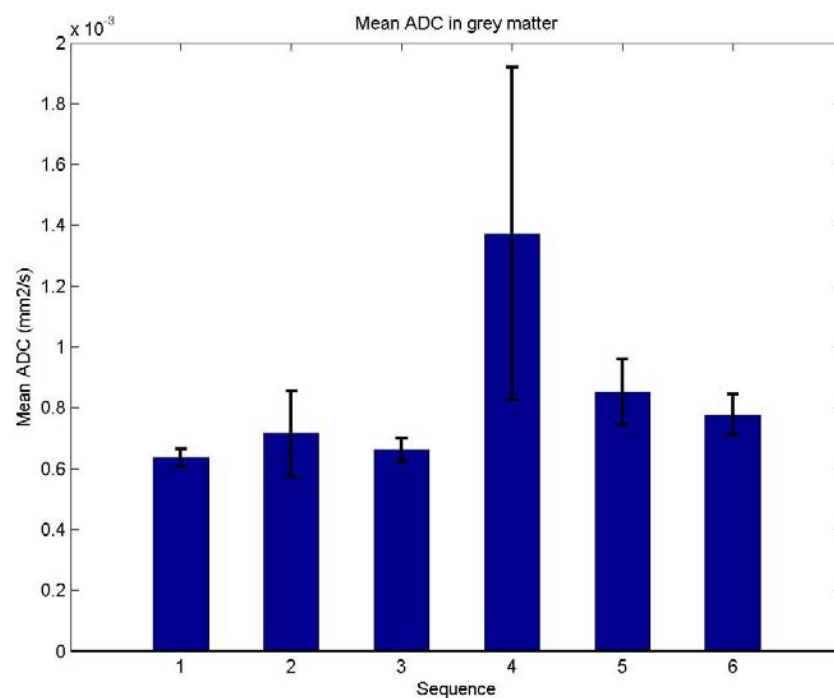


Figure 5-16 Mean ADC data measured in grey matter of free-breathing mouse in-vivo at 9.4T using various acquisition and reconstruction methods: 1) ssDW-EPI, 2) msDW-EPI, 3) DW-EPI-PROPELLER, 4) ssDW-FSE, 5) msDW-FSE & 6) DW-FSE-PROPELLER.

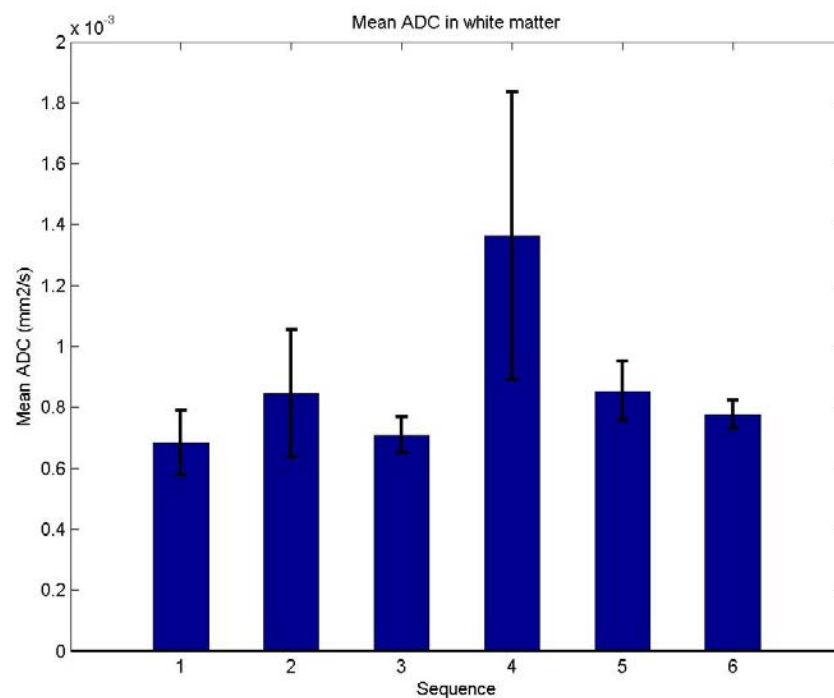


Figure 5-17 Mean ADC data measured in white matter of free-breathing mouse in-vivo at 9.4T using various acquisition and reconstruction methods as given in Figure 5-16.

SNR and AP in the measured ADC data are presented in Figure 5-18 & Figure 5-19 respectively. Here, the SNR of the multi-shot data were better than single-shot data, although this can be attributed to the 16-fold increase in scan time. The SNR data were generally not significantly different, although DW-FSE-PROPELLER exhibited the highest value ($p=0.16$ compared to DW-FSE). Single-shot methods and msDW-EPI exhibited high values of AP, reflecting poor repeatability in the same subject. The large error bars signify poor inter-subject repeatability. In general, the multi-shot FSE data were more consistent than the multi-shot EPI data, and PROPELLER acquisitions exhibited the lowest intra- and inter-subject variability. This may be attributed to the reduction of motion artifacts. Although AP in DW-FSE-PROPELLER was not significantly lower than msDW-FSE ($p=0.08$), the data had much lower inter-subject variability.

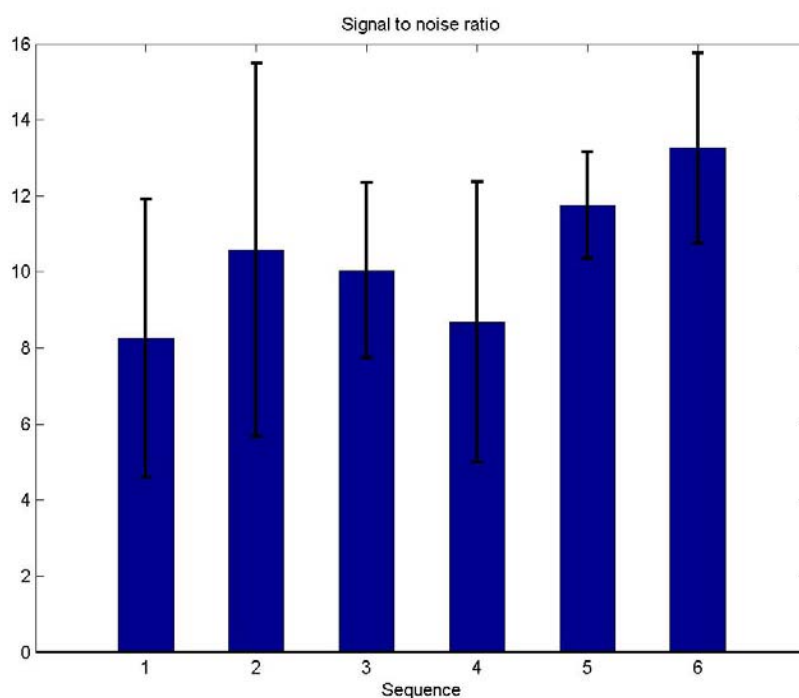


Figure 5-18 SNR of mean ADC data measured in whole brain of free-breathing mouse in-vivo at 9.4T using various acquisition and reconstruction methods as given in Figure 5-16

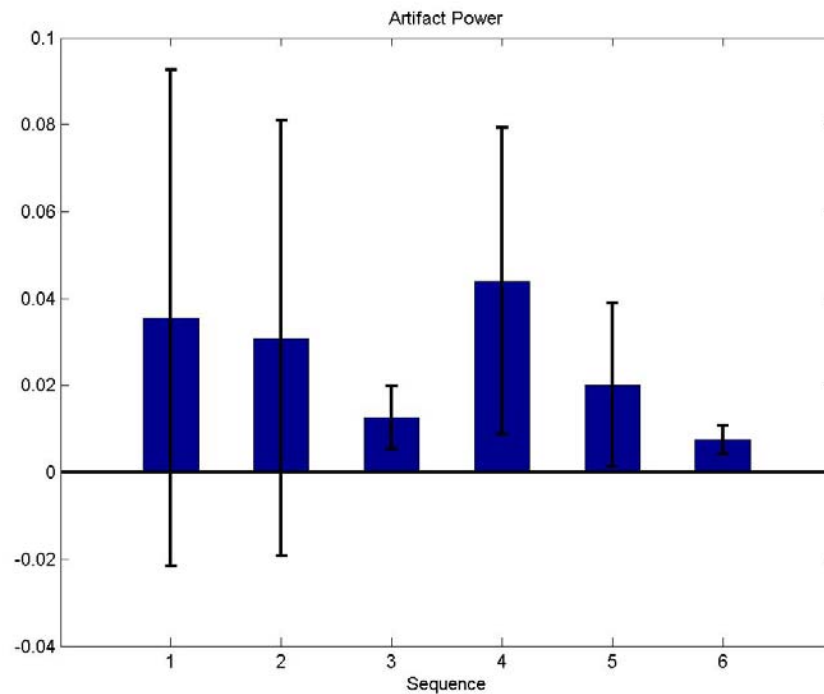


Figure 5-19 AP of mean ADC data measured in whole brain of free-breathing mouse in-vivo at 9.4T using various acquisition and reconstruction methods as given in Figure 5-16

DWI in the mouse body presents the additional major challenges of shorter T_2 and significant physiological motion due to respiration and gastrointestinal movement. Correspondingly, few studies of DWI in the body of live rodents at high field strengths have been published (71,161). In addition, severe T_2^* and susceptibility preclude EPI-based methods. Figure 5-20 shows DW images and mean ADC maps measured in the liver of free breathing in-vivo mice at 9.4T. Motion artifacts catastrophically degraded the ssDW-FSE and msDW-FSE data, and led to ghosting and signal dropout that enhanced the mean and standard deviation of the ADC. Motion artifacts were greatly reduced using both respiratory triggering with Cartesian sampling and PROPELLER sampling without triggering, and data were more consistent.

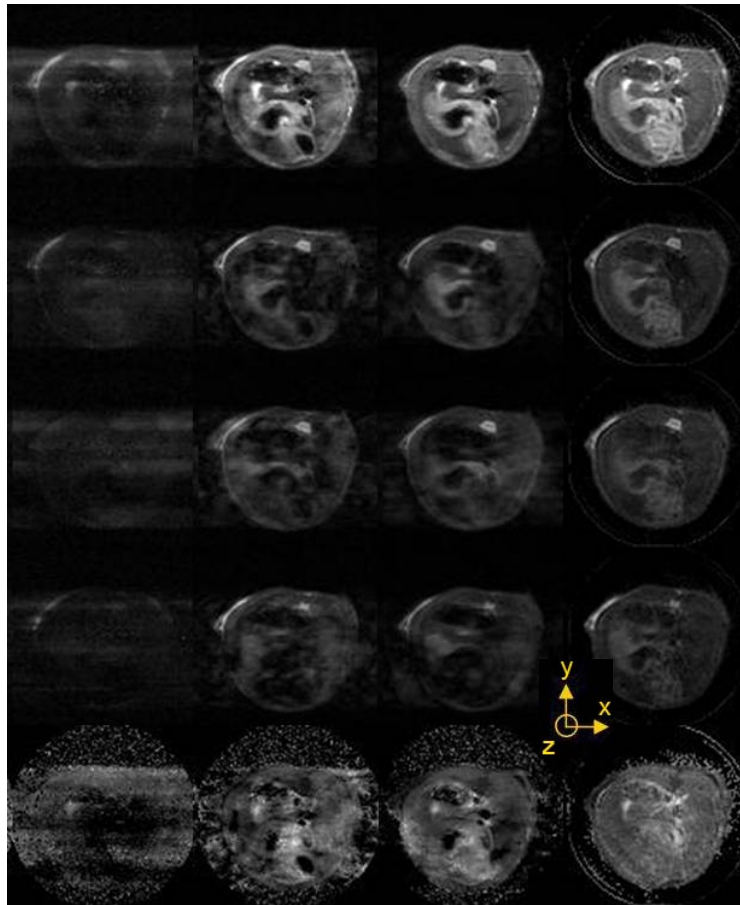


Figure 5-20 Diffusion weighted imaging of free-breathing mouse liver in-vivo at 9.4T using four acquisition methods. From left to right are ssDW-FSE, msDW-FSE, msDW-FSE with respiratory triggering & DW-FSE-PROPELLER without triggering. From top to bottom are $b=0$, $b=800\text{s/mm}^2$ (y), $b=800\text{s/mm}^2$ (x), $b=800\text{s/mm}^2$ (z) images & mean ADC maps. Nominal resolution = 96×96 and a single slice is displayed.

There is a lack of published ADC values of mouse liver measured at high field strengths. Based on the images acquired and from Figure 5-21, it was deduced that the generally higher ADC in ssDW-FSE and msDW-FSE was due to signal losses stemming from motion artifacts and blurring. Intersubject variability was correspondingly large, and the smaller error in the DW-FSE-PROPELLER reflects more consistent data and robustness to motion. This trend was seen similarly in muscle. Although in this case, the ADC was significantly lower in triggered msDW-FSE ($p=0.023$) and FSE-PROPELLER ($p=9\text{e-}3$) compared to DW-FSE.

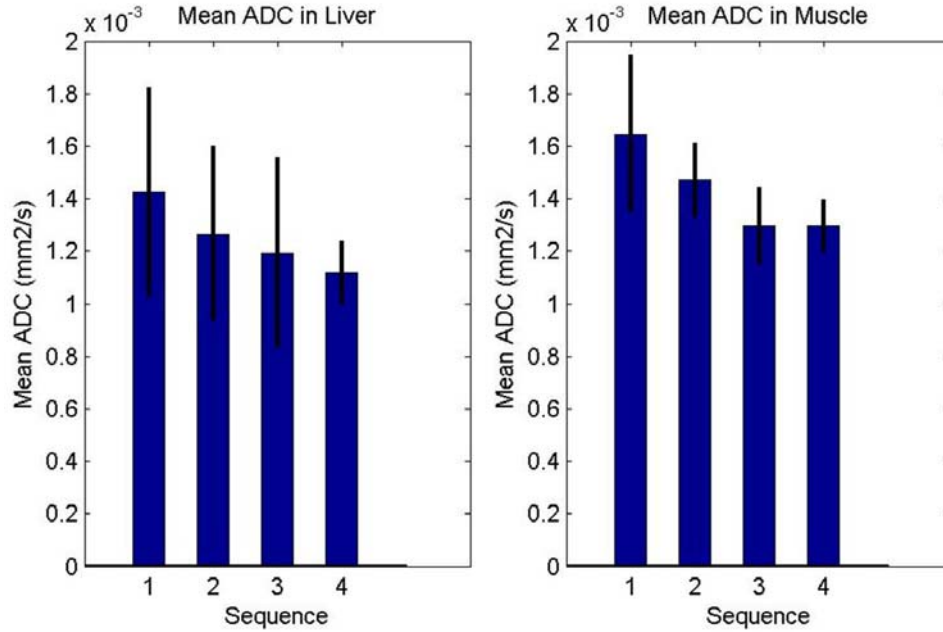


Figure 5-21 Mean ADC data measured in the liver (left) and muscle (right) of free-breathing mice in-vivo at 9.4T using various acquisition and reconstruction methods: 1) ssDW-FSE, 2) msDW-FSE, 3) msDW-FSE with triggering & 4) DW-FSE-PROPELLER without triggering.

As a result of the small voxel size, high b-value, residual non-CPMG effects and respiratory motion, measured SNR was relatively low. Figure 5-22 shows that the SNR in triggered msDW-FSE and DW-FSE-PROPELLER ADC maps were significantly higher than that of non-triggered msDW-FSE with $p=0.014$ and $p=5.1e-6$ respectively. The reverse was true in the measurement of AP of the mean ADC data, with significantly lower AP in msDW-FSE ($p=3.1e-3$) and DW-FSE-PROPELLER ($p=4.2e-4$) compared to non-triggered msDW-FSE. Intra- and inter-subject variability in mean ADC measurements were much greater in ssDW-FSE and msDW-FSE acquisitions. This was mainly due to intrashot motion and blurring in the former and intershot motion in the latter.

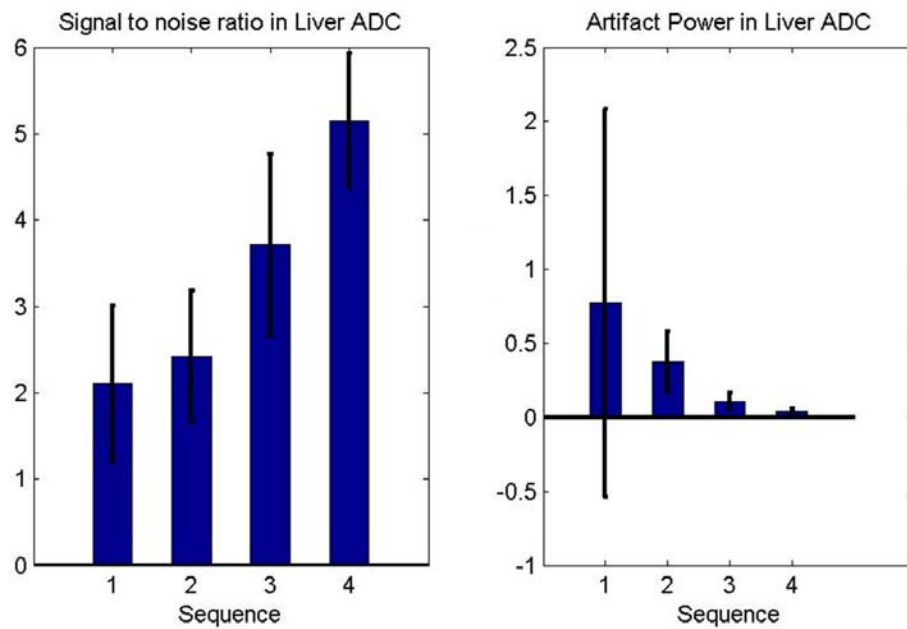


Figure 5-22 SNR of mean ADC data (left) and AP of mean ADC data (right) measured in the liver of free-breathing mice in-vivo at 9.4T using various acquisition and reconstruction methods: 1) ssDW-FSE, 2) msDW-FSE, 3) msDW-FSE with triggering & 4) DW-FSE-PROPELLER.

While significance of improvements in the mean ADC measurement in the mouse brain using DW-FSE-PROPELLER over msDW-FSE was not established, the images in the former consistently exhibited a lower degree of ghosting and signal loss due to uncorrected motion compared to the latter. A possible cause as mentioned was the possible inclusion of data that fit poorly to the exponential diffusion model resulting in a wider error. Acquiring additional data at multiple b-values might help exclude poorly fitting data and help establish significance in the improvements. Also the relatively poor SNR gave rise to large error and inter-subject variability in all cases, reducing significance of the findings. This may be increased by acquiring additional averages. Further, our measurements of ADC using PROPELLER may have been overestimated, according to our simulations, by a factor of 5.9% to 15% in GM and WM respectively. Finally, the relative homogenous nature of the ADC in the mouse brain meant that the ADC measured in the msDW-FSE acquisition was not reflective of actual image degradation due to motion artifacts.

The improvements were more obvious in the liver where motion was relatively severe. Signal losses from uncorrected motion contributed to artificially raised mean ADC values, SNR was reduced and AP was raised. Respiratory triggering is commonly employed to reduce motion artifacts in in-vivo small animal imaging, and it resulted in significant improvement to the consistency of the data. However, triggering relies on a steady respiration rate throughout

the acquisition to achieve the desired TR and acquisition time. In practice, this can be achieved by intubating and artificially ventilating the animal, however these methods are invasive and not ideal (162). Not doing so invariably entails respiration that varies if the acquisition time is more than a few minutes, thereby introducing a variable TR and often increasing the total acquisition time. Motion correction methods that circumvent the need for triggering would be preferred.

5.3.4 Human Studies

Pilot stroke data acquired with ssDW-EPI and DW-FSE-PROPELLER in one patient at 3T are given in Figure 5-23 & Figure 5-24 respectively. DW-EPI with SENSE allowed for rapid data acquisition within 25s. The DW images had good visual contrast and resolution, and stroke lesions were clearly visible in the right middle frontal gyrus. This was accompanied by a reduction in ADC, confirming the diagnosis of acute stroke. The patient was diagnosed with right middle cerebral artery (MCA) infarct with haemorrhage conversion in the right frontal lobe. The drawback of ssDW-EPI however is the geometric distortions that have to be tolerated, hampering the diagnosis of lesions in areas prone to susceptibility artifacts such as nearer the sinuses and the brain stem. DW-FSE-PROPELLER data were resistant to susceptibility and off-resonance artifacts. Contrast was reduced in general owing to rotationally varying T_2 , but although there was a drop in GM-WM contrast, adequate contrast remained to identify stroke regions correctly. The ADC was reduced in stroke lesions as well.

DW-FSE-PROPELLER has been demonstrated to improve our ability to diagnose stroke in regions prone to susceptibility in patients at 1.5T (125). Scanning at 3T offers improved SNR over 1.5T without a large increase in T_2 decay compared to 9.4T. Preliminary data suggests that DW-FSE-PROPELLER can offer the same improvements in diagnosis as at 1.5T, with the benefit of higher SNR. Acquisition times can be reduced by the incorporation of parallel imaging, undersampling in k-space, and reducing the number of diffusion directions required to acquire isotropic DW. The current data could be improved by enabling RF refocusing pulses with a better slice profile than the current Gaussian used, and visual contrast could be improved using PETALS as shown in Figure 5-25 and discussed in Chapter 3.

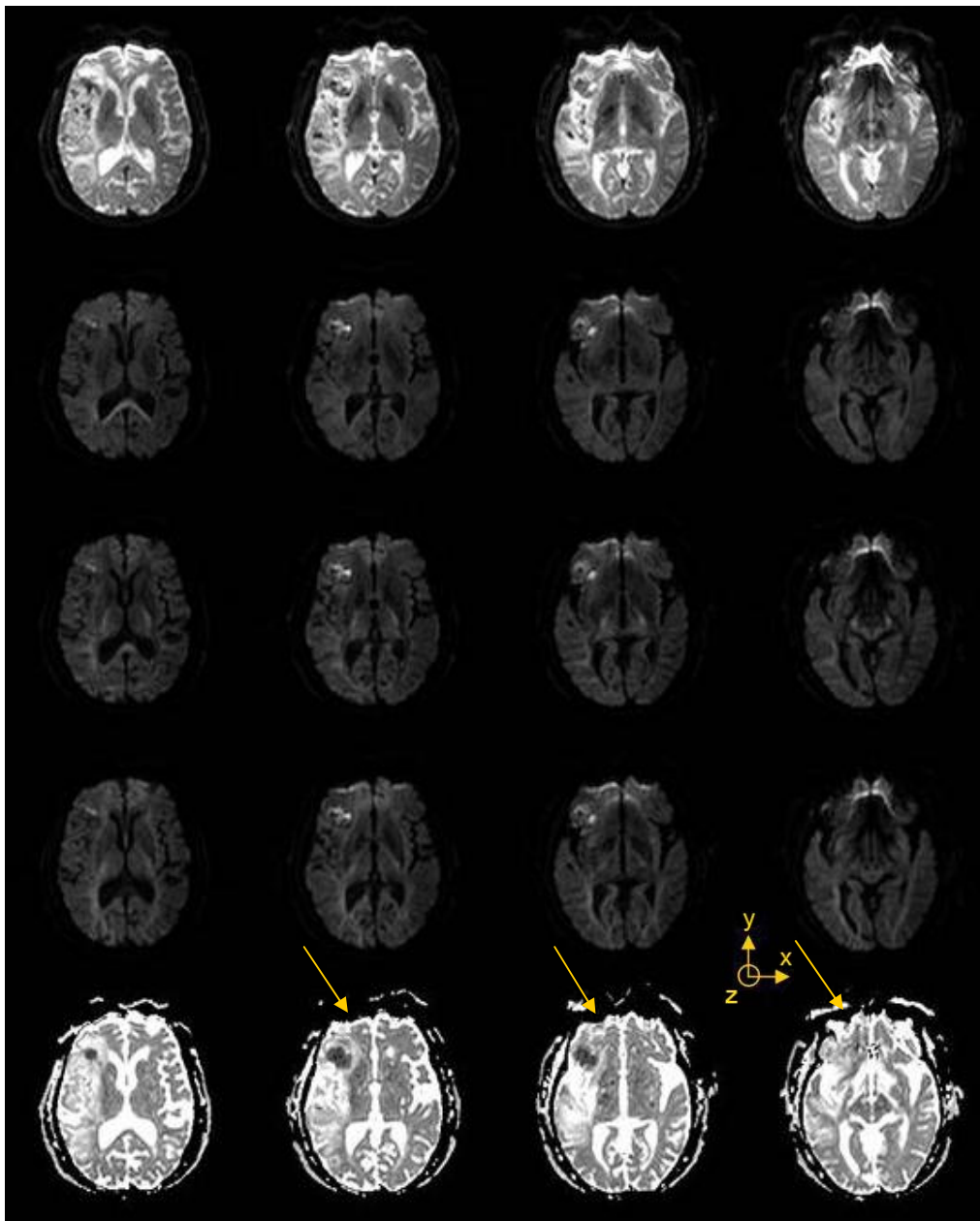


Figure 5-23 Diffusion weighted imaging of patient brain with acute infarct in the right MCA using ssDW-EPI. Four slices are given from left to right. From top to bottom are $b=0$, $b=800\text{s/mm}^2$ (y), $b=800\text{s/mm}^2$ (x), $b=800\text{s/mm}^2$ (z) images & mean ADC maps. Note geometric distortions that potentially confound diagnoses in the regions highlighted.

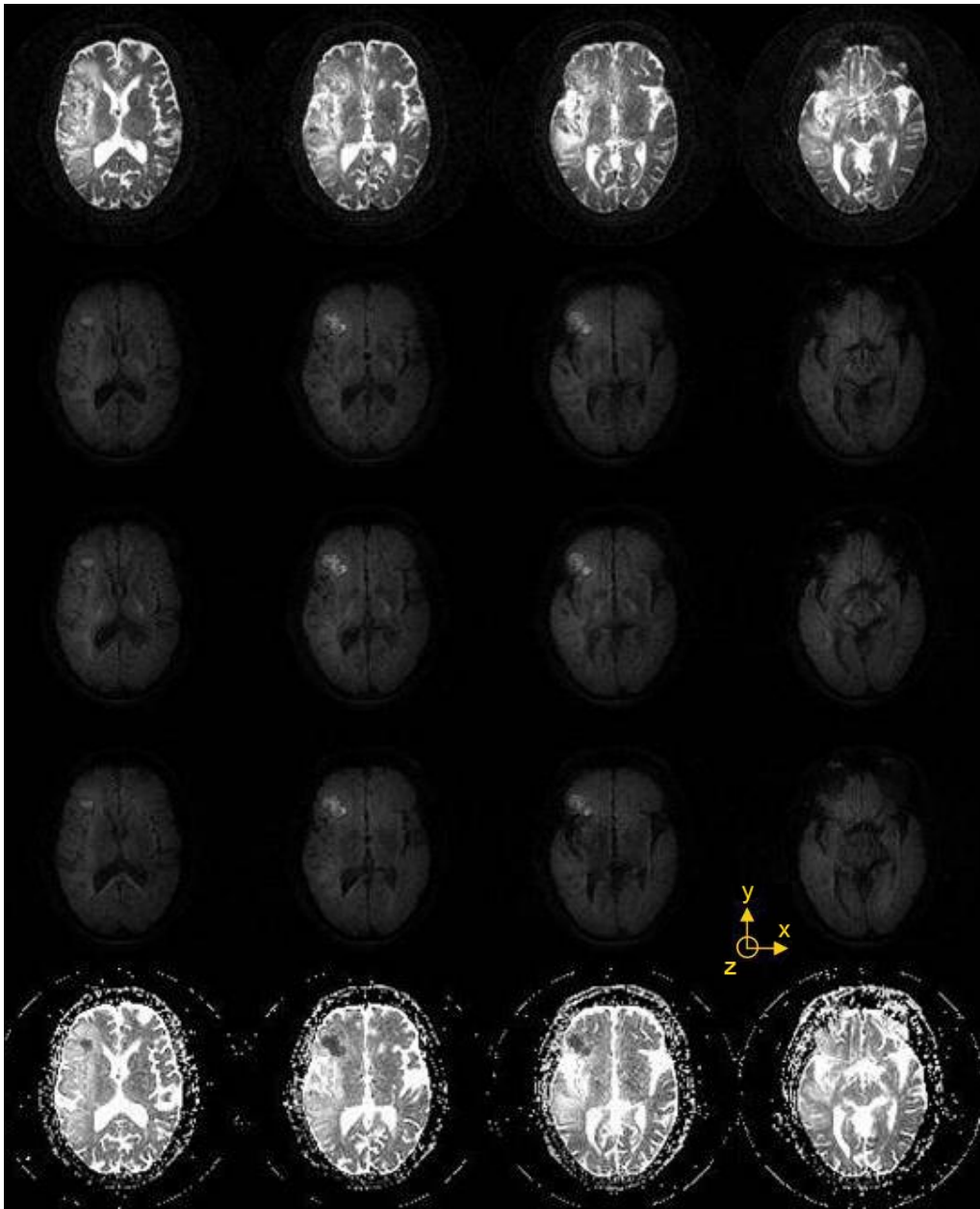


Figure 5-24 Diffusion weighted imaging of the same patient brain using DW-FSE-PROPELLER. Four slices are given from left to right. Data was robust to geometric distortions but suffered reduced contrast.

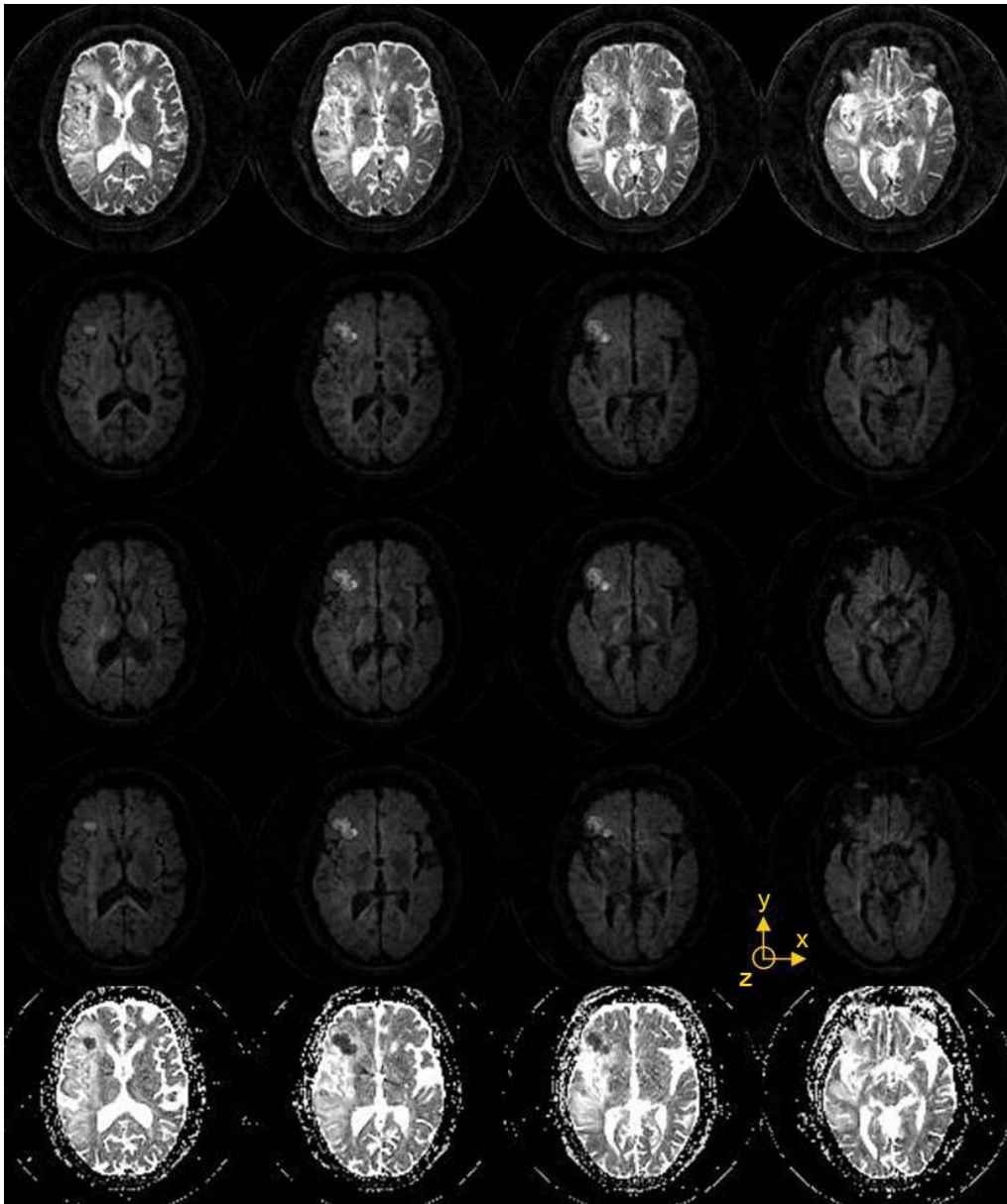


Figure 5-25 Diffusion weighted imaging of same patient brain using DW-FSE-PETALS. Images exhibited better contrast than DW-FSE-PROPELLER.

5.4 Conclusion

The measurement of ADC depends on many factors including pulse sequence design, eddy currents, off-resonance, non-CPMG effects, subject motion, temperature, tissue diffusion properties, SNR and field strength. The use of PROPELLER adds additional factors including blade configuration, choice of phase encoding, heterogeneity of directions of tissue anisotropy and k-space undersampling.

A series of simulations were tested to explore the relation between the latter group of factors and the measured ADC. It was found that the ADC depended on the blade width and phase encoding used due to T_2 and corresponding rotational modulations in k-space. Depending on the choice of phase encoding, the ADC showed different sensitivities to tissue geometry and may be either overestimated or underestimated by a degree directly related to blade width and FA.

DWI in small animals is challenging due to small voxel sizes, short T_2 , severe susceptibility and sensitivity to motion. The increased off-resonance artifacts preclude the use of ssDW-EPI. These can be mitigated using msDW-EPI and DW-EPI-PROPELLER, but they are still more susceptible to distortion and eddy currents artifacts than FSE-based methods. ssDW-FSE results in intolerable blurring and intrashot motion due to the long echo train, while msDW-FSE suffers from intershot motion artifacts that are exacerbated by the diffusion weighting preparation. Data acquired in the mouse brain showed that DW-FSE-PROPELLER provided more consistent data with higher SNR and lower errors than other single-shot, EPI and Cartesian-based sequences at 9.4T. This was due to its self-navigating properties, rotational acquisition, and insensitivity to off-resonance. The benefits of which are more clearly appreciated at 9.4T compared to lower fields where for instance EPI-based methods become feasible with appropriate distortion correction methods.

Sensitivity to motion in DWI at 9.4T led to catastrophic artifacts in imaging mouse liver in-vivo. Respiratory triggering was not only less than ideal as discussed, but produced data that were inferior to DW-FSE-PROPELLER data acquired without triggering. DW-FSE-PROPELLER was implemented and significantly reduced the sensitivity to motion and improved the quality of DW data. This would be essential in in-vivo body DWI in small animals at high field strengths.

Pilot stroke data were presented and demonstrated that DW-FSE-PROPELLER could be used at 3T to improve diagnostic capability in areas prone to susceptibility and distortion, just as it had been used at 1.5T. Acquiring data in more patients and having independent assessment of the image fidelity is the subject of ongoing research.

As with any multi-shot FSE method, acquisition time is significant. Fortunately, the multi-shot rotational nature of the PROPELLER acquisition lends well to undersampling techniques which can be combined with non-Cartesian reconstruction methods like NUFFT to produce good quality data. K-space undersampling by blades has been demonstrated in Chapter 4

and its use in DWI has been validated in simulations. Another option that will be explored in the next chapter is the use of rotating DW gradients to obtain pseudo-isotropically DW data in a single-shot.

6 Rapid Isotropic Diffusion-weighted Imaging at High Field Strength

6.1 Introduction

Measuring the mean ADC provides valuable contrast in studying disease processes such as stroke and tumours. In the brain for instance, grey matter-white matter ADC contrast is poor, and anomalies in the ADC due to pathological processes can quickly be detected against this uniform background. In humans, measuring the mean ADC provides a sensitive biomarker for the diagnosis of stroke that precedes changes in T_2 (30,163). The ADC changes significantly over the evolution of stroke and this has been well characterized (152,164). In rodent models of stroke by middle cerebral artery occlusion, reduced ADC during occlusion is followed by a raised ADC during reperfusion, subject to regional differences (165,166). It was reported that these ADC changes were closely linked to changed in tissue energy metabolism (167).

Early changes in the ADC have also been observed in tumour growth and regression in response to chemotherapy (168). For example, regions of tumour necrosis could be identified by increased ADC due to reduced cellularity, haemorrhage and debris (169). Studies have been conducted towards validating changes in ADC as a surrogate marker for monitoring early tumour progression and response to treatment preceding changes in tumour volume (128,142).

In this chapter, possible methods for rapid isotropic DWI which exploit the rotational symmetry of the PROPELLER acquisition are explored. DW-FSE-PROPELLER was shown to perform significantly better at 9.4T compared to acquisitions based on single-shot, EPI and Cartesian methods. However it may require long acquisition times depending on the desired resolution and image quality. The mean ADC is conventionally obtained by taking the average of the diffusion coefficients from three DWI scans with DW applied in orthogonal directions. Single-shot DW Cartesian methods have been explored to reduce the total acquisition time by reducing the number of DW images required from three to one (36,37,170,171). These methods concurrently apply DW gradients along x, y, and z axes in such a manner as to generate isotropic DW.

Mori and van Zijl proposed an efficient method by using a series of bipolar DW gradients that were set to $\pm$ the maximum gradient strength available (36). By suitably alternating the signs

of the gradients, they were able to maximize the efficiency of the DW in Cartesian acquisitions and achieve the maximum possible b-value using bipolar gradients within the time available. Chun, et al. implemented variations of this method in human patients and concluded that variations in gradient performance had an effect on which isotropic DW scheme was optimal (170). While bipolar methods have decreased sensitivity to eddy currents, these DW methods are limited to gradient lobes of equal length and magnitude. Wong, et al. approached this by numerically optimizing DW schemes to achieve greatest efficiency, without the constraint of equal gradient lobes (37). The result was asymmetrical, non-equal gradient lobes that alternated in polarity at different times along the x, y and z axes. This achieved higher efficiency during the DW period. However, the DW could not be separated such that half of it was on either side of the spin echo, as it could in the earlier method. This reduced the overall efficiency of the DW when using spin echo methods, as there was no DW after the refocusing pulse. These multipolar single-shot isotropic DW methods reduce the total acquisition time at the expense of an extended DW preparation period, leading to greater T_2 or T_2^* decay. At high field strengths, this quickly becomes a problem.

The rotational symmetry of PROPELLER is highly compatible with the use of rotating DW gradients to obtain pseudo-isotropic diffusion weighting in a single acquisition. Due to the multiple sampling of the central region of k-space, it is proposed that this region can be effectively isotropically DW, while the outer regions have anisotropic DW. This could be a viable strategy since most of the signal and contrast information comes from the central part of k-space. This would potentially allow the total acquisition time to be halved by acquiring one image with low or no DW, together with isotropically DW data in a single scan rather than in three separate acquisitions.

Dietrich, et al. showed in rotating DW radial simulations that the estimated ADC was dependent on the DW direction, object geometry and FA (172). He concluded that the method would be inferior to standard fixed DW direction methods in objects with anisotropy and sharp geometric features. Cheryauka, et al. had made the case for rotating DW gradients in DTI-PROPELLER using both k-space undersampling and rotating DW gradients (173). They simulated 2D anisotropic cardiac tissue, resolved for the diffusion parameters using an iterative conjugate gradient reconstruction method and showed a three-fold time saving using both methods. However, the simulations were limited to a small range of anisotropies in 2D, and they had not implemented these in-vivo due to hardware limitations.

A radial DW-FSE sequence for single-shot isotropic DW was implemented by Sarlls, et al. (174). It comprised a twice refocused spin echo (TRSE) DW preparation (51) with a FSE echo train of four echoes. Taking advantage of the high rotational sampling frequency in radial acquisitions, they proposed that by acquiring each successive radial view with a different DW weighting, they could obtain an effectively isotropically DW image in one fully sampled radial acquisition. To do so, they employed a tetrahedral DW encoding scheme (175) such that successive views within a group of four adjacent views, each had a different DW corresponding to one of the directions of the tetrahedral DW scheme. Due to the high frequency rotational modulation of the DW directions, the effective DW weighting was taken to be isotropic. The constraints of this method are limited motion correction compared to PROPELLER due to minimal overlap of data between shots, potential artifacts in the PSF (176), asymmetric modulation of TE in k-space, and a long DW preparation period due to the TRSE preparation.

Engstrom, et al. recently proposed to use PROPELLER to speed up the acquisition of DTI data by applying a different DW direction for each blade and using a keyhole-like method to denote the primary contrast in a given image (177). That is, instead of acquiring PROPELLER images with say ten blades per DW direction in ten DW directions, they acquired as few as one blade per DW direction in ten DW directions. In combining data from the blades using regridding, one k-space blade was selected and any k-space from the other nine blades that overlapped with the first blade was excluded from regridding. This led to an overall image contrast that was dominated by the contrast of the first blade. For resolution of DTI parameters, this DW image was assigned the DW parameters used in the first blade. This process was repeated for successive blades. Although this method did not use rotating DW gradients, it was based on the principle that the overall image contrast was determined largely by the contribution from the central part of k-space, and that imperfect DW at the periphery may be an acceptable compromise in light of the time savings achieved.

It is proposed that the wider overlap of blades in PROPELLER would lead to a rotating diffusion scheme that is more robust than using radial sampling. This would speed up DWI acquisitions, and find utility in imaging pathology where the expected change in ADC greatly exceeds the potential error due to anisotropic DW towards the periphery of k-space. One such example is in the imaging of acute stroke where the observed drop in ADC has been reported as 60-70% (178). To reduce this dependence on geometry and anisotropy factors, it is further proposed that a rotating DW scheme that alternates in the readout and phase encoding directions across successive blades, could improve the degree of isotropy in DW in

the periphery of k-space due to the effective averaging of the DW. This could be seen as analogous to the radial sampling method with cycling tetrahedral DW scheme as proposed earlier (174).

This chapter first describes how rotating DW gradients were implemented. A comparison is made between different DW preparation schemes to justify the choice of DW method used. Simulations were constructed with varying tissue properties and DW schemes. The accuracies of the ADC measurements were quantified using four different DW schemes with different phase encoding methods and a wide range of anisotropies. In-vivo data were acquired in healthy wildtype mouse brains, as well as MT-ret/AAD mouse models of spontaneous melanoma. Pilot data were acquired in a stroke patient to test applicability of this strategy at 3T. Finally, simulations were designed to study the effective **b**-tensor associated with the different DW schemes in a bid to improve the degree of isotropy in the diffusion weighting.

6.2 Materials & Methods

6.2.1 Rotating DW gradients

Rotating DW was achieved using three methods, aligning the DW along the blade readout direction (DW_{ro}), along the phase encoding direction (DW_{pe}), and alternating between the two with successive blades (DW_{alt}). These are collectively referred to as DW_{rot} . They are illustrated in Figure 6-1, and compared to a DW scheme using standard DW in three fixed orthogonal directions (DW_{fix}).

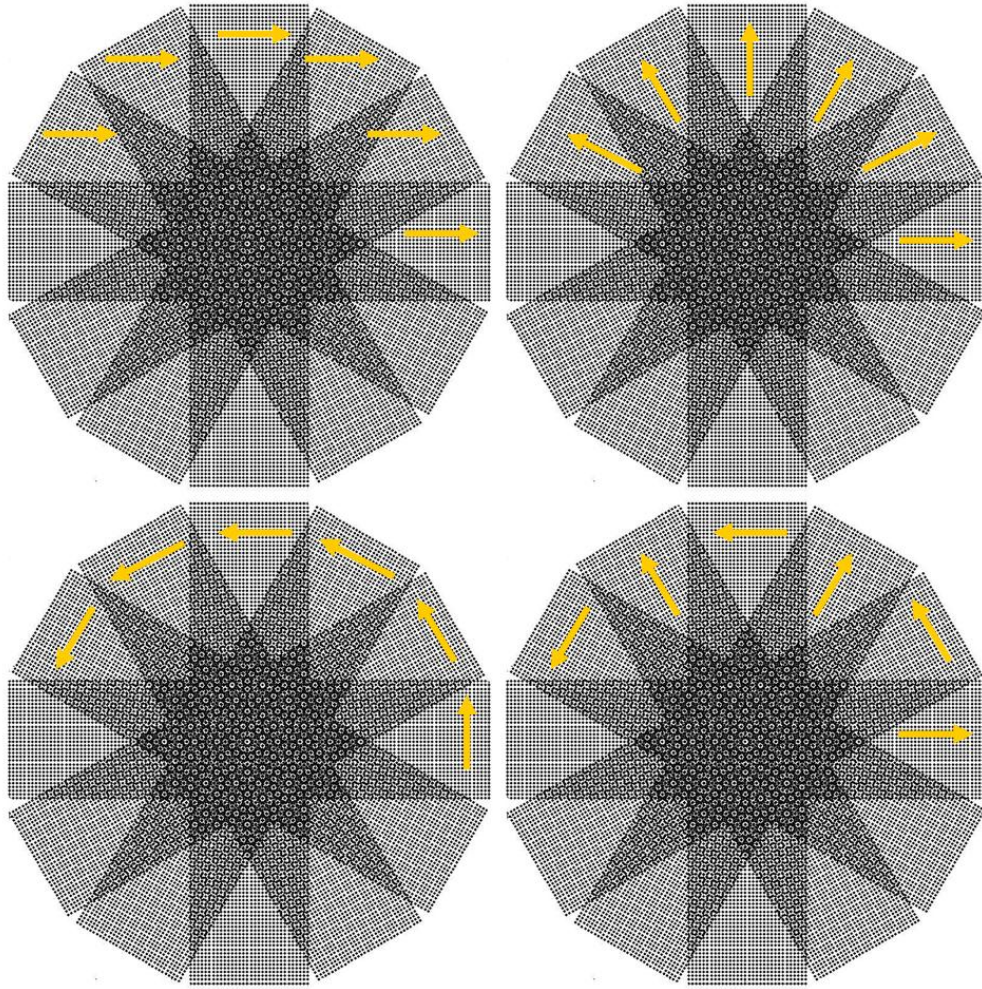


Figure 6-1 Various diffusion weighting schemes used. Direction of DW indicated by the arrows. Standard fixed DW shown in one direction, DW_{fix} (top left), rotating DW aligned to blade readout direction, DW_{ro} (top right), rotating DW aligned to blade phase encoding direction, DW_{pe} (bottom left), and rotating DW alternating in blade readout and phase encoding direction, DW_{alt} (bottom right).

In conventional DWI with DW in three orthogonal directions, the effective b-value for any one direction using a PGSE DW preparation with trapezoidal gradients is given by Eqn 2.5. In rotating DW, the total effective **b**-tensor at the central overlapping region in k-space is the average of **b** from each blade, while that in the peripheral regions of k-space are an average of the combinations of **b** from the respective overlapping blades at a given region in k-space.

Rotating DW, as seen in DW_{ro} and DW_{pe} , reduces the DW in a given fixed direction according to the blade angle. From the b-value equation using trapezoidal DW gradients (See Eqn 2.5), it can be seen that b is proportional to G^2 . As **G** rotates by θ , then b in a given fixed direction in each blade will be modulated by $\cos^2(\theta)$. Taking the vector mean over all

angularly equidistant blades will lead to a nett effective b-value as described in Eqn 6.1. At the same time, it is necessary to apply DW in the slice select direction. Since this is constant across all blades, then b_{ss} is half the value of b_{ro} and b_{pe} . For a more thorough analysis of rotating b-values, refer to Section 6.3.6.

$$b_{xx} = b_{yy} = b_{zz} = \frac{1}{2} b_{ro} = \frac{1}{2} b_{pe} = b_{ss} \quad 6.1$$

Where b_{xx} , b_{yy} and b_{zz} are the effective averaged b-values in the final image, and b_{ro} , b_{pe} and b_{ss} are the maximum nominal b-values applied across individual blades.

As a result of the application of concurrent gradients in multiple axes, the effective b-value in PROPELLER can be increased by a factor of 50% over standard PGSE DW schemes in a single direction using the same maximum gradient strength. A look at the DW gradients in Figure 6-2 shows the rotational modulation of the in-plane DW gradients while DW through-plane remains constant across all blades. The figure features a DW_{ro} scheme. Since the focus is on the DW scheme with respect to the PROPELLER k-space sampling, it excludes all pulse sequence features other than the DW gradients for clarity, and concatenates DW from 12 rotating blades. The DW scheme was a PGSE preparation, with the second lobe on every blade inverted in polarity to account for the effect of the 180° refocusing pulse. The effective 3D projection of the combined gradients G_x , G_y and G_z is illustrated in Figure 6-3, where each of the 12 rotating lines corresponds to the projection of DW in one blade in the PROPELLER acquisition.

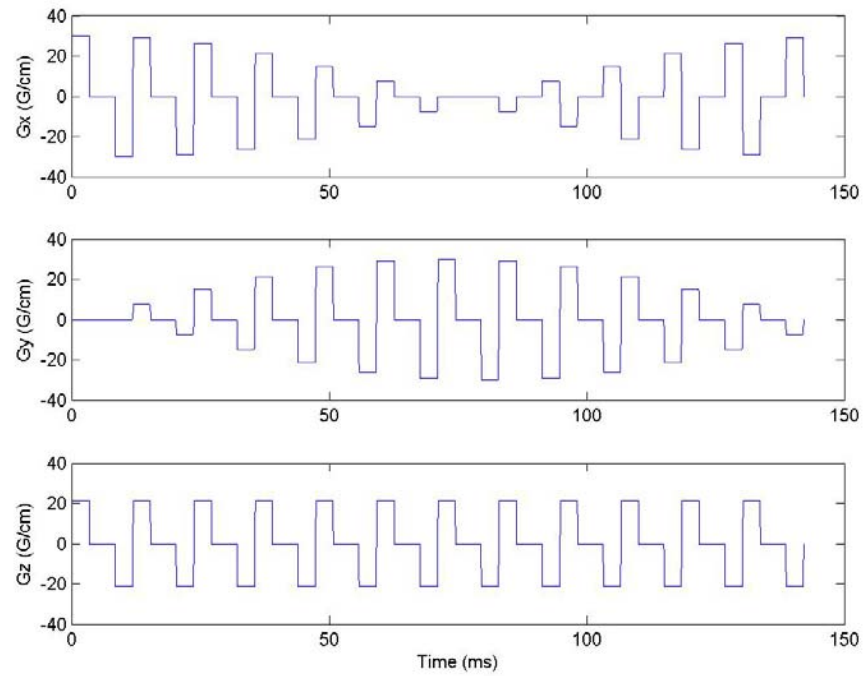


Figure 6-2 Example of rotating DW_{ro} scheme on DW gradient behaviour with respect to the fixed scanner frame of reference. Rotational modulation of the in-plane DW gradients can be seen while through-plane DW gradients remain constant.

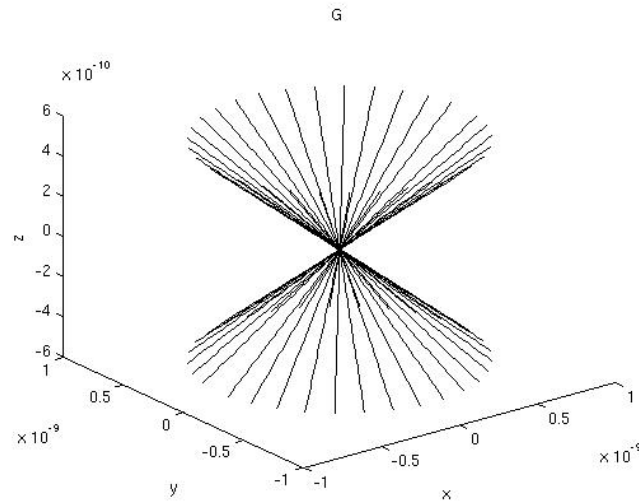


Figure 6-3 3D projection of effective isotropic DW at the central part of k-space where PROPELLER blades overlap.

6.2.2 Comparison of DW Schemes

A number of single-shot isotropic DW schemes have been described. These however make use of extended DW preparation periods to obtain isotropic DW and eliminate off-diagonal terms. At 9.4T, short T_2 predicates the use of short TEs, and hence DW preparation. The most efficient method to do so is by using the PGSE method where two unipolar DW gradients are separated by a delay, Δ . The averaging of $\mathbf{b}$ in the multiple rotated blades is then used to cancel out the effect of off-diagonal terms.

A simulation of five DW preparation schemes was created to examine the time necessary to achieve a specified b-value. These were PGSE, a single bipolar pulse, a double bipolar pulse, a double bipolar pulse with in-plane and through-plane gradients staggered in time and the multiple bipolar method by Mori, et al. (36). The maximum gradient strength was applied in all cases which was 30G/cm, with a zero-max slew time of 0.13ms, to achieve a b-value of 800s/mm².

6.2.3 Tumour ADC Simulations

The mean ADC simulations as described in Section 5.2.2 were used to simulate the effects of rotating DW gradients. The object consisted of a number of tumour lesions of varying geometries, embedded in GM. GM principal diffusivity was oriented in-out of the page and tumour principal diffusivity was oriented left-right. All reconstructed matrix sizes were 256 x 256, using $b=800\text{s/mm}^2$ for fixed DW and $b=1200\text{s/mm}^2$ for rotating DW schemes. This was due to the 50% higher b-values achievable for the same maximum gradient strength, using concurrent DW gradients along multiple axes. This matched in-vivo experiments, and the difference in measured ADC due to different b-values should be minimal in simulations without noise. Off-diagonal terms were set to zero and ESP=5.38ms. In the case where the DW gradients were aligned to the blade, the value of θ as used in Eqn 5.6 remained constant across all blades (ie. $\theta_{\text{DW(ro)}}=0$, $\theta_{\text{DW(pe)}} = \pi/2$). For alternating rotating diffusion, $\theta_{\text{DW(alt)}}$ alternated between 0 and $\pi/2$ between successive blades.

i) For each of the four DW schemes as given in Figure 6-1, the effects of blade width on the image fidelity and accuracy of the mean ADC were first simulated neglecting T_2 . Blade widths were 1, 2, 4, 8, 16, 32 and 64. The corresponding number of blades used was 384, 192, 96, 48, 24, 12 and 6. In rotating DW acquisitions, wider blades contain a larger central (and isotropically weighted) overlap and may produce results that are less sensitive to geometry and anisotropy effects. The experiment was repeated with centric phase encoding with

effective TE=28ms and linear phase encoding with minimum effective TE = 28, 28, 33.4, 44.1, 87.2, 109 and 195ms respectively.

ii) Next, the relationship between the FA and measured ADC was examined for the four DW schemes. FAs between 0 and 1 were used, in steps of 0.1. The matrix size was 256 x 8 x 48. As FAs in-vivo are widely variable, ideally this dependence would be minimal. However, increasing FAs are anticipated to be directly related to the error in the measured ADC, particularly in regions near the edges of tissue which have more high spatial frequency content. The simulation was repeated with T_2 to better appreciate in-vivo behaviour at 9.4T. Centric phase encoding with TE=28ms and linear phase encoding with TE=44.1ms were used.

iii) In order to separate the effects of tissue geometry and the direction of tissue principal diffusivity, the principal diffusivities in a number of tumour regions were changed from the left-right direction to the up-down direction. Subsequently, the principal diffusivity of the GM was changed from the in-out direction to the left-right direction. The simulations in (ii) were repeated without T_2 using exactly the same parameters.

iv) Having identified the rotating DW scheme that was least dependent on tissue geometry and FA, the FA-ADC relationship of this scheme was characterized over a range of practical blade widths, 8, 16, 24 and 32. Corresponding blade numbers were 48, 24, 16 and 12. Simulations were tested without T_2 , and with T_2 with centric phase encoding and TE=28ms, and linear phase encoding and TE=44.1ms. This helped optimise the combination of blade configuration, DW scheme and phase encoding for use in in-vivo experiments.

6.2.4 Animal Studies

The DW-FSE-PROPELLER sequence with PGSE DW preparation (See Section 5.2) was used to acquire in-vivo mouse DW data on the 9.4T MRI scanner (Varian, Palo Alto, CA), with the gradient coil and RF coil setup as described in Chapter 3. 8 healthy wildtype C57/Bl6 mouse datasets were acquired in-vivo, in accordance to local IACUC guidelines. Experiments were performed at the Lab of Molecular Imaging, Singapore Bioimaging Consortium, Singapore. Brain data were acquired with animals secured with a nosecone and bitebar. Anaesthesia was induced with 3.5% isoflurane and maintained at 1-1.5% isoflurane in a 55%:45% mixture of N_2 : O_2 . Respiration was monitored using an air pillow transducer and controlled between 60-80 breaths/min. Animals were free breathing. Body temperature was measured using a rectal probe and maintained at 36.5°C by circulating warm air.

Each animal was scanned in the brain using the following DW schemes: DW_{fix} , DW_{ro} , DW_{pe} and DW_{alt} with linear and centric phase encoding schemes. All sequences used $TR=4000ms$, $ETL=8$, $ESP=5.38ms$, $FOV=25.6 \times 25.6mm$, acquisition matrix= $128 \times 8 \times 32$, reconstructed matrix= 128×128 , thickness= $1mm$, gap= $0.5mm$, slices= 5 , slice order=interleaved, orientation=axial, averages= 1 and readout bandwidth= $208kHz$. $TE_{centric}=28ms$ and $TE_{linear}=44.1ms$.

For fixed DW, one image was acquired at nominal $b=30s/mm^2$ and three images with DW along the fixed x, y and z directions respectively were acquired with nominal $b=800s/mm^2$. For rotating DW, one image was acquired at nominal $b=30s/mm^2$, and two images with DW along the rotating RO and PE directions respectively, were acquired with $b=1200s/mm^2$. These were used to separately reconstruct ADC maps for DW_{ro} and DW_{pe} schemes using the same b_0 image. The DW_{alt} scheme was reconstructed using alternate blades from these two DWI datasets.

The DW_{alt} scheme should alternate the DW along the RO and PE directions within a single scan, however due to technical limitations at the time, the DW images acquired using the DW_{ro} and DW_{pe} schemes were acquired consecutively, and so were separated by the time required to obtain one image, that is 2m 10s. It was assumed that the difference in remaining magnetization between the DW_{ro} and DW_{pe} schemes at the end of each TR was negligible due to the strong DW and long TR of 4s. Consequently, the extraction of alternate blades from the above two schemes to form the DW_{alt} image was felt to be reasonable. Acquisition times for DW_{fix} was 8m 40s and effectively half that in any of the rotating DW schemes.

From these experiments, the mean ADC was measured in ROIs in WM and GM. ROIs were manually drawn for each subject, in a manner described in Section 3.2.3. SNR, contrast and AP of the ADC measurements were found to determine the consistency of the ADC data. Contrast was calculated by the difference between ADC_{GM} and ADC_{WM} . P-values were cited using one way ANOVA and $p<0.05$ was used to determine if a result was significant.

The rapidity and robustness to motion of DW_{rot} methods, led me to consider their potential application in whole body screening of tumour metastases. To do this, a collaboration was established with a group at the Singapore Immunology Network (SIgN), Singapore. Four metallothionein (MT)-ret/AAD mouse models of spontaneous melanoma (179) were obtained from SIgN. Whereas anisotropy is clearly defined in the brain and white matter, the

heterogeneous nature of spontaneous tumour growths suggest that anisotropy effects arising from the different DW schemes will be more subtle. The scans described above were repeated using the MT-ret/AAD mice to see how well tumour regions could be distinguished using the ADC, and to investigate the effect of unknown tissue anisotropy on the DW_{rot} reconstruction. Parameters were identical to those used in the healthy mouse experiments. Here, ADCs were measured in ROIs in tumour tissue, and examined in terms of SNR and AP.

6.2.5 Human Studies

Pilot human data were acquired in a cooperative 70 year old, female patient exhibiting acute infarct in the left MCA. Clinical symptoms were dizziness, vomiting and fainting. This work was carried out on a 3T Achieva scanner (Philips, Best, Netherlands) using a whole body transmit coil and an 8-Ch birdcage receive coil. Studies were conducted at the National Neuroscience Institute, Singapore, in accordance to the sequence development protocol under local IRB guidelines.

Experimental parameters were $TR=4000ms$, $FOV=240 \times 240mm$, $Matrix=128 \times 32 \times 6$, $b=1000s/mm^2$, $thickness=4mm$, $gap=6mm$, $slice=transverse$, $number\ of\ slices=9$ and $phase\ encoding=centric$. One experiment was conducted using DW-FSE-PROPELLER and DW_{fix} . The acquisition time was 1m 44s. As the scanner was not readily compatible with using a combination of PROPELLER and rotating DW gradients, an improvised method was used. One b_0 PROPELLER image was obtained followed by a series of six fully sampled (ie. six blades) DW-FSE-PROPELLER images with DW arrayed in six directions as shown by the relative gradient strengths in Table 6.1. Essentially, the DW directions were rotated according to the blade rotation, allowing the extraction of blades that had coincident in-plane DW and k-space orientation. The first blade with $DW_dir=1$ was combined with the second blade with $DW_dir=2$ and so forth to reconstruct a DW_{ro} image. The first blade with $DW_dir=4$ was combined with the second blade with $DW_dir=5$ and so forth to reconstruct the DW_{pe} image. Finally, the DW_{alt} image was reconstructed using alternate blades from the DW_{ro} and DW_{pe} data. The total time to acquire these 1+6 datasets was 2m 56s, however, the theoretical time with properly implemented rotating DW gradients should be 50s, or half that using the DW_{fix} scheme.

DW_dir	Gro	Gpe	Gss
1	1	0	0.71
2	0.87	-0.5	0.71
3	0.5	-0.97	0.71
4	0	-1	0.71
5	-0.5	-0.87	0.71
6	-0.87	-0.5	0.71

Table 6.1 Relative DW gradient strengths arrayed in 6 directions on the Philips 3T scanner in order to extract rotating DW data.

6.2.6 B-tensor simulations

In response to some puzzling experimental results (See Section 6.3.4), the assumption that off-diagonal terms were automatically cancelled using DW_{rot}-PROPELLER was explored using a series of careful calculations. A thorough analysis of **b** was implemented and the evolution of **b** across blades was examined together with the averaged effective **b** at the central overlapping k-space using various DW schemes. These were calculated numerically using Matlab (The Mathworks, Natick, CA) and Eqn 5.2.

The values of **b** including on- and off-diagonal terms were calculated for DW_{ro} and DW_{alt} over a range of blade numbers 6, 12, 16, 24, 32, 48, 64, 96 and 192. DW_{pe} was excluded as it behaved similarly to DW_{ro}, only with the DW gradients along the x and y axes reversed. **b** was also calculated in the same instances with alternating G_z to examine how this approach could minimize off-diagonal terms. The maximum gradient strength specified was 30G/cm with a zero-max slew time of 0.13ms and a desired b-value of 800s/mm². As b-value is related to the square of the cumulative gradients, the magnitude of G_z which does not oscillate with blades, should be equal to $1/\sqrt{2} G_{x,max}$ and $1/\sqrt{2} G_{y,max}$.

6.3 Results & Discussion

6.3.1 Comparison of DW Schemes

DW schemes were simulated based on a desired b-value, for a specified maximum slew rate and gradient strength available. Figure 6-4 illustrates the DW gradients for five different DW schemes, arranged about the refocusing pulse at t=20ms. Out of these, only the method used by Mori, et al. and Chun, et al. applied isotropic DW in a single scan, while the rest relied on multiple blade averaging to achieve effectively isotropic DW. For a start, DW within a single blade is examined.

PGSE DW preparation had the shortest total time for the application of DW, t_{DW} at 11.9ms. This was due to the continued DW through the refocusing pulse whereas all bipolar pulses had zero DW after the second DW lobe of each bipolar pair. The usefulness of this method is mitigated by the generation of cross-terms due to the interaction of the slice refocusing gradient and crushers with the DW gradients, and the imperfect rephasing of the magnetization after the refocusing pulse due to bulk motion and imperfect 180° refocusing pulses.

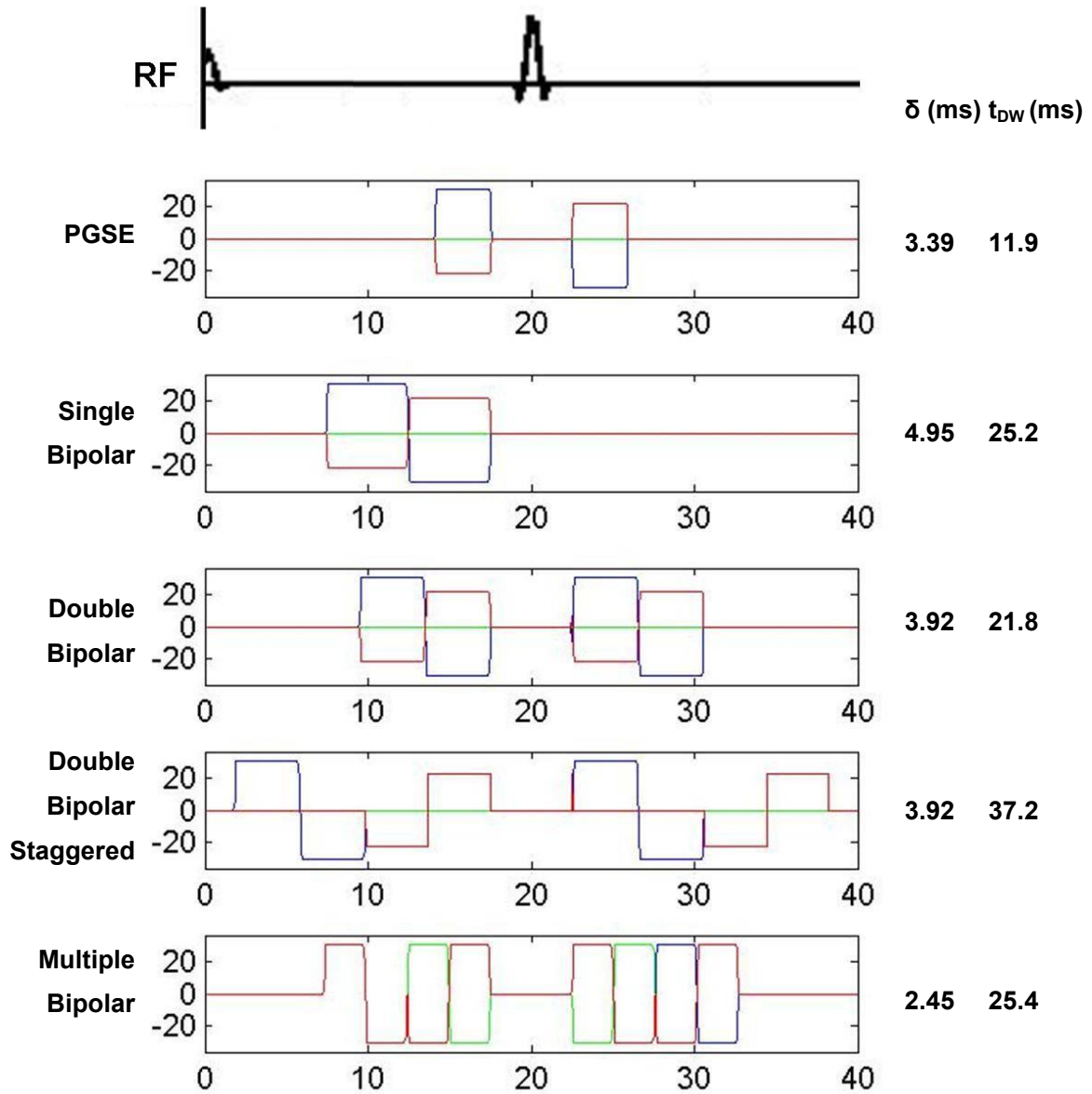


Figure 6-4 DW gradients using various DW schemes presented in a simplified pulse sequence diagram. The excitation and refocusing pulses (top) were set at 0ms and 20ms respectively. The following five rows illustrate DW gradients set about the refocusing pulse using the PGSE, single bipolar, double bipolar, staggered double bipolar and multiple bipolar method respectively. DW gradients along the RO, PE and SS directions are given in blue, green and red respectively. DW gradients after the refocusing pulse were inverted in polarity to illustrate the effect of the refocusing pulse on the effective DW. In all methods, a minimum time of ± 2.5 ms about the refocusing pulse was specified for the refocusing pulse and crushers. The time required for each gradient lobe, δ , and the total time for the application of DW (from the start of the first DW lobe to the end of the last one), t_{DW} , was determined for nominal $b=800\text{s/mm}^2$.

Bipolar methods avoid these problems and have improved resistance to eddy current artifacts (49). The drawbacks being lower DW efficiency and a longer time necessary to acquire equivalent b-values. The single bipolar method had $t_{DW}=25.2\text{ms}$ and did not apply DW between the refocusing pulse and the spin echo. The double bipolar method was more efficient as it used this time to apply another set of DW gradients. Less efficient was the double bipolar method with in-plane and through-plane DW staggered in time. The benefit of this was the avoidance of off-diagonal terms generated through the interaction of the two sets of DW gradients. The final method used multiple bipolar (MBP) pulses (36,170) applied at the maximum DW in each orthogonal direction with alternating polarities. This was the most efficient method to obtain isotropic DW in a single scan but did not take advantage of the rotating gradients in PROPELLER to further reduce t_{DW} .

Assuming that the TE at the first echo could be calculated from t_{DW} plus some arbitrary time, t_{IM} , for the application of the excitation pulse, imaging gradients, crushers and timing delays, the approximate signal decay due to T_2 in the brain at 9.4T can be estimated. If $t_{IM}=10\text{ms}$, then $TE_{1,PGSE}=21.9\text{ms}$ and $TE_{1,MBP}=35.4\text{ms}$. In terms of remaining signal magnitude as a function of T_2 where $T_{2,\text{brain},9.4T}\sim 40\text{ms}$, this corresponds to $S_{1,PGSE}=58\%$ and $S_{1,MBP}=41\%$. In regions in the body with lower T_2 , this signal decay is more severe. The robustness of the motion and phase correction in PROPELLER depends on the quality of data within each blade of each scan, and averaging of multiple blades to improve SNR prior to NUFFT reconstruction is not possible. This imposes a minimum threshold for the quality of data acquired in a single scan. As such the approach taken was to use the PGSE method despite its shortcomings, and avoid the 40% relative SNR penalty using the multiple bipolar method.

6.3.2 Tumour ADC Simulations

Simulations of multiple tumour lesions embedded in GM were constructed to investigate the image fidelity using the various DW_{rot} methods. Figure 6-5 is a colour FA map and serves as a reference image to orientate the reader to the geometry and orientation of principal diffusivities associated with the simulated object.

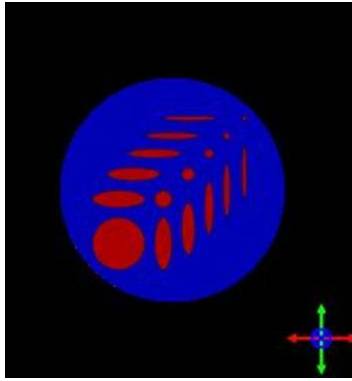


Figure 6-5 Colour FA map of simulated tumours embedded in GM. FA_dir_{ROI 1}=left-right, FA_dir_{ROI 2}=left-right, FA_dir_{GM}=in-out. Tissue FA was 0.38 in both tissues and oriented as indicated. ADC were $0.85 \times 10^{-3} \text{mm}^2/\text{s}$ and $0.59 \times 10^{-3} \text{mm}^2/\text{s}$ respectively. Other parameters listed in Table 5.2.

Figure 6-6 illustrates a transition from radial sampling where $n\text{PE}=1$ to PROPELLER sampling with increasing blade widths up to 64. Radial data suffer a high degree of artifacts associated with spurious ringing artifacts in the PSF, take a longer time to acquire than PROPELLER data and offer limited options for motion correction. PROPELLER using DW_{fix} at $n\text{PE}=8$ and $n\text{PE}=64$ provided good image fidelity. Looking at the centre two images, it was found that local geometry and diffusion anisotropy had an effect on local artifacts and the estimation of the mean ADC, particularly at regions with greater geometric anisotropy, in DW_{ro} and DW_{pe} data. These effects were minimized using a wider blade width of 64 and supported the hypothesis that a wider central overlap would improve the degree of DW isotropy over the final image. Acquisitions with narrower blades, had a smaller central overlap and hence a greater dependence on tissue anisotropy due to the anisotropic DW outside of the central region. When DW_{alt} was used, the artifacts were reduced, suggesting that the alternating DW in the periphery of k-space helped improve the degree of isotropy in DW in this region, due to the effective averaging of the DW.

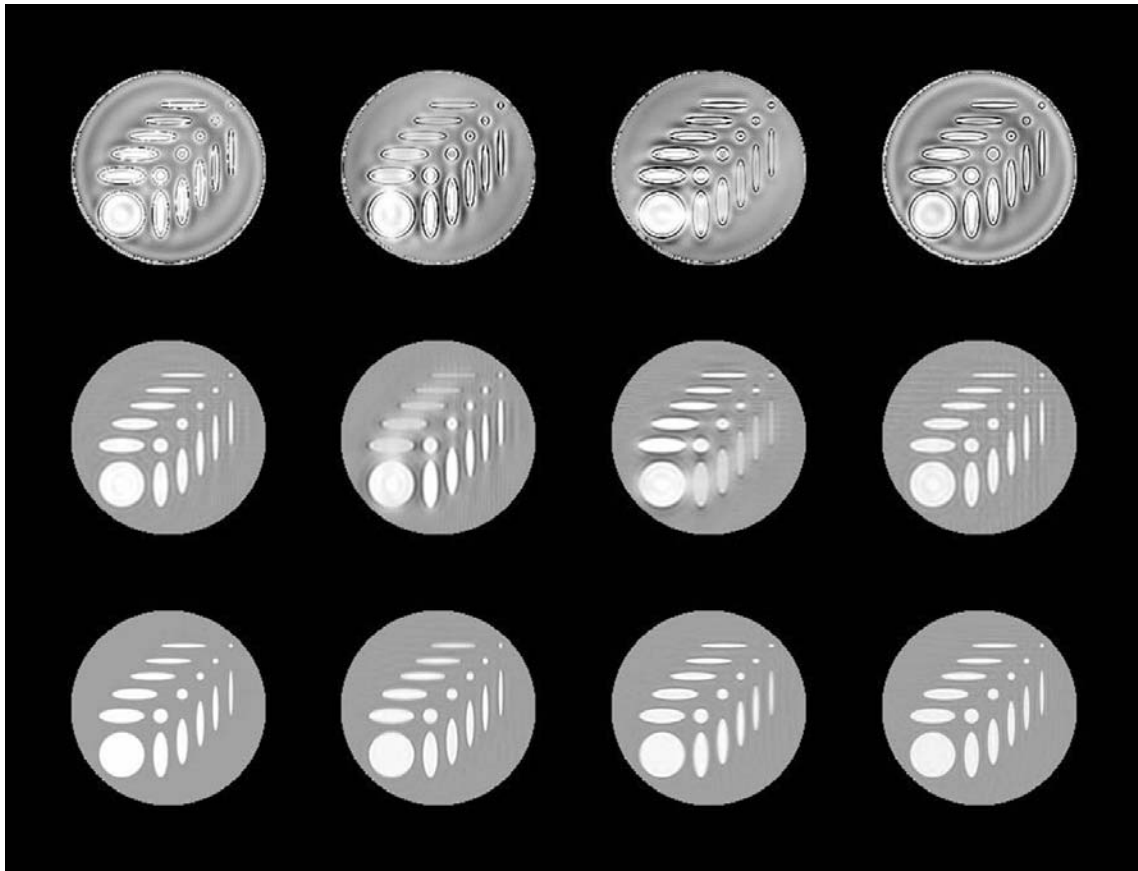


Figure 6-6 Mean ADC images reconstructed using various blade widths and DW schemes. From top to bottom row, $nPE=[1, 8, 64]$, and from left to right, DW Scheme= $[DW_{fix}, DW_{ro}, DW_{pe}, DW_{alt}]$. T_2 , motion and noise were neglected. The $nPE=1$ acquisition was effectively a radial acquisition.

These simulations were repeated over a range of blade widths from 1 to 64, and the mean ADC data from ROIs 1 & 2 (See Figure 5-2) are presented in Figure 6-7. It was found that the ADCs measured using DW_{fix} and DW_{alt} schemes were fairly independent of tissue geometry, and discounting blade widths < 8 due to artifacts in the PSF, both ROIs demonstrated a consistent slight overestimation of the nominal ADC value of $0.85 \times 10^{-3} \text{mm}^2/\text{s}$. With DW_{ro} , ROI 1 exhibited a greater overestimation of the ADC that diminished at wider blade widths. ROI 2 exhibited an underestimation of the ADC that also diminished at wider blade widths. The reverse behaviour was observed using DW_{pe} . In all cases, the ADC obtained with blade widths < 8 were unreliable due to reconstruction artifacts.

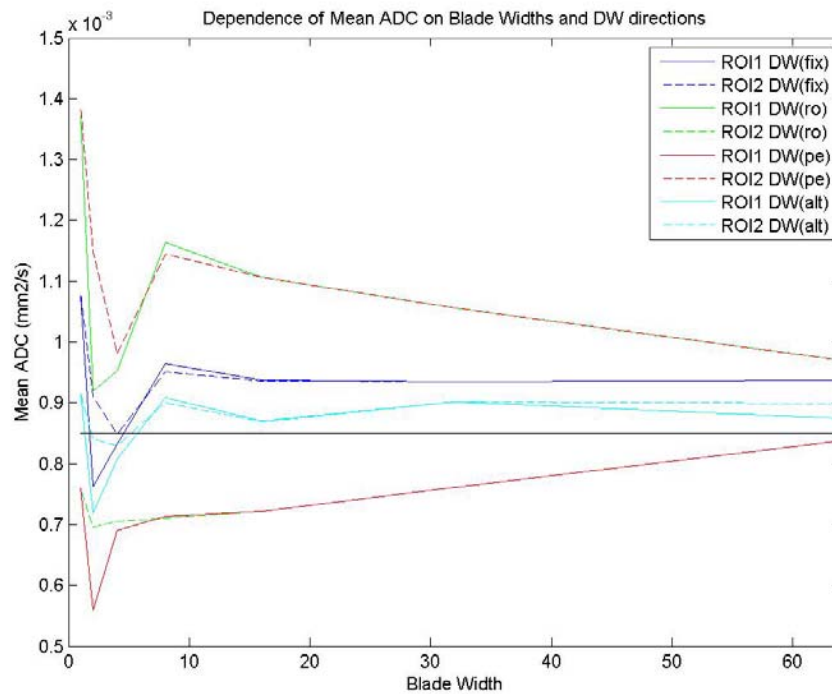


Figure 6-7 Dependence of the mean ADC on blade widths and DW scheme. ADCs in ROIs 1 & 2 reflect a dependence on tissue geometry and anisotropy. T_2 , motion and noise were neglected.

The variation in ADC can be explained by the relationship between the orientation of tissue geometry, tissue anisotropy and the diffusion weighting direction. Using a DW_{ro} scheme, consider first ROI 1. Its narrow horizontal profile and sharp vertical edges meant that it was more greatly influenced by high spatial frequencies in the horizontal direction, corresponding to the data at the left and right sides of k-space. DW in the readout translated to DW along the horizontal direction at the left and right of k-space, and in the vertical direction at the top and bottom of k-space. Signal decay due to DW is greatest when the orientations of the DW and the tissue principal diffusivity are aligned, which here lay in the left-right direction. Hence, in tissues with principal diffusivities oriented left-right, a reduced signal was observed at the left and right of k-space and a raised signal was observed at the top and bottom of k-space. Since the signal from ROI 1 was determined to a greater degree by the left and right regions of k-space, that led to an enhanced signal loss that corresponded to an overestimated mean ADC. The reverse was true for ROI 2, as it was influenced more greatly by the top and bottom portion of k-space, and thus the ADC was underestimated.

In the DW_{pe} scheme, the direction of DW with respect to location in the periphery of k-space was reversed, leading to the opposite effect seen in DW_{ro} . The greater signal loss due to

diffusion now corresponded to the top and bottom of k-space. Where the geometry was more influenced by k-space in this region (ROI 2), then greater signal loss was observed and a hyperintensity in the ADC images was observed. In both DW_{ro} and DW_{pe} , ADC measurements improved in accuracy with wider blade lengths reflecting the improving degree of isotropy associated with a greater central region of k-space overlap.

When the DW_{alt} scheme was used, the slow rotational modulation in effective DW at the k-space periphery was replaced by a rapid modulation across each blade. The corresponding effect was an averaging of the effective DW in these regions which improved the isotropy of the DW and reduced the errors in ADC estimation.

Another observation was that the GM adjacent to tumour lesions exhibited deviations as well from their nominal mean ADC. Returning to the example looking at using DW_{ro} , a decreased ADC in the GM at the left and right edges of tumours was accompanied by an increased ADC at the top and bottom edges of tumours. This enhanced and diminished GM-tumour contrast accordingly, depending on their location with respect to the tumours. Since the principal diffusion direction in GM was aligned through-plane, the rotating DW would not be expected to directly affect the measured ADC in the GM. However, it would seem that the anisotropies in the ROIs do have an effect on the regions adjacent to them. In more consistent data with wider blades, the modulation in ADC in the GM was considerably reduced.

The dependence of ADC on blade width and DW scheme was repeated in the presence of T_2 at 9.4T with centric phase encoding and linear phase encoding. These are given in Figure 6-8 & Figure 6-9. In general, the data were consistent with the data without T_2 , in that DW_{ro} and DW_{pe} variably overestimated and underestimated the nominal ADC in ROIs 1 & 2 depending on the orientation of the tumour geometry. DW_{fix} and DW_{alt} produced intermediate results that were more independent of tumour geometry.

In centric phase encoding, there appeared to be a general bias towards underestimating the mean ADC whereas in linear phase encoding, there appeared to be a bias towards overestimating the mean ADC. These effects were directly related to the blade width and T_2 and were sensitive to object geometry and the differences in T_2 in GM and tumour tissue. In addition, wide blades meant that linear phase encoding methods led to impractically long effective TEs of 195ms as in the case of blade width=64.

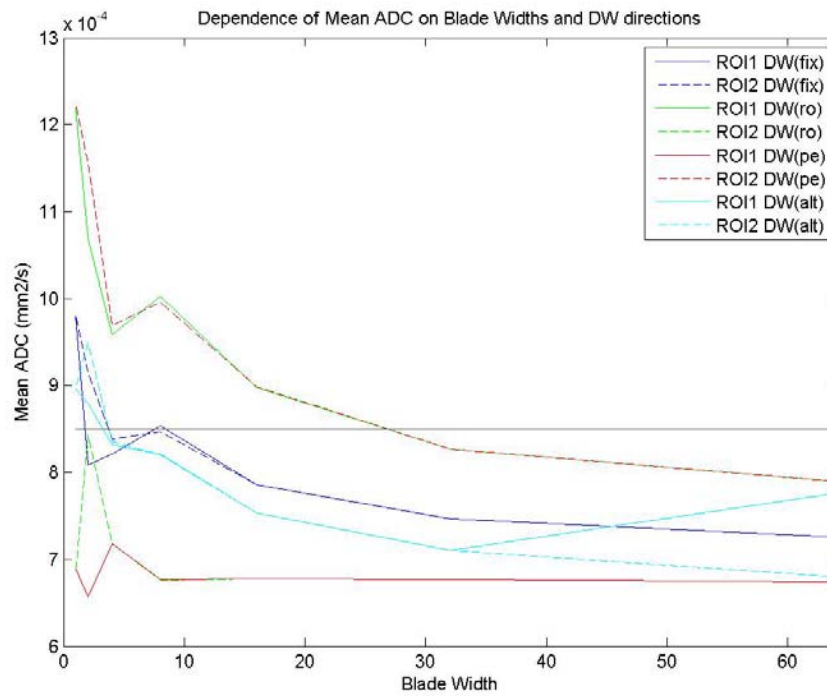


Figure 6-8 Dependence of the mean ADC on blade widths and DW scheme using centric phase encoding at 9.4T. $TE_{\text{eff}}=28\text{ms}$. Motion and noise were neglected.

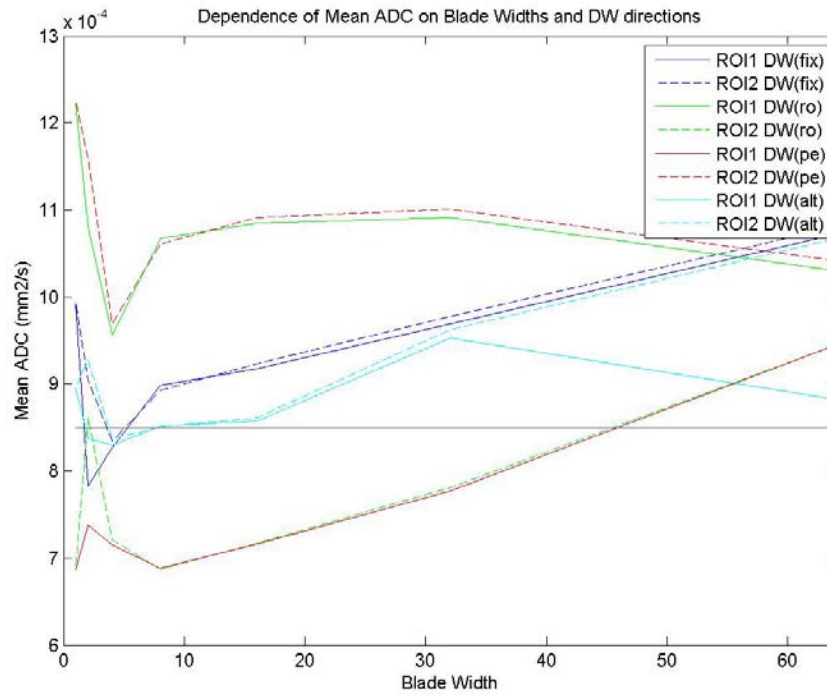


Figure 6-9 Dependence of the mean ADC on blade widths and DW scheme using linear phase encoding at 9.4T. $TE_{\text{eff}}=44.1\text{ms}$. Motion and noise were neglected.

A blade width of 8 was selected based on minimizing the error in the ADC measurement in the DW_{fix} and DW_{alt} schemes, without introducing PSF artifacts due to excessively narrow blade widths. This modest blade width and corresponding ETL was feasible at 9.4T without too severe T_2 and provided better motion and phase correction than radial sampling methods. Images using a blade width of 8 with no T_2 , and T_2 with centric and linear phase encoding are displayed in Figure 6-10. Effective TEs in the latter two cases were 28ms and 44.1ms. Images were slightly blurred as a function of T_2 , but in general displayed the same properties as data previously discussed.

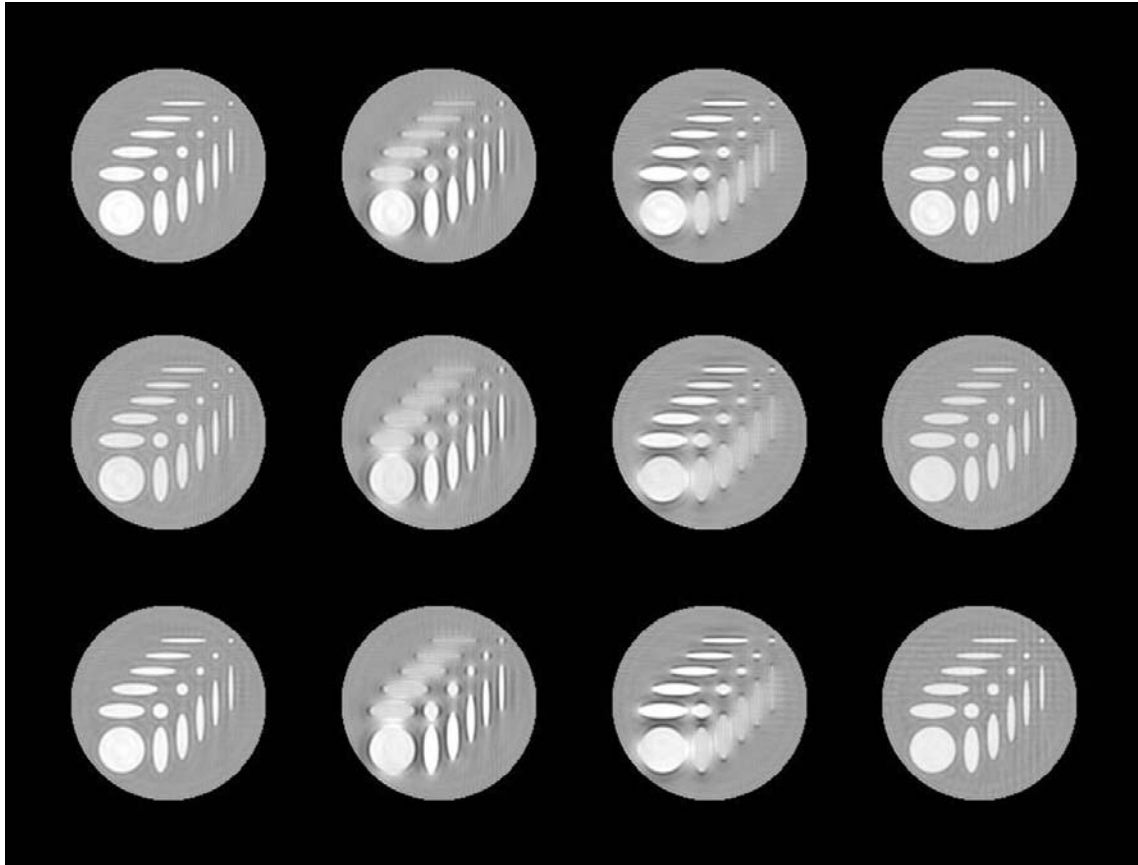


Figure 6-10 Mean ADC images reconstructed using various phase encoding and DW schemes. From top to bottom row: [No T_2 , T_2 with centric phase encoding at 9.4T, T_2 with linear phase encoding at 9.4T] and from left to right, DW Scheme=[DW_{fix} , DW_{ro} , DW_{pe} , DW_{alt}]. Matrix=256 x 8 x 48. Motion and noise were neglected.

Another set of simulations investigated the effects of the degree of anisotropy on the measured ADC. Using the same four DW schemes, tumours of varying FA values were simulated. Orientations of principal diffusivities and other tissue properties were otherwise

unchanged. Figure 6-11 shows images with tumours of varying anisotropies using the four DW schemes.

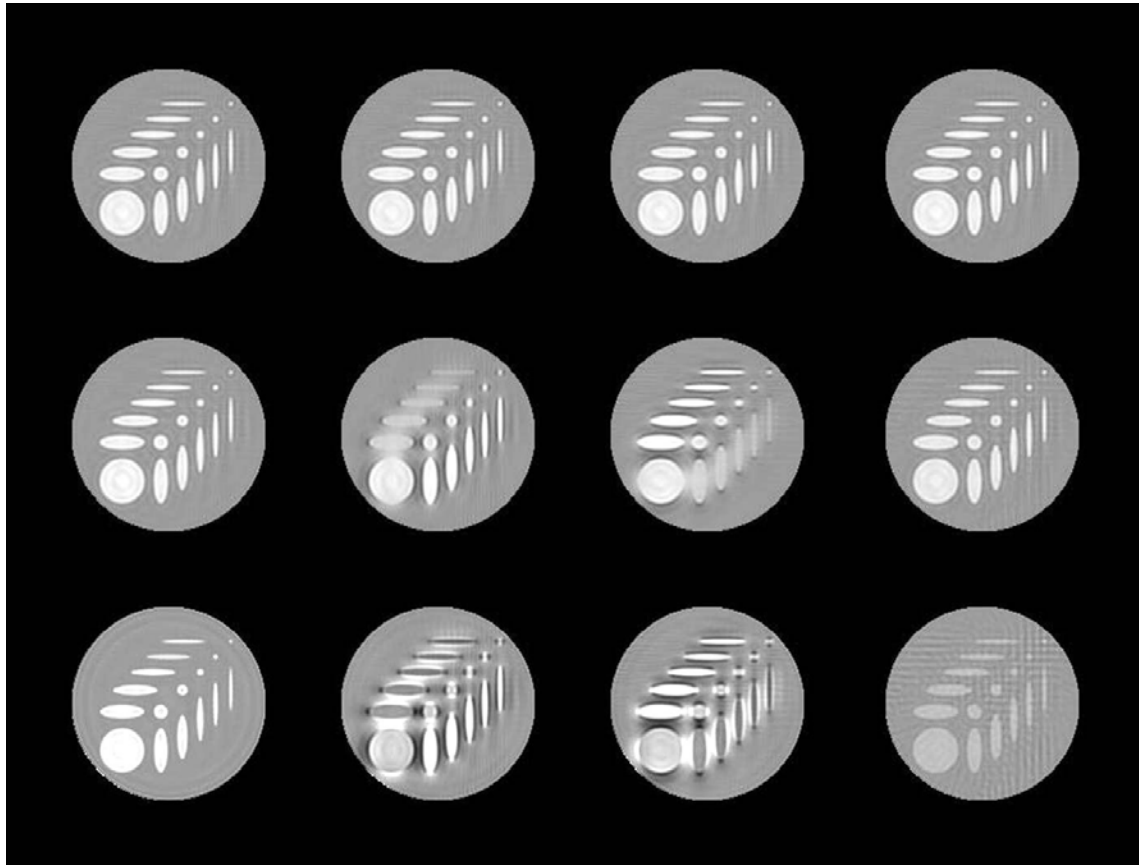


Figure 6-11 Mean ADC images reconstructed using various FAs and DW schemes. From top to bottom row, FA=[0, 0.4, 0.8] and from left to right, DW Scheme=[DW_{fix}, DW_{ro}, DW_{pe}, DW_{alt}]. Matrix=256 x 8 x 48. T₂, motion and noise were neglected.

It can be seen that FA introduces minimal artifacts in the DW_{fix} data at physiological FAs. Increasing FA however in DW_{ro} and DW_{pe} acquisitions, greatly enhanced the anisotropic DW in the periphery of k-space, leading to an enhancement in errors in mean ADC estimation. In DW_{alt}, the ADCs in tumours were progressively underestimated with FA, and there was an enhancement in streaking artifacts arising from increasingly severe rotational modulation of the signal in k-space.

Mean ADC was measured in a series of simulations with FAs ranging from 0 to 1 with (i) no T₂, (ii) T₂ at 9.4T with centric phase encoding and effective TE=28ms, and (iii) T₂ at 9.4T with linear phase encoding and effective TE=44.1ms. The results are given in Figure 6-12, Figure 6-13 & Figure 6-14 respectively.

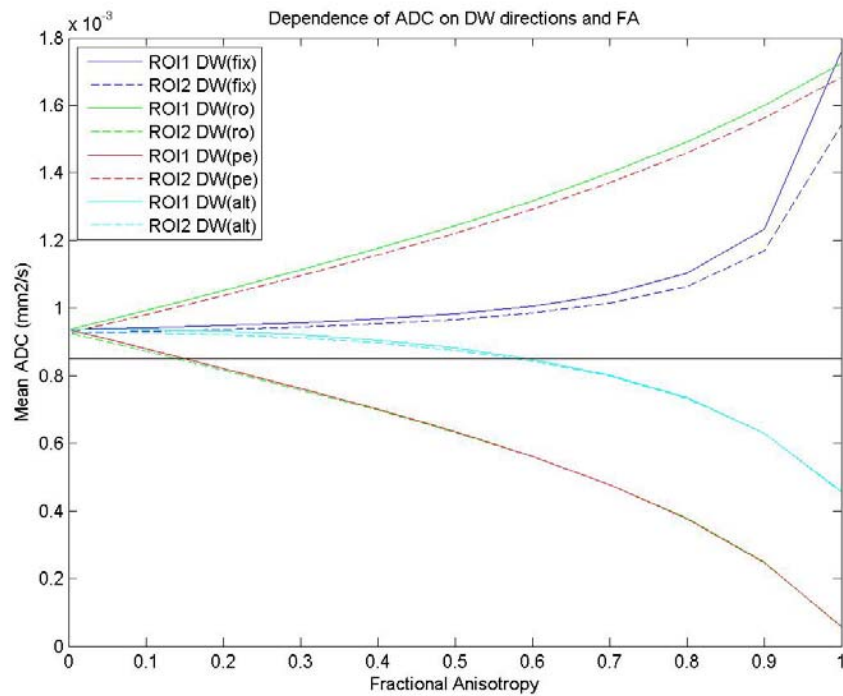


Figure 6-12 Dependence of the mean ADC on FA and DW scheme. Matrix=256 x 8 x 48. T₂, motion and noise were neglected.

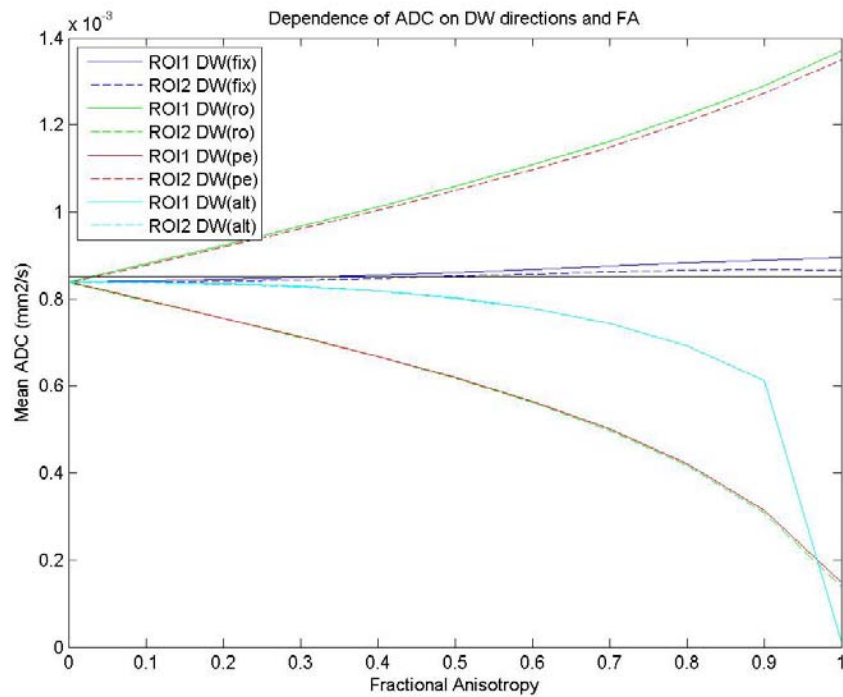


Figure 6-13 Dependence of the mean ADC on FA and DW scheme. Matrix=256 x 8 x 48, centric phase encoding, TE_{eff}=28ms. Motion & noise were neglected.

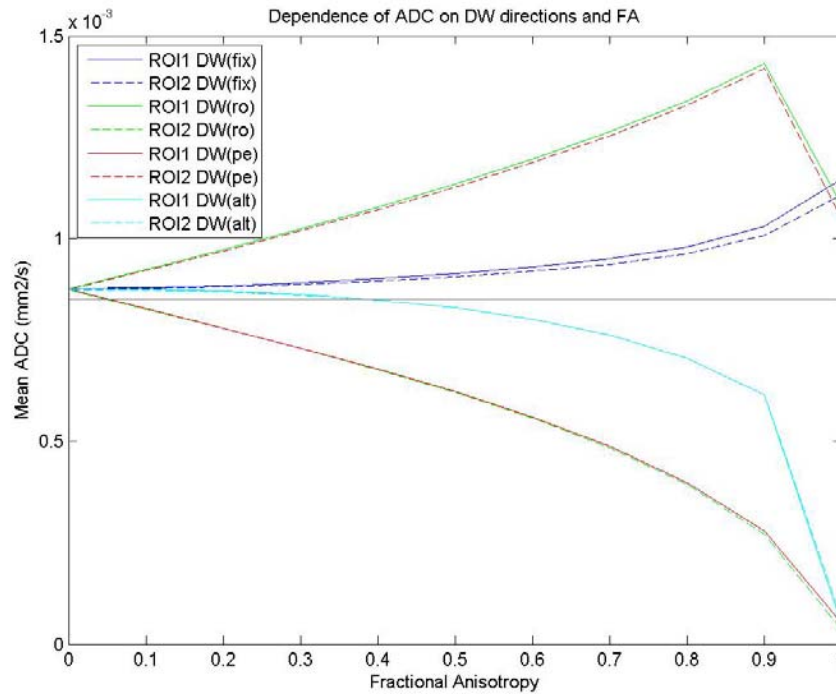


Figure 6-14 Dependence of the mean ADC on FA and DW scheme. Matrix=256 x 8 x 48, linear phase encoding, $TE_{eff}=44.1ms$. Motion & noise were neglected.

As with the earlier data, DW_{ro} and DW_{pe} resulted in ADC measurements that were sensitive to the geometry of the measured tissue. That is, errors in ADC measured in ROI 1 & 2 were inversely related to one another. DW_{fix} and DW_{alt} continued to demonstrate relative insensitivity to geometry effects. In all cases, deviation from the nominal ADC was enhanced at higher FAs. This was consistent with the reasoning that rotating DW in the presence of anisotropic tissues led to anisotropic DW. It was also consistent with the increased errors in interpolation and reconstruction when dealing with tissues of high FA using DW_{fix} methods (See Section 5.3.2). This dependence on FA was consistent with previous data using radial sampling methods (172). However, previous simulations had only simulated FA values of up to 0.5, and did not investigate the potential of DW_{alt} .

At a physiological FA value in GM of 0.4 with realistic T_2 , it was found that centric phase encoding with DW_{fix} maintained an error in ADC estimation of under +1%, while DW_{alt} resulted in a maximum error of -4%. At FA=0.8, the errors rose to up to +4% and -20% respectively.

To isolate the effects of the orientations of tissue geometry and anisotropy, the simulations were repeated, changing the direction of principal diffusion in five tumour regions from the left-right orientation to the up-down orientation. These include ROI 1 and are given in Figure 6-15.

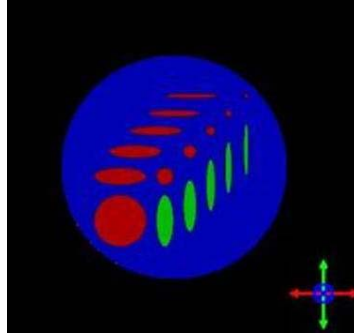


Figure 6-15 Colour FA map of simulated tumours embedded in GM. $FA_{dir_{ROI\ 1}}=up-down$, $FA_{dir_{ROI\ 2}}=left-right$, $FA_{dir_{GM}}=in-out$.

Reconstructing a series of images using the four DW schemes, over a range of FAs produced Figure 6-16. The behaviour in the data acquired with DW_{fix} and DW_{alt} were visually identical to the original object with all tumour principal diffusivities oriented left-right. In contrast, the ADCs measured in tumours with up-down orientations of principal diffusion using DW_{ro} and DW_{pe} , had their errors reversed, and the ADCs now resembled the opposite set of horizontally aligned tumours with left-right principal diffusivities.

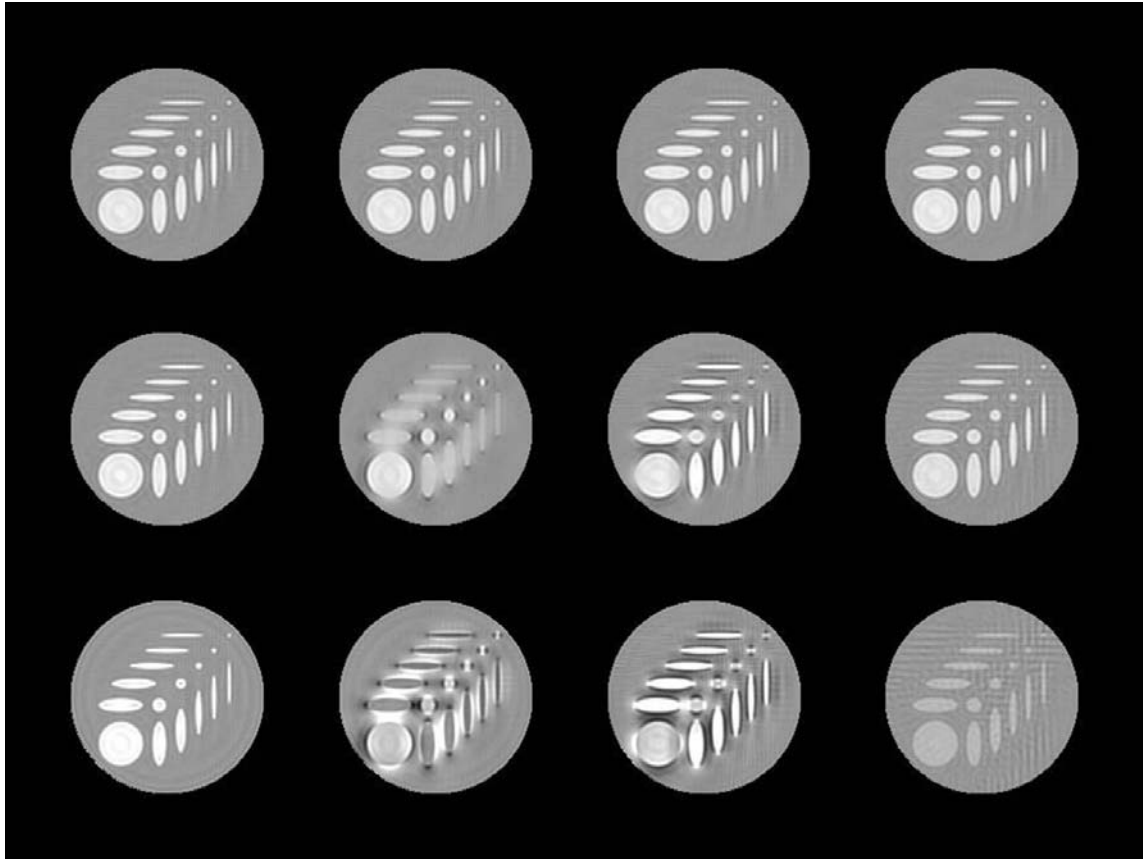


Figure 6-16 Mean ADC images reconstructed using various FAs and DW schemes, with direction of tumour principal diffusivity defined in Figure 6-15. From top to bottom row, $FA=[0, 0.4, 0.8]$ and from left to right, DW Scheme= $[DW_{fix}, DW_{ro}, DW_{pe}, DW_{alt}]$. Matrix= $256 \times 8 \times 48$. T_2 , motion and noise were neglected.

Figure 6-17 illustrates the behaviour of ADC estimation using the four DW schemes over FAs ranging from 0 to 1, without T_2 , and for the case that the vertically aligned tumour regions possess vertically aligned principal diffusivities. The effect of changing the principal diffusion direction in ROI 1 can be clearly seen in the reversal of its error in ADC estimation, using both DW_{ro} and DW_{pe} .

In the case of DW_{ro} , this can be explained by the fact that the tissue geometries are now aligned with the directions of principal diffusivity. Thus for a tumour region oriented vertically (ROI 1), the major influence to its signal intensity arises from the left-right regions of k-space. However, these areas now see a reduced DW due to the orthogonal relationship between the applied DW in the blade readout and the up-down principal diffusivity in the tissue. This leads to lower signal loss and an underestimation of the mean ADC. The same applies for ROI 2 and tissues aligned horizontally with left-right orientations of principal diffusivity.

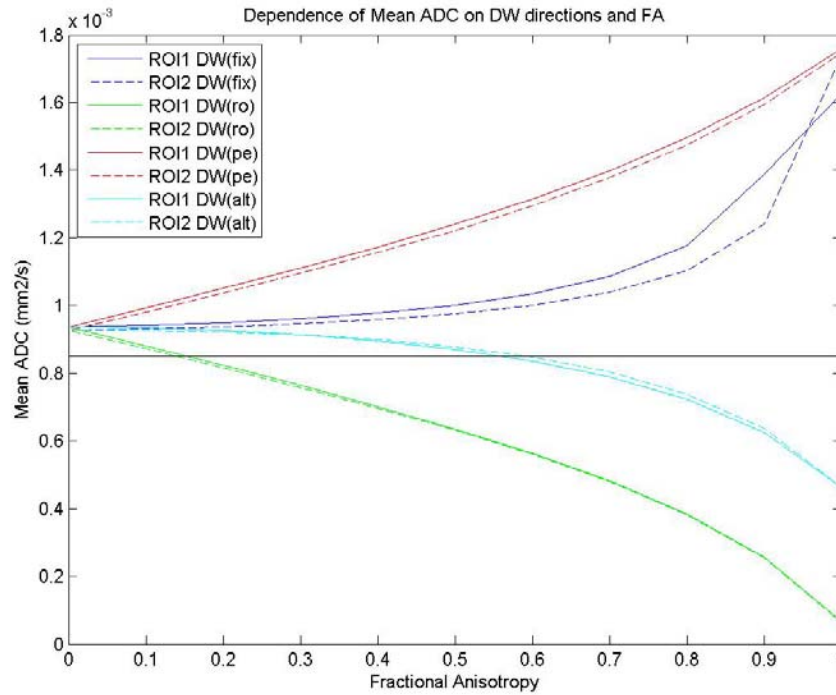


Figure 6-17 Dependence of the mean ADC on FA and DW scheme. Matrix=256 x 8 x 48. FA_dir_{ROI 1}=up-down, FA_dir_{ROI 2}=left-right, FA_dir_{GM}=in-out. T₂, motion and noise were neglected.

These data showed that the sign of the errors were not determined by the absolute tissue geometry or orientation of principal diffusivity with respect to the rotating DW direction, but by the relative dependence of all three. As a rule of thumb, using DW_{ro} will result in an FA-dependent overestimation of the mean ADC for tissues with orthogonal geometry and principal diffusivity, and an underestimation of the mean ADC in tissues with collinear geometry and principal diffusivity. Using DW_{pe} leads to the opposite effect where tissues with orthogonal geometry and principal diffusivity will exhibit underestimated ADCs, and tissues with collinear geometry and principal diffusivity will exhibit overestimated ADCs.

Acquiring the same data, with a different orientation of GM principal diffusivity based on Figure 6-18, yielded images similar to those in Figure 6-16.

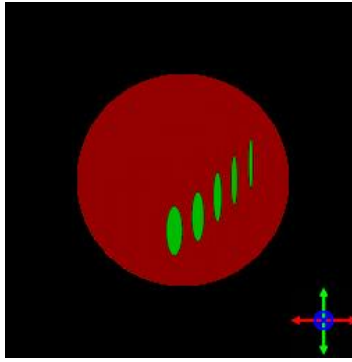


Figure 6-18 Colour FA map of simulated tumours embedded in GM. FA_dir_{ROI 1}=up-down, FA_dir_{ROI 2}=left-right, FA_dir_{GM}=left-right.

However, there were further variations to the ADC as estimated with DW_{ro} and DW_{pe} methods and given in Figure 6-19. Looking at DW_{ro} , it was observed that the ADC in ROI 1 was underestimated and the ADC in ROI 2 was overestimated relative to data in Figure 6-17. Since the GM principal diffusivity was oriented left-right, and its large and varied geometry meant that its signal contribution was spread across k-space, that compounded the signal loss as contributed by tumours with left-right principal diffusivity (ROI 2), increasing the mean ADC observed relative to that in Figure 6-17. The reverse was true for ROI 1 whose own contribution to the signal loss was negated in part by that of the GM, reducing the measured ADC.

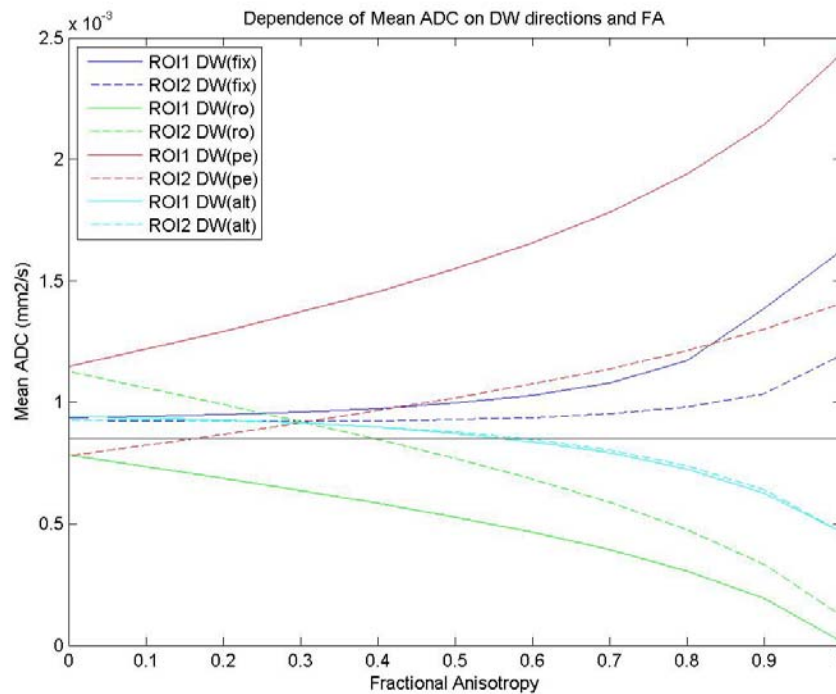


Figure 6-19 Dependence of the mean ADC on FA and DW scheme. Matrix=256 x 8 x 48. FA_dir_{ROI 1}=up-down, FA_dir_{ROI 2}=left-right, FA_dir_{GM}=left-right. T₂, motion and noise were neglected.

This showed that the ADC measurement using DW_{ro} and DW_{alt} was dependent not only on the geometry and anisotropy of the ROIs, but also that of the surrounding tissue. Estimations of ADC using DW_{fix} and DW_{alt} remained largely independent of the relationship between tissue geometries and anisotropies. Data acquired in the presence of T₂, using centric and linear phase encoding, consistently demonstrated that the most accurate ADC measurements were made using DW_{fix} and DW_{alt}.

In studying tissue pathology, the degree and direction of principal diffusion is generally unknown. For this reason, it is important that the acquisition and reconstruction be able to accurately estimate the mean ADC over the range of physiologic tissue geometries and FAs. The simulations have thus far shown DW_{alt} to provide the most accurate measures of ADC of the rotating DW schemes used. Figure 6-20 examines this DW scheme in more detail, and presents DW_{alt} data for a range of FAs and blade widths.

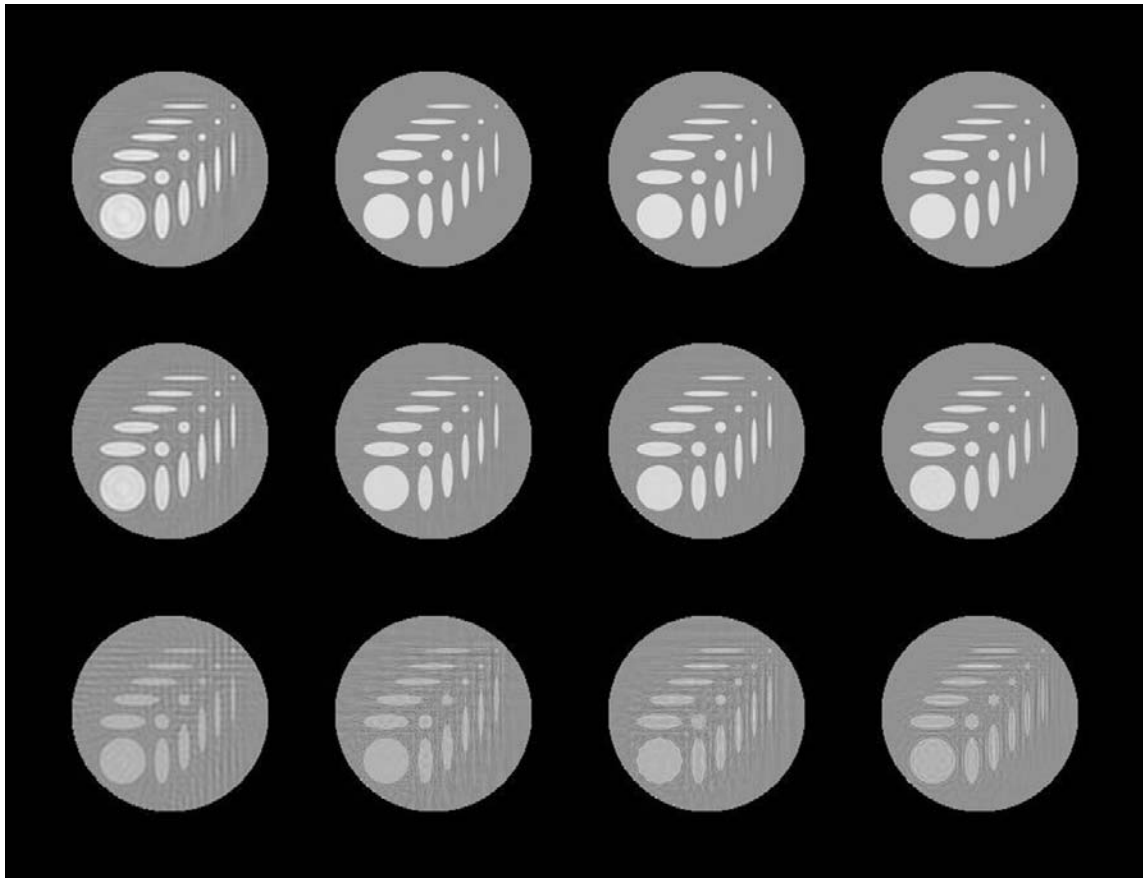


Figure 6-20 Mean ADC images reconstructed using DW_{alt} at various FAs and blade widths. From top to bottom row, $FA=[0, 0.4, 0.8]$, and from left to right, $nPE=[8, 16, 24, 32]$ with corresponding number of blades= $[48, 24, 16, 12]$. T_2 , motion and noise were neglected.

The result was high resolution data with minimal artifacts up to $FA=0.4$, across blade widths 8 to 64. At $FA=0.8$ however, a marked drop in tumour ADC was observed for all blade widths, along with streaking artifacts. While data improved in quality with wider blade widths, this data did not incorporate T_2 . Graphs depicting the dependence of mean ADC on FA and blade widths are given in Figure 6-21, Figure 6-22 & Figure 6-23. The first neglects T_2 , while the latter include T_2 with centric phase encoding ($TE=28ms$) and linear phase encoding ($TE=44.1ms$) respectively. The original object with anisotropies defined in Figure 6-5 was used.

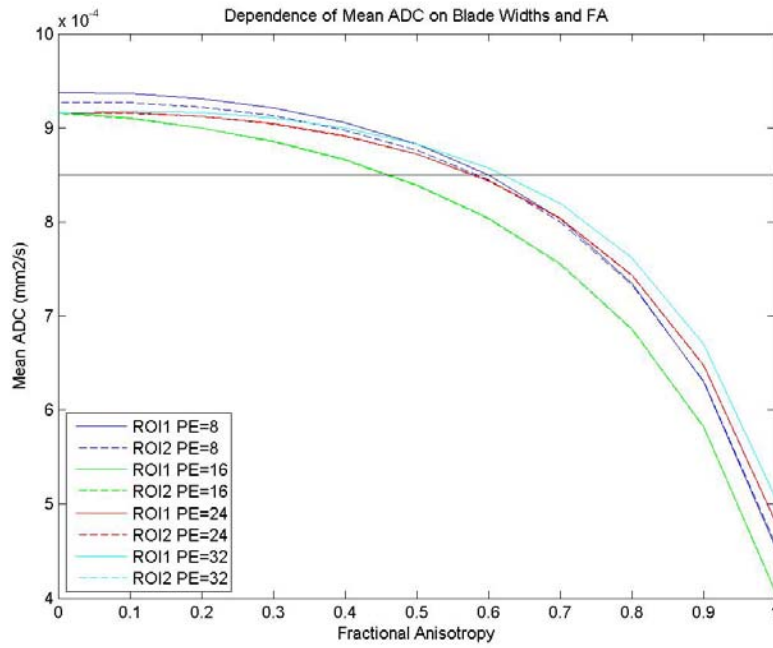


Figure 6-21 Dependence of the mean ADC on FA and blade width, using DW_{alt} . $FA_{dir_{ROI\ 1}}$ =left-right, $FA_{dir_{ROI\ 2}}$ =left-right, $FA_{dir_{GM}}$ =in-out. T_2 , motion and noise were neglected.

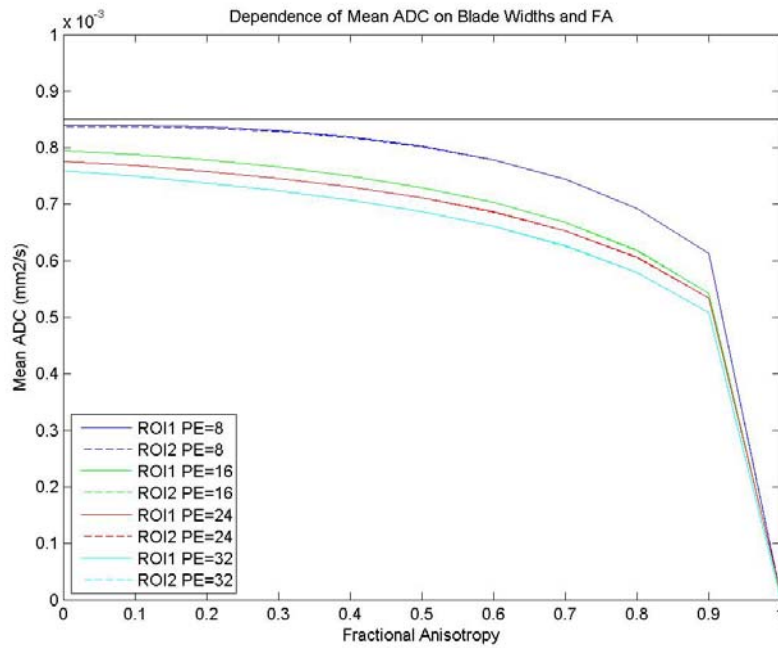


Figure 6-22 Dependence of the mean ADC on FA and blade width, using DW_{alt} . $FA_{dir_{ROI\ 1}}$ =left-right, $FA_{dir_{ROI\ 2}}$ =left-right, $FA_{dir_{GM}}$ =in-out. Centric phase encoding, TE_{eff} =28ms. Motion & noise were neglected.

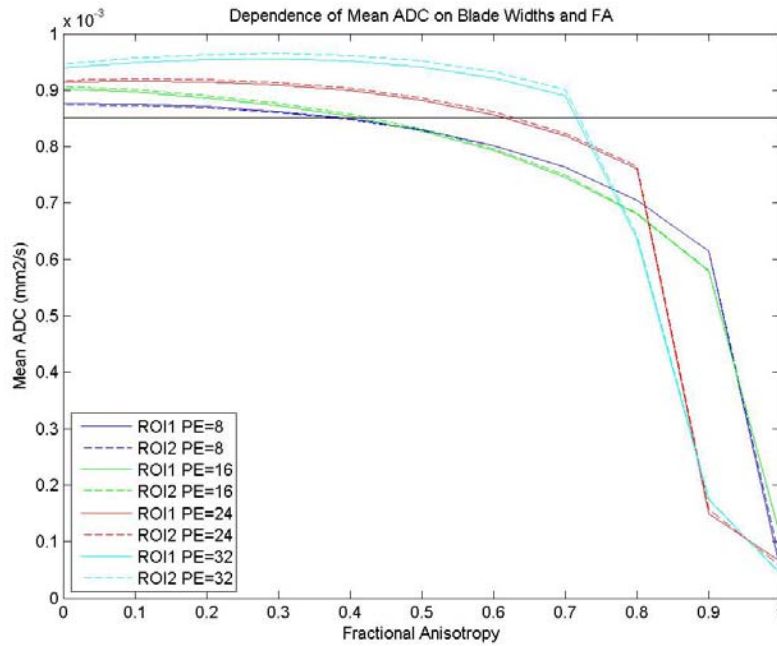


Figure 6-23 Dependence of the mean ADC on FA and blade width, using DW_{alt} . $FA_{dir_{ROI\ 1}}$ =left-right, $FA_{dir_{ROI\ 2}}$ =left-right, $FA_{dir_{GM}}$ =in-out. Linear phase encoding, TE_{eff} =44.1ms. Motion & noise were neglected.

In the presence of T_2 , the error in the measured ADC was lowest when $nPE=8$. Centric phase encoding methods yielded an error of -3.5% at $FA=0.4$ and -19% at $FA=0.8$. Linear phase encoding yielded slightly more accurate results with errors of -0.1% and -18% respectively.

The simulation data demonstrated a complex relationship between the measured ADC, applied diffusion weighting and tissue properties including geometries, FAs and directions of principal diffusivity. In general, higher FAs led to greater signal modulations over k-space and higher errors. The relative orientation of the ROI geometry with the tissue principal diffusivity and direction of DW determined whether the ADC was over or underestimated, by a degree determined largely by FA. Since each tissue type and region had some contribution to all parts of k-space, it was found that the tissue properties in a given ROI influenced the measured ADC in the tissue directly surrounding it, and vice versa. Using centric phase encoding at 9.4T, it was shown that the error in the measured ADC at physiological FA values up to 0.8, ranged from -49% to +44% of the nominal ADC (See Figure 6-13). This effect would be impossible to isolate in in-vivo data. Maintaining rotating gradients in the manner of DW_{ro} and DW_{pe} would thus be unlikely to provide a robust measure of ADC in-vivo.

On the other hand, it was shown that DW_{alt} produced more consistent data that was independent of the orientations of tissue geometry and diffusion weighting, and had an error of -1% to -8% which depended on the FA (See Figure 6-13). This was due to the averaging of DW at the k-space periphery arising from the alternating DW directions. This effect improved the reconstruction accuracy despite the reduction in the central region of overlap between blades. However, reducing the blade width further causes artifacts in the PSF and limits motion correction between shots. The optimized blade width of 8 was used for further in-vivo experiments. DW_{alt} yielded errors that were significantly lower than might be expected in the scenario of acute stroke, and could give rise to clinically valuable data while halving the acquisition time of a standard DW-FSE-PROPELLER acquisition.

6.3.3 Healthy Mouse Studies

Figure 6-24 shows b_0 , DW images and mean ADC maps of healthy mouse brain imaged in-vivo at 9.4T using various DW-FSE-PROPELLER methods and linear phase encoding. The first used a standard DW_{fix} scheme with DW data acquired in three orthogonal directions. The subsequent four datasets are DW_{fix} with 2x undersampling by blades, and rotating DW schemes – DW_{ro} , DW_{pe} and DW_{alt} . These four datasets had acquisition times half that of DW_{fix} .

The data with 2x undersampling looked similar to that without undersampling, albeit with lower SNR. DW images in the DW_{rot} schemes were hypointense compared to the DW_{fix} schemes due to the higher b-values used. The DW image signal intensity was higher in the corpus callosum using DW_{ro} compared to DW_{fix} , and the ADC measured was correspondingly lower. No obvious difference was seen in the GM. This contrasted with the hyperintensity in the corpus callosum in the mean ADC map as measured using DW_{pe} . In the axial view, the corpus callosum had a thin, horizontally aligned geometry with principal diffusivity oriented along the left-right direction. This corresponded with ROI 2 in the simulation data, and the deviations in ADC measurement in the in-vivo data were consistent with the simulation data as shown in Figure 6-14. Likewise, the data obtained with DW_{alt} appeared more similar to DW_{fix} than did DW_{ro} and DW_{pe} .

Figure 6-25 depicts the same data as Figure 6-24, using a centric phase encoding scheme instead. The appearance of the corpus callosum was replicated here, and was consistent with simulations in Figure 6-13.

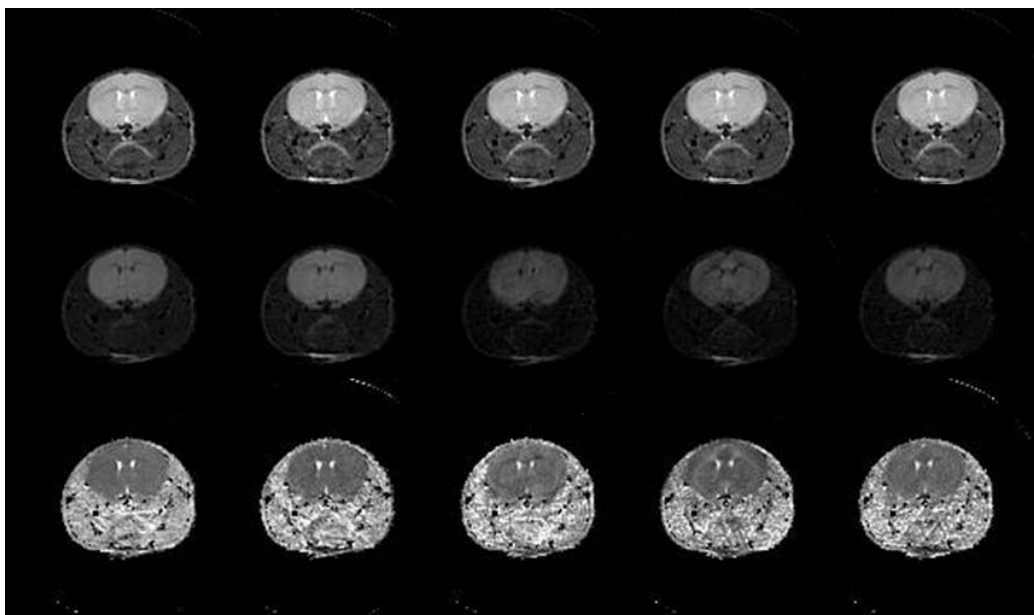


Figure 6-24 Diffusion weighted images of in-vivo brain in a free-breathing mouse at 9.4T using five acquisition methods and linear phase encoding. From left to right are DW_{fix} -PROPELLER, DW_{fix} -PROPELLER with 2x undersampling by blades, DW_{rot} -PROPELLER, DW_{pe} -PROPELLER & DW_{alt} -PROPELLER. From top to bottom are b_0 images ($b=30s/mm^2$), mean DW images ($b=800s/mm^2$ for DW_{fix} and $b=1200s/mm^2$ for DW_{rot}), and mean ADC maps. Matrix = $128 \times 8 \times 32$ and a single slice is displayed.

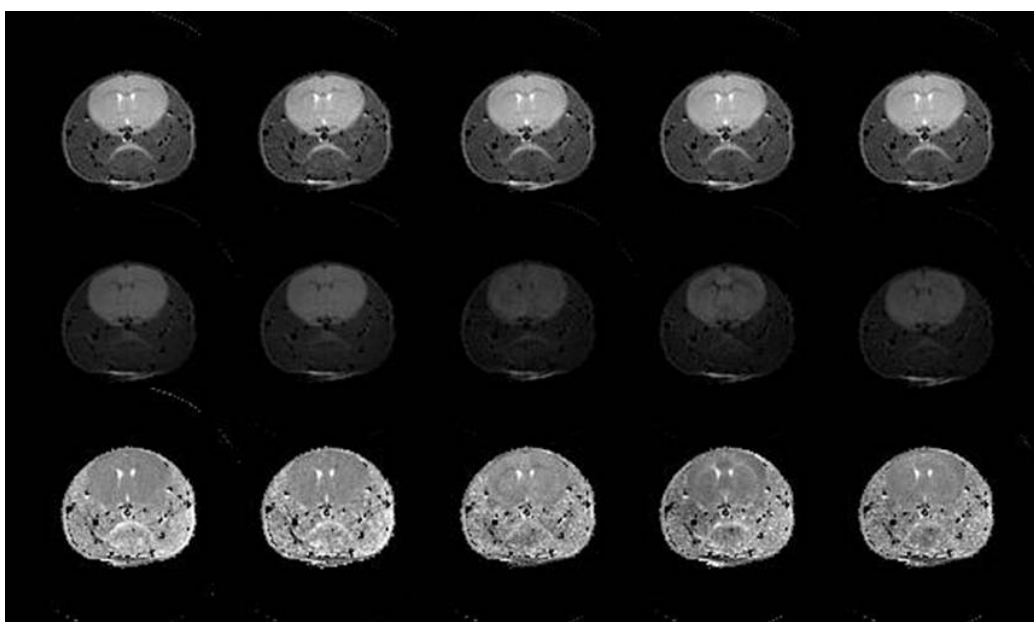


Figure 6-25 Diffusion weighted images of in-vivo brain in a free-breathing mouse at 9.4T using five acquisition methods and centric phase encoding. Parameters as given in Figure 6-24.

Plotting the mean ADC from ROIs in the GM and WM of the 8 healthy mice gave Figure 6-26 & Figure 6-27 respectively. Unsurprisingly, no significant differences were detected in the GM, since it was a relatively large and homogenous region with moderate FA. A slight trend towards a higher ADC value was detected however using centric phase encoding compared to linear phase encoding.

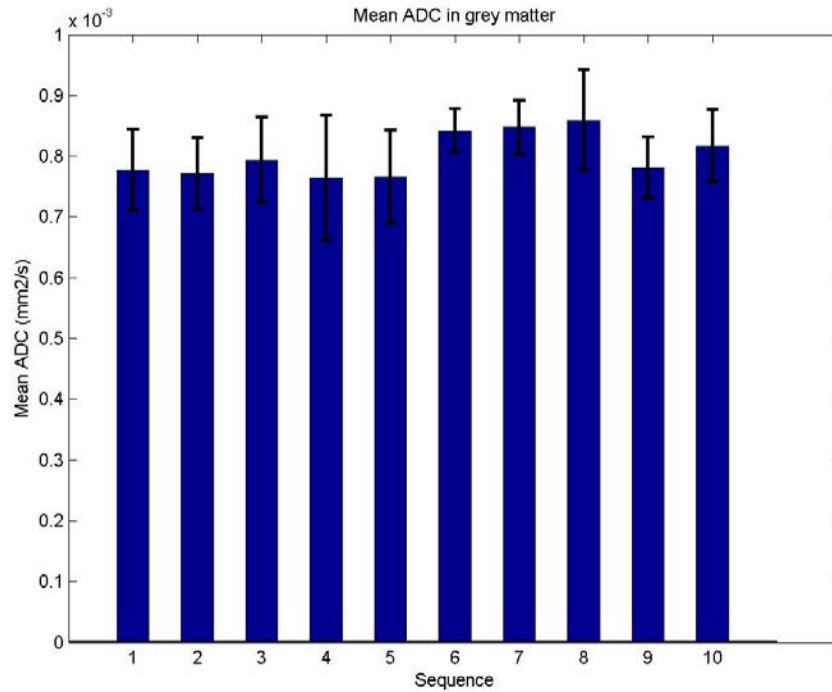


Figure 6-26 Mean ADC data measured in grey matter of free-breathing mice in-vivo at 9.4T using various acquisition methods. Columns 1-5: DW_{fix} -PROPELLER, DW_{fix} -PROPELLER with 2x undersampling by blades, DW_{ro} -PROPELLER, DW_{pe} -PROPELLER & DW_{alt} -PROPELLER with linear phase encoding and $TE_{eff}=44.1ms$. Columns 6-10: As per columns 1-5, but with centric phase encoding and $TE_{eff}=28ms$.

In WM, significant changes in the mean ADC were reported in $DW_{ro,linear}$ ($p=1.3e-4$), $DW_{pe,linear}$ ($p=0.017$) and $DW_{ro,centric}$ ($p=9.1e-3$). The reference image used was DW_{fix} with corresponding phase encoding. The errors in the mean ADC in $DW_{ro,linear}$, $DW_{pe,linear}$, $DW_{ro,centric}$, $DW_{pe,centric}$ were -16% , $+15\%$, -10% and $+4.1\%$ respectively. These were consistent with the simulation data. The same trend towards higher ADC using centric phase encoding was observed despite the simulations showing that it should result in a slightly lower ADC estimation than linear phase encoding. The likely reason for this was residual non-CPMG effects resulting in an odd-even echo oscillation of the signal intensity. A quick inspection of the echo train using a non-phase encoded acquisition confirmed this, where the

signal magnitude in the first echo was about 90% of the second echo. This led to an undesired signal drop and an overestimation of the ADC which was more prominent using a centric phase encoding scheme where the first echo corresponded to $k=0$.

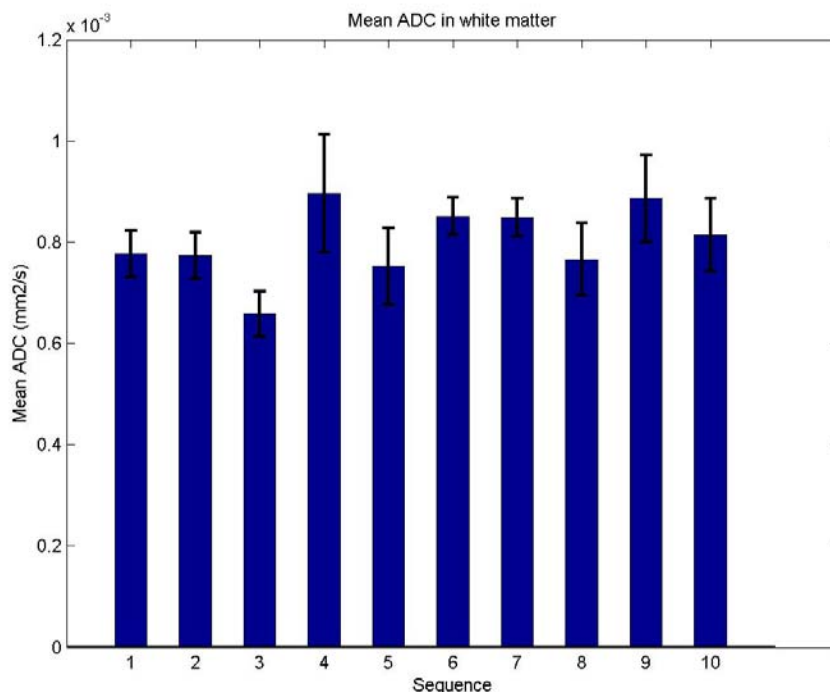


Figure 6-27 Mean ADC data measured in white matter of free-breathing mice in-vivo at 9.4T. Sequences described in Figure 6-26.

Figure 6-28 & Figure 6-29 illustrate the SNR and AP of the mean ADC data using the 5 acquisition methods and two phase encoding schemes. They show that centric encoding schemes result in higher SNR and lower AP due to shorter effective TEs, and undersampled and rotating DW schemes have lower SNR than DW_{fix}-PROPELLER, due to reduced data collected.

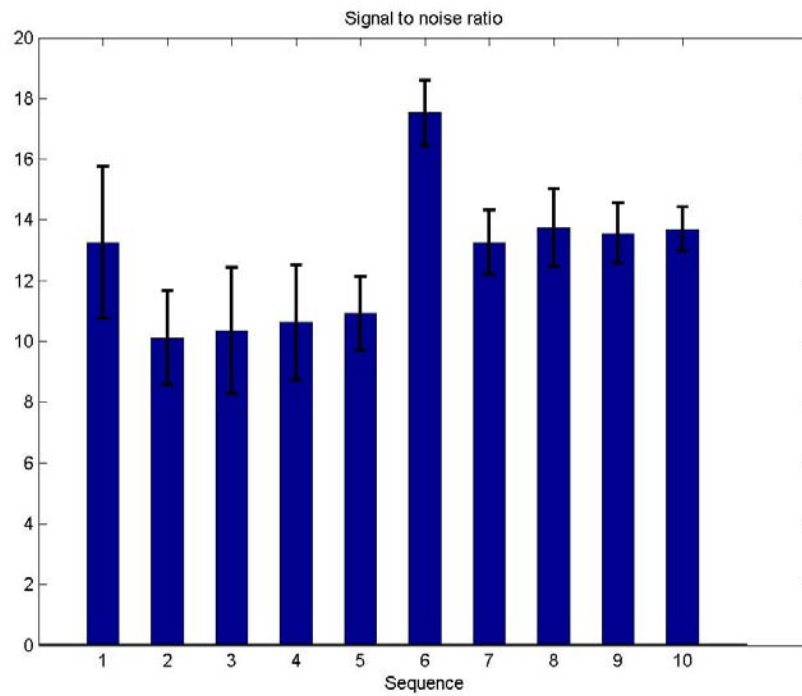


Figure 6-28 SNR of mean ADC data measured in grey matter of free-breathing mice in-vivo at 9.4T. Sequences described in Figure 6-26.

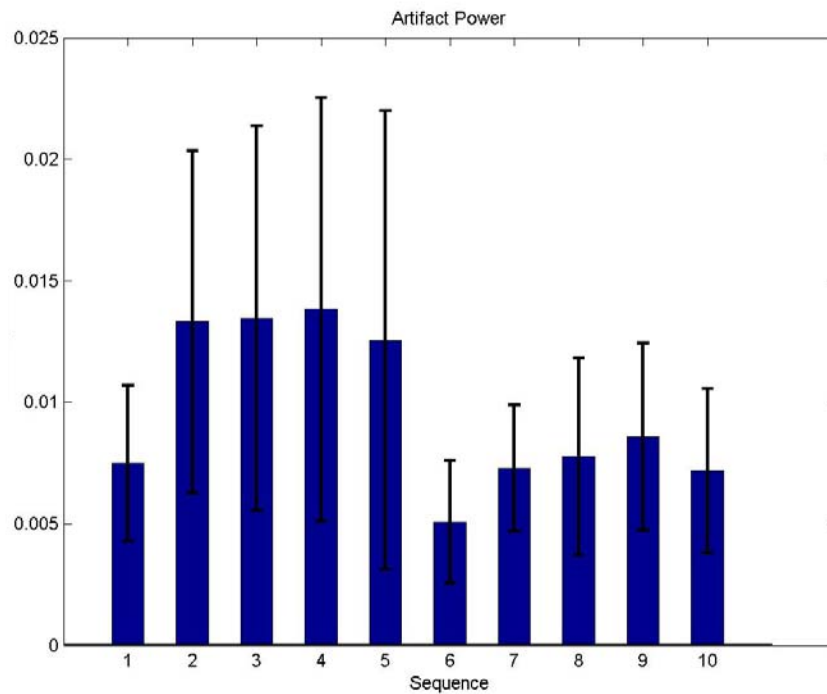


Figure 6-29 AP of mean ADC data measured in grey matter of free-breathing mice in-vivo at 9.4T. Sequences described in Figure 6-26.

In the mouse brain, GM-WM contrast is poor in ADC maps, and would be $-0.2 \times 10^{-4} \text{mm}^2/\text{s}$ according to the ADC values reported in literature (137). Contrast obtained from DW_{ro} and DW_{pe} acquisitions in the in-vivo data show a significant deviation from the data acquired using DW_{fix} . There was however no significant difference using DW_{fix} with undersampling or DW_{alt} .

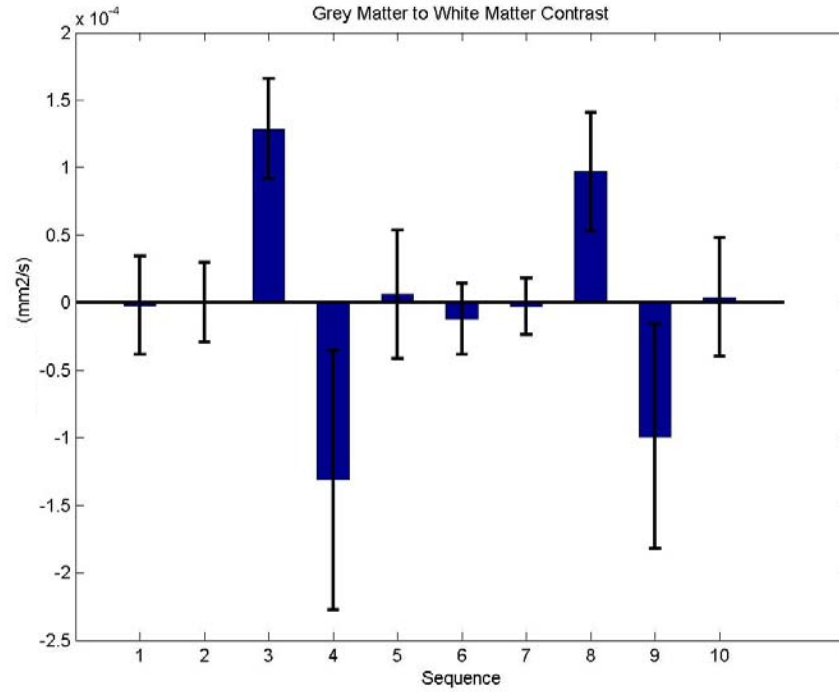


Figure 6-30 GM-WM contrast in mean ADC data measured in free-breathing mice in-vivo at 9.4T. Sequences described in Figure 6-26.

The healthy mouse brain ADC data is summarized in Table 6.2. Significant differences from the DW_{fix} data with corresponding phase encoding are highlighted. Overall, the images and errors in ADC measurement using DW_{ro} and DW_{pe} corresponded well with the simulation data. They confirmed that these methods are unsuitable for obtaining isotropic DW in highly anisotropic tissues. Both DW_{alt} and undersampled DW_{fix} acquisitions resulted in data that were not significantly different from using DW_{fix} , with the exception of lower SNR which would be expected due to acquiring only half the data. These support the hypothesis that these methods may be used to reduce acquisition time and allow one to obtain effectively isotropic DW data in a single-shot.

		Linear					Centric				
		DW (Fix)	DW (Fix) USB2	DW (RO)	DW (PE)	DW (Alt)	DW (Fix)	DW (Fix) USB2	DW (RO)	DW (PE)	DW (Alt)
Mean ADC in GM ($\times 10^{-3}$ mm ² /s)	Mean	0.777	0.771	0.794	0.764	0.766	0.842	0.848	0.859	0.781	0.817
	SD	0.067	0.058	0.071	0.103	0.076	0.037	0.044	0.082	0.050	0.060
	p	1	0.85	0.64	0.76	0.76	1	0.77	0.59	0.16	0.34
Mean ADC in WM ($\times 10^{-3}$ mm ² /s)	Mean	0.777	0.773	0.658	0.896	0.753	0.851	0.849	0.766	0.886	0.815
	SD	0.046	0.045	0.045	0.117	0.075	0.037	0.037	0.071	0.085	0.072
	p	1	0.89	1.3e-4	0.017	0.46	1	0.89	0.0091	0.31	0.22
SNR	Mean	13.3	10.1	10.3	10.6	10.9	17.5	13.3	13.7	13.6	13.7
	SD	2.5	1.5	2.1	1.9	1.2	1.1	1.0	1.3	1.0	0.7
	p	1	0.0092	0.024	0.033	0.032	1	1.3e-6	1.7e-5	2.3e-6	8.3e-7
Artifact Power ($\times 10^{-2}$)	Mean	0.75	1.33	1.35	1.38	1.25	0.51	0.73	0.78	0.86	0.72
	SD	0.32	0.7	0.79	0.87	0.94	0.25	0.26	0.4	0.39	0.34
	p	1	0.052	0.068	0.074	0.17	1	0.11	0.13	0.05	0.18
GM-WM Contrast ($\times 10^{-4}$ mm ² /s)	Mean	-0.020	2.9e-3	1.286	-1.315	0.061	-0.120	-0.030	0.970	-0.992	0.041
	SD	0.363	0.295	0.371	0.959	0.475	0.264	0.207	0.439	0.832	0.440
	p	1	0.89	5.2e-6	0.0031	0.71	1	0.46	3.1e-5	0.014	0.39

Table 6.2 Summary of mean ADC data from in-vivo brain imaging in healthy mice at 9.4T. Data with linear and centric phase encoding were separately examined, and significant differences from respective DW_{fix} acquisitions are highlighted in red.

6.3.4 Tumour Mouse Model Studies

The work so far indicated there may be limitations in the absolute quantification of ADC using rotating DW methods. However, their rapid acquisition and robustness to motion suggested they could potentially be used in whole body screening applications. As a result, DW_{rot} was tested using MT-ret/AAD mouse models of tumour metastases. Figure 6-31 illustrates the typical phenotypic expression of tumour development in these mouse models. The metastases were aggressive and heterogeneous. They commonly developed around the face, eyes, lungs and genital regions, but have also been identified in the abdomen and muscles. This heterogeneity is illustrated in a series of T₂-weighted MRI scans in different anatomy and mice given in Figure 6-32. Early histology work confirmed the presence of necrotic cores within tumours as identified. These areas of necrosis possessed lower cell density and oedema which led to elevated T₂ and ADCs.



Figure 6-31 Dissections showing the typical phenotype of tumour expression in MT-ret/AAD mice. Tumours identified included a large multilobular chin tumour (left), multiple genital metastases in fatty tissue (top right) and tumours associated with the leg muscles (bottom right).

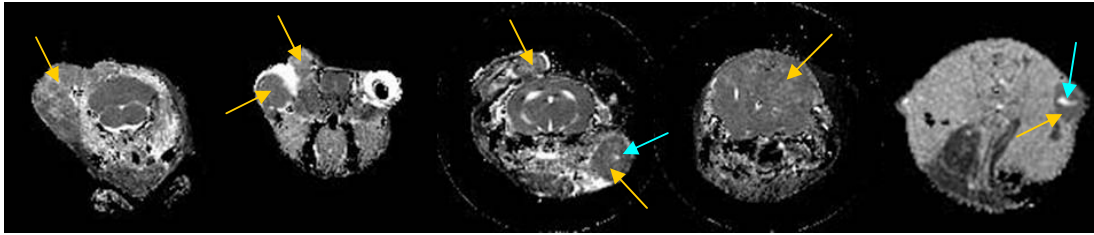


Figure 6-32 Five T₂-weighted MRI images at different slice positions in various mice illustrating tumour heterogeneity. Tumours and regions of necrosis are highlighted in yellow and blue respectively.

A series of images were acquired with the five sequences and two phase encoding schemes as per the healthy mouse experiments. Sample data in one slice of one mouse using linear phase encoding is given in Figure 6-33. The DW images and ADC maps provided similar observations as before. Using the DW_{fix} acquisition as a reference, the mean ADC in the corpus callosum was underestimated and overestimated using DW_{ro} and DW_{pe} respectively. The data using DW_{fix} with 2x blade undersampling and DW_{alt} were much more consistent with the DW_{fix} data. DW_{rot} methods produced DW images with lower signal intensity than DW_{fix} methods due to the higher b-value used. The ADC values in the former however, were also lower after accounting for different b-values. DW_{ro} data showed an increase in streaking artifacts, particularly in the muscle, possibly due to anisotropy effects and low SNR due to T₂.

Qualitatively however, much of the ADC contrast in DW_{fix} was retained using undersampling by blades as well as DW_{alt} .

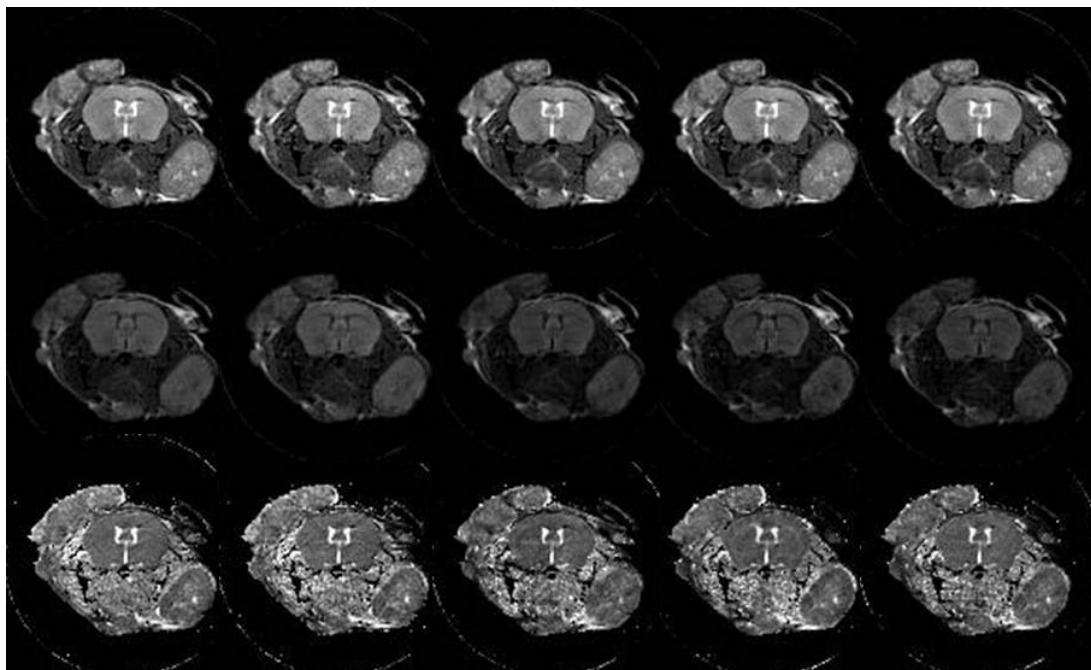


Figure 6-33 Diffusion weighted images of in-vivo brain and metastases in a free-breathing MT-ret/AAD mouse at 9.4T using five acquisition methods and linear phase encoding. From left to right are DW_{fix} -PROPELLER, DW_{fix} -PROPELLER with 2x undersampling by blades, DW_{rot} -PROPELLER, DW_{pe} -PROPELLER & DW_{alt} -PROPELLER. From top to bottom are b_0 images ($b=30s/mm^2$), mean DW images ($b=800s/mm^2$ for DW_{fix} and $b=1200s/mm^2$ for DW_{rot}), and mean ADC maps. Matrix = $128 \times 8 \times 32$ and a single slice is displayed.

ROI data were obtained from tumour regions around the brain and the mean ADC variation using the different acquisition methods are given in Figure 6-34. The data showed some variation in the measured ADC, and that DW_{alt} yielded results that were intermediate to DW_{rot} and DW_{pe} . However, there were no significant differences from DW_{fix} in any of the data. This was due to large error arising from the comparison of different tumours with variable unknown ADCs, FAs and orientations of principal diffusivity. This was compounded by the lack of existing DW data in MT-ret/AAD mouse tumours with which to compare the data against.

Table 6.3 summarised the tumour mean ADC, and its SNR and AP. Some significant changes in the SNR and AP data in centric phase encoding were detected, reflecting once again the higher SNR using centric phase encoding and the lower SNR using DW_{rot} methods.

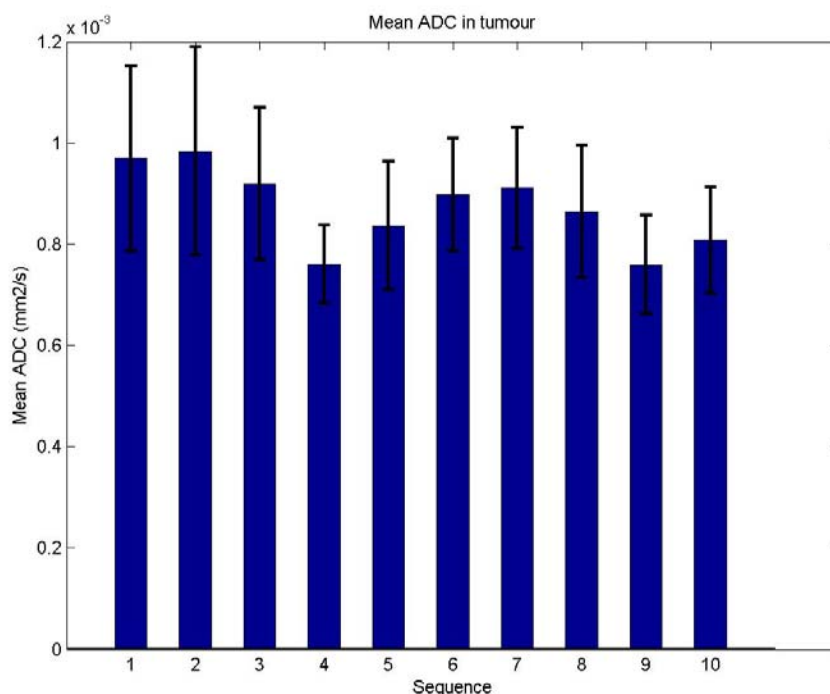


Figure 6-34 Mean ADC data measured in tumours of free-breathing MT-ret/AAD mice in-vivo at 9.4T using various acquisition methods. Columns 1-5: DW_{fix}-PROPELLER, DW_{fix}-PROPELLER with 2x undersampling by blades, DW_{ro}-PROPELLER, DW_{pe}-PROPELLER & DW_{alt}-PROPELLER with linear phase encoding and TE_{eff}=44.1ms. Columns 6-10: As per columns 1-5, but with centric phase encoding and TE_{eff}=28ms.

		Linear					Centric				
		DW (Fix)	DW (Fix) USB2	DW (RO)	DW (PE)	DW (Alt)	DW (Fix)	DW (Fix) USB2	DW (RO)	DW (PE)	DW (Alt)
Mean ADC in GM (x10 ⁻³ mm ² /s)	Mean	0.97	0.98	0.92	0.76	0.84	0.90	0.91	0.86	0.76	0.81
	SD	0.18	0.21	0.15	0.078	0.13	0.11	0.12	0.13	0.10	0.10
	p	1	0.93	0.72	0.12	.34	1	0.90	0.74	0.16	0.34
SNR	Mean	9.5	7.0	6.7	7.3	8.0	17	10	11	9.5	11
	SD	2.4	0.96	1.6	1.4	2.2	2.5	1.7	2.6	2.2	3.1
	p	1	0.14	0.14	0.20	0.46	1	8.1e-3	2.2e-2	7.8e-3	4.0e-2
Artifact Power (x10 ⁻²)	Mean	1.4	2.2	2.8	4.2	2.7	0.41	1.0	1.6	1.7	1.5
	SD	0.39	0.69	1.17	4.0	1.5	0.15	0.31	1.1	0.88	0.75
	p	1	0.12	0.09	0.27	0.21	1	0.017	0.11	0.050	0.047

Table 6.3 Summary of mean ADC data from in-vivo MT-ret/AAD tumour imaging at 9.4T. Data with linear and centric phase encoding were separately examined, and significant differences from respective DW_{fix} acquisitions are highlighted in red.

6.3.5 Human Studies

Preliminary data using ssDW-EPI, DW_{fix} and DW_{rot} schemes were acquired in a patient (70/F) diagnosed with acute infarct in the left MCA. These are presented in Figure 6-35. The ssDW-EPI reference data were acquired rapidly and demonstrated good stroke contrast as well as good GM-WM contrast. Geometric distortion at this level in the brain was mild. DW-FSE-PROPELLER methods in general produced images that were insensitive to geometric distortion at the cost of longer acquisition time. GM-WM contrast was reduced, but good stroke contrast was maintained in all sampling methods, and identifiable lesions matched those in the ssDW-EPI scan in the majority of regions in the brain.

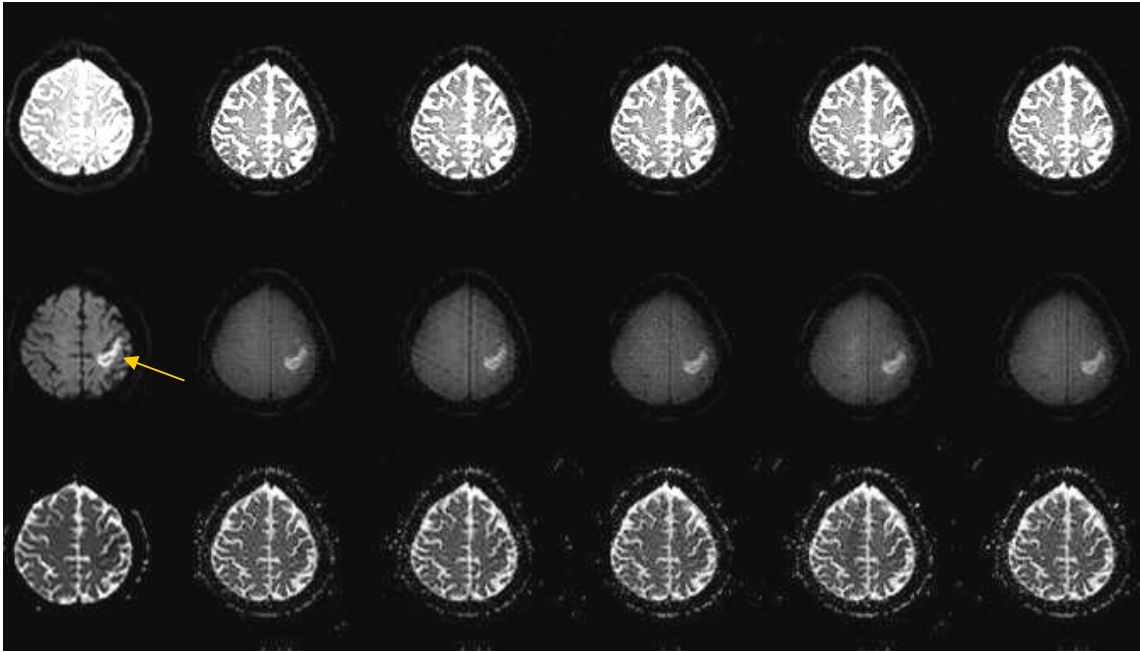


Figure 6-35 Diffusion weighted images of the brain in a 70/F patient with acute stroke in the left MCA at 3T using five acquisition methods and centric phase encoding. Stroke lesion is highlighted. From left to right are ssDW-EPI, DW_{fix}-PROPELLER, DW_{fix}-PROPELLER with 2x undersampling by blades, DW_{ro}-PROPELLER, DW_{pe}-PROPELLER & DW_{alt}-PROPELLER. From top to bottom are b_0 images ($b=0s/mm^2$), mean DW images ($b=1000s/mm^2$), and mean ADC maps. Matrix = 128 x 32 x 6 and a single slice is displayed.

However, this was not universally the case as shown in data taken from another slice in the brain as found in Figure 6-36. Here, both DW_{fix} and DW_{fix} with 2x undersampling by blades produced DW images that led to identifiable lesions that matched the ssDW-EPI scan in all cases.

In contrast, the DW images from the DW_{rot} scans failed to positively identify the lesion in the region of the left middle frontal gyrus. This could have been due to a combination of factors. First, the particular stroke lesion may have had some combination of small geometry, lesser reduction of ADC due to stroke and high FA that led to overestimation of the lesion ADC. More likely, the blade width of 32 may have been too wide, leading to T_2 blurring and anisotropic DW in the periphery of k-space. The choice of blade width was restricted by the fact that the DW data were acquired using N blades in N DW directions, rather than 1 blade in N DW directions as it ideally should be. To keep the scan time under 3m, N was capped at 6, which dictated a blade width of 32 for full k-space sampling.

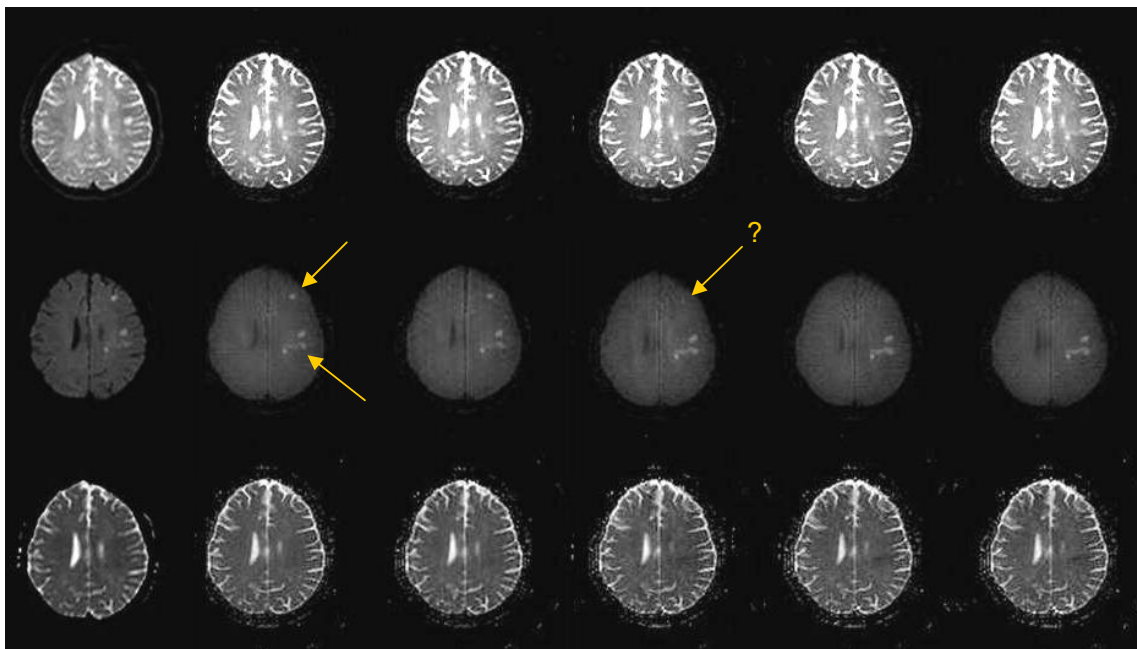


Figure 6-36 Identical acquisition in the same patient as Figure 6-35, showing a different slice. Stroke lesions are highlighted.

6.3.6 B-tensor simulations

The inconclusive result in the mouse tumour imaging and the lesion-dependent performance in using rotating DW methods in the human stroke patient motivated a closer examination of the full $\mathbf{b}$, including the off-diagonal terms, to see if there were any unexpected perturbations to the effective DW.

Figure 6-37 is a representation of the DW gradients in x, y and z directions from a DW_{ro} acquisition with 12 blades, and their contribution to the b-value. Ignoring imaging gradients,

the DW gradients from all blades were concatenated in time. Successive pairs of gradients (green) represent DW in successive blades. The polarity of every other DW gradient was reversed due to the RF refocusing pulse. These are illustrated in the fixed scanner frame of reference, hence the oscillation in the magnitude of G_x and G_y across rotated blades. The integral of the gradient terms F_{ii}^2 (blue) and F_{ij}^2 (green) were determined by Eqn 5.2. These terms gave rise to the on-diagonal and off-diagonal terms of $\mathbf{b}$ respectively.

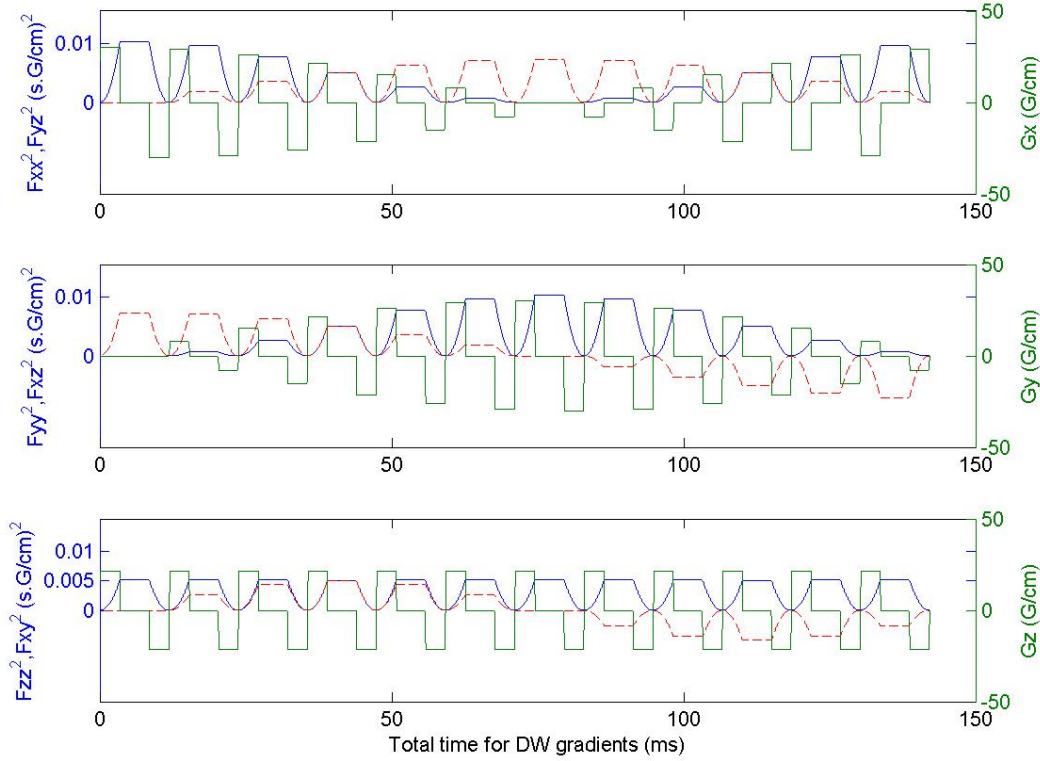


Figure 6-37 DW gradients and corresponding effective field gradients for simulated DW_{ro} G_{z,fix} for 12 blades. DW gradients (green), on-diagonal F_{ii}^2 terms (blue) and off-diagonal F_{ij}^2 terms (red) given. $G_{\max}=30\text{G/cm}$, zero-max slew= 0.13ms and $b=800\text{s/mm}^2$. Display excludes all pulse sequence elements except for DW gradients, and concatenates 12 blades worth of rotating DW sequentially. Imaging gradients were neglected. Every second DW lobe was reversed to account for the refocusing pulse.

For isotropic diffusion weighting, the cumulative sum of F_{xx}^2 , F_{yy}^2 and F_{zz}^2 , and hence the b-value along the principal directions, across all blades must be equal and the cumulative sum of F_{xy}^2 , F_{yz}^2 and F_{zx}^2 across all blades should each equal zero. Extracting these values for each blade and multiplying by the square of the gyromagnetic ratio gives Table 6.4. This shows how $\mathbf{b}$ varied across each blade. The result was a net averaging of on-diagonal terms

that summed to give the desired b-value, where $b=b_{xx}+b_{yy}+b_{zz}$. In the original DW_{ro} implementation, fixed DW gradients in the z-direction, $G_{z,fix}$, were applied concurrently with G rotating in the x-y plane. These imparted a degree of anisotropy to $\mathbf{b}$ that did not eventually cancel out. The remaining non-zero b_{xz} and b_{yz} were a likely factor that degraded the DW_{rot} in-vivo data, in the presence of heterogeneous and anisotropic tissues.

Blade	1	2	3	4	5	6	7	8	9	10	11	12	
Angle (°)	0	15	30	45	60	75	90	105	120	135	150	165	Mean
b_{xx} (s/mm ²)	533	498	400	267	133	36	0	36	133	267	400	498	267
b_{yy} (s/mm ²)	0	35	134	267	400	498	533	498	400	267	134	35	267
b_{zz} (s/mm ²)	267	267	267	267	267	267	267	267	267	267	267	267	267
b_{xy} (s/mm ²)	0	133	231	267	231	133	0	-133	-231	-267	-231	-133	0
b_{xz} (s/mm ²)	377	364	326	267	189	98	0	-98	-189	-267	-326	-364	32
b_{yz} (s/mm ²)	0	98	188	267	327	364	377	364	327	267	188	98	239
b (s/mm ²)	800	800	800	800	800	800	800	800	800	800	800	800	800

Table 6.4 Nominal on-diagonal & off-diagonal b-values across blades 1 to 12 using DW_{ro} $G_{z,fix}$.

Similarly, when DW_{alt} was used in conjunction with fixed G_z gradients (See Figure 6-38), the on-diagonal terms were equal and their net averages summed to give the desired b-value, but the off-diagonal terms in b_{xz} and b_{yz} failed to cancel out.

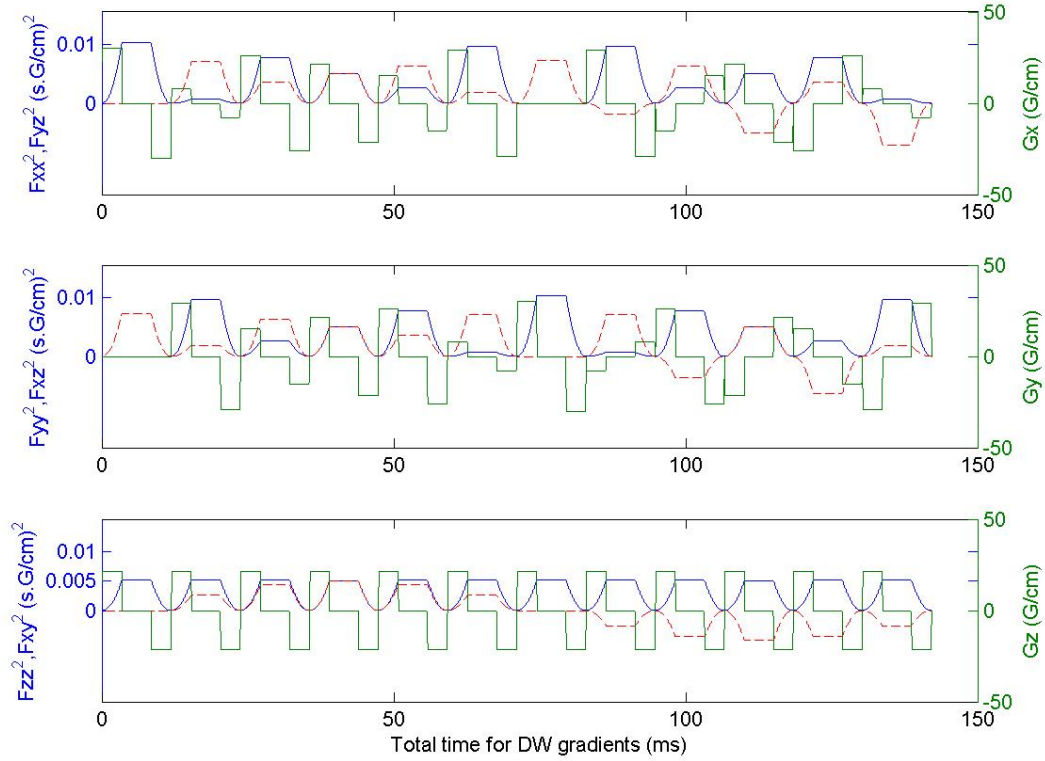


Figure 6-38 DW gradients and corresponding effective field gradients for simulated $DW_{alt} G_{z,fix}$ for 12 blades. DW gradients (green), on-diagonal F_{ii}^2 terms (blue) and off-diagonal F_{ij}^2 terms (red) given.

A summary of $\mathbf{b}$ for $DW_{ro} G_{z,fix}$ and $DW_{alt} G_{z,fix}$ are given in Table 6.5 over a range of blade numbers from 6 to 192. The net average terms of b_{xx} , b_{yy} , b_{zz} , b_{xy} , b_{xz} and b_{yz} are given. The data show that the on-diagonal terms were consistently equal and summed to the desired b -value, while the off-diagonal terms consistently failed to cancel out. Expressing the anisotropy in $\mathbf{b}$ in terms of the error between the maximum off-diagonal terms and the mean of on-diagonal terms, $\overline{b_{ij,max}}/\overline{b_{ii}}$, as a percentage, gave values of about 90% in the DW_{ro} case and between 46% to 71% in the DW_{alt} case. These sizeable off-diagonal terms would have led to effectively non-isotropic DW weighting.

DW_{ro} G_{z,fix}								
Number of blades	6	12	16	24	32	48	96	192
$\overline{b_{xx}}$ (s/mm ²)	266.6	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{yy}}$ (s/mm ²)	266.6	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{zz}}$ (s/mm ²)	266.6	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{xy}}$ (s/mm ²)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\overline{b_{xz}}$ (s/mm ²)	63.2	31.7	23.8	15.9	11.9	7.9	4.0	2.0
$\overline{b_{yz}}$ (s/mm ²)	234.4	238.7	239.2	239.8	239.9	240.1	240.1	240.1
$\overline{b}$ (s/mm ²)	799.8	800.7	800.1	800.7	800.4	800.7	800.4	800.4
$\overline{b_{ij,max}}/\overline{b_{ii}}$ (%)	87.9	89.4	89.7	89.8	89.9	90.0	90.0	90.0
DW_{alt} G_{z,fix}								
Number of blades	6	12	16	24	32	48	96	192
$\overline{b_{xx}}$ (s/mm ²)	268.2	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{yy}}$ (s/mm ²)	266.4	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{zz}}$ (s/mm ²)	267.3	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{xy}}$ (s/mm ²)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\overline{b_{xz}}$ (s/mm ²)	189.6	152.9	144.6	136.3	132.1	128.1	124.0	122.0
$\overline{b_{yz}}$ (s/mm ²)	108.8	117.5	118.4	119.4	119.6	119.9	120.0	120.0
$\overline{b}$ (s/mm ²)	801.9	800.7	800.1	800.7	800.4	800.7	800.4	800.4
$\overline{b_{ij,max}}/\overline{b_{ii}}$ (%)	70.9	57.3	54.2	51.1	49.5	48.0	46.5	45.7

Table 6.5 Mean b-terms over a range of blade numbers using DW_{ro} G_{z,fix} and DW_{alt} G_{z,fix} schemes.

To improve the degree of isotropic DW, the DW gradients in the z-axis were reversed in polarity in alternate blades in the manner, $G_z = [-1, 1, -1, 1, \dots]$. In the case of DW_{ro}, this led to oscillating F_{xy} and F_{yz} terms that largely cancelled out (See Figure 6-39). A closer look at the b-terms for each of 12 blades (See Table 6.6), confirmed that there were no changes to the on-diagonal terms, while the b_{yz} term was reduced from 239s/mm² to 4s/mm².

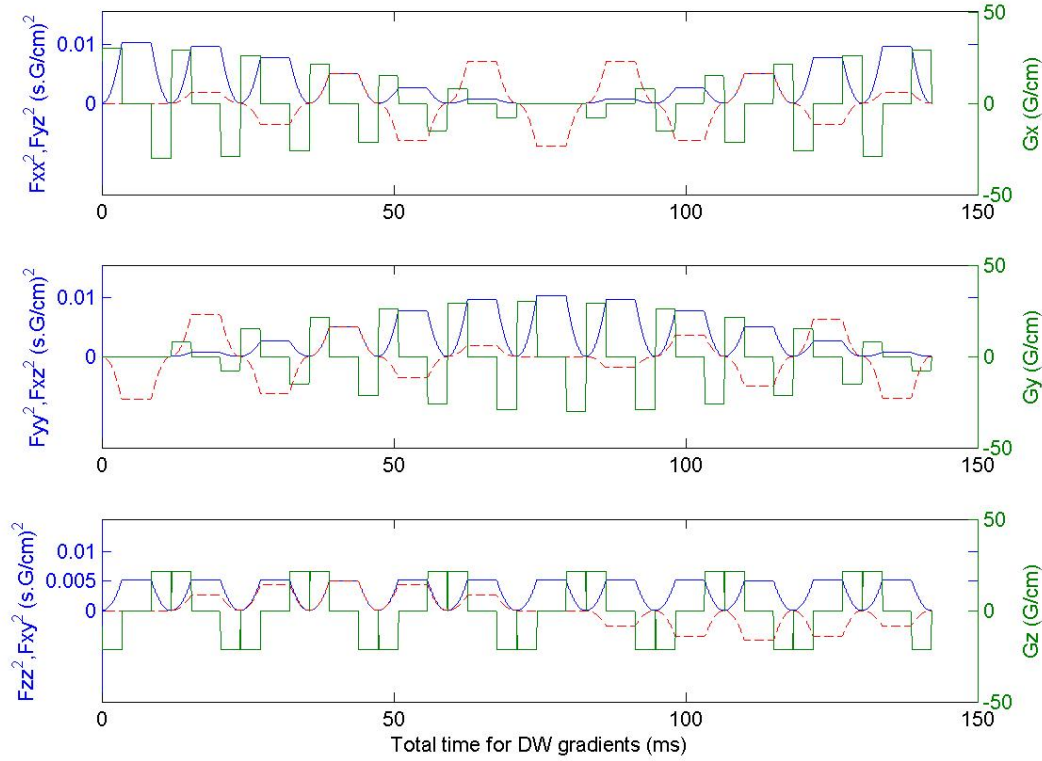


Figure 6-39 DW gradients and corresponding effective field gradients for simulated $DW_{ro} G_{z,alt}$ for 12 blades. DW gradients (green), on-diagonal F_{ii}^2 terms (blue) and off-diagonal F_{ij}^2 terms (red) given.

Blade	1	2	3	4	5	6	7	8	9	10	11	12	
Angle (°)	0	15	30	45	60	75	90	105	120	135	150	165	Mean
b_{xx} (s/mm ²)	533	498	400	267	133	36	0	36	133	267	400	498	267
b_{yy} (s/mm ²)	0	35	134	267	400	498	533	498	400	267	134	35	267
b_{zz} (s/mm ²)	267	267	267	267	267	267	267	267	267	267	267	267	267
b_{xy} (s/mm ²)	0	133	231	267	231	133	0	-133	-231	-267	-231	-133	0
b_{xz} (s/mm ²)	-377	364	-326	267	-189	98	0	-98	189	-267	326	-364	-32
b_{yz} (s/mm ²)	0	98	-188	267	-327	364	-377	364	-327	267	-188	98	4
b (s/mm ²)	800	800	800	800	800	800	800	800	800	800	800	800	800

Table 6.6 Nominal on-diagonal & off-diagonal b-values across blades 1 to 12 using $DW_{ro} G_{z,alt}$.

This G_z reversal in polarity was replicated in DW_{alt} . Due to the alternating nature of the in-plane DW component, it was necessary to alternate the G_z gradient in groups of 2 blades at a time, in the manner, $G_z=[1, -1, -1, 1, \dots]$. This led to a rather complicated evolution in the off-diagonal terms (See Figure 6-40). However, due to the halving of the effective frequency in alternating G_z , reductions in off-diagonal terms were observed to a lesser degree compared to when using DW_{ro} .

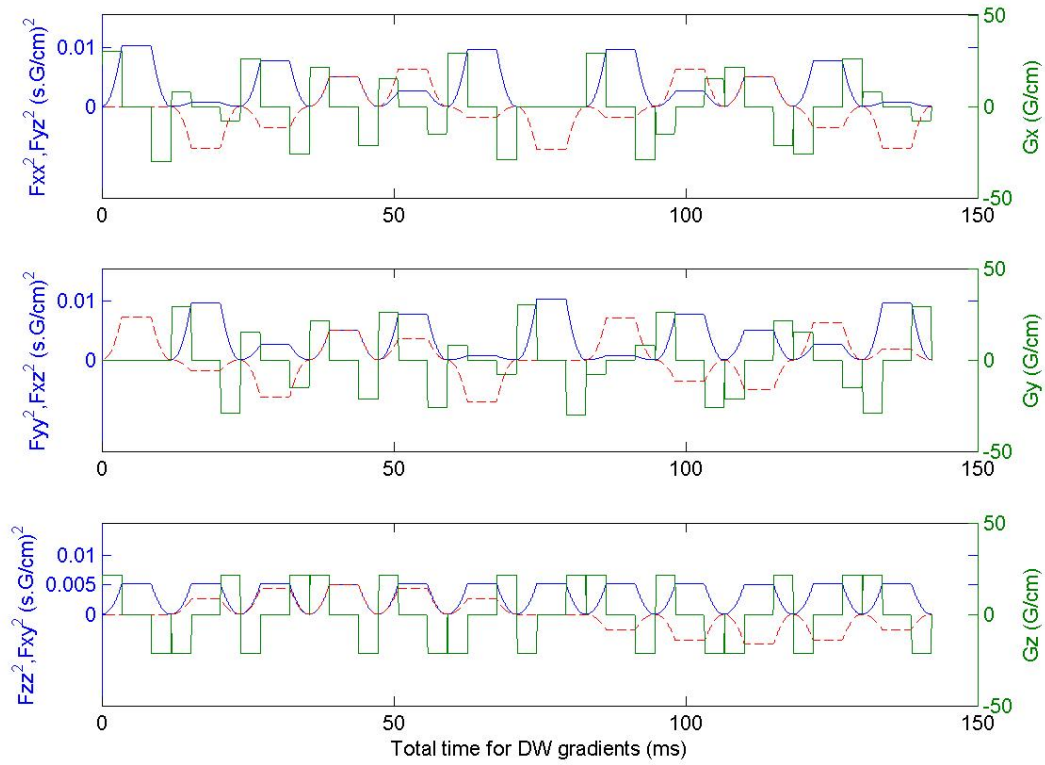


Figure 6-40 DW gradients and corresponding effective field gradients for simulated $DW_{alt} G_{z,alt}$ for 12 blades. DW gradients (green), on-diagonal F_{ii}^2 terms (blue) and off-diagonal F_{ij}^2 terms (red) given.

A summary of mean b-terms using this alternating G_z scheme with DW_{ro} and DW_{alt} is given in Table 6.7. This showed that on-diagonal terms were in general unaffected by alternating G_z . Off-diagonal terms were reduced by a degree that was dependent on the number of blades used. This resulted from the more effective cancellation of off-diagonal terms between blades when more blades were used. For number of blades=12, alternating G_z reduced the absolute $\overline{b_{ij,max}}/\overline{b_{ii}}$ in DW_{ro} from 89.4% to 11.9%, and in DW_{alt} from 57.3% to 15.8%. These reductions were increasingly evident at higher blade numbers, reaching a minimum of 0.7% at 192 blades in both cases.

DW_{ro} G_{z,alt}								
Number of blades	6	12	16	24	32	48	96	192
$\overline{b_{xx}}$ (s/mm ²)	266.6	266.9	266.7	266.2	266.8	266.2	266.8	266.8
$\overline{b_{yy}}$ (s/mm ²)	266.6	266.9	266.7	266.2	266.8	266.2	266.8	266.8
$\overline{b_{zz}}$ (s/mm ²)	266.6	266.9	266.7	266.2	266.8	266.2	266.8	266.8
$\overline{b_{xy}}$ (s/mm ²)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\overline{b_{xz}}$ (s/mm ²)	-63.2	-31.7	-23.8	-15.8	-11.9	-7.9	-4.0	-2.0
$\overline{b_{yz}}$ (s/mm ²)	17.4	3.7	2.5	1.1	0.6	0.2	0.0	0.0
$\overline{b}$ (s/mm ²)	799.8	800.7	800.1	798.6	800.4	798.6	800.4	800.4
$\overline{b_{ij,max}}/\overline{b_{ii}}$ (%)	-23.7	-11.9	-8.9	-5.9	-4.5	-3.0	-1.5	-0.7
DW_{alt} G_{z,alt}								
Number of blades	6	12	16	24	32	48	96	192
$\overline{b_{xx}}$ (s/mm ²)	268.2	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{yy}}$ (s/mm ²)	266.4	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{zz}}$ (s/mm ²)	267.3	266.9	266.7	266.9	266.8	266.9	266.8	266.8
$\overline{b_{xy}}$ (s/mm ²)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\overline{b_{xz}}$ (s/mm ²)	1.2	31.7	23.8	15.9	11.9	7.9	4.0	2.0
$\overline{b_{yz}}$ (s/mm ²)	0.0	-42.3	-29.4	-17.9	-13.2	-8.5	-4.1	-2.0
$\overline{b}$ (s/mm ²)	801.9	800.7	800.1	800.7	800.4	800.7	800.4	800.4
$\overline{b_{ij,max}}/\overline{b_{ii}}$ (%)	0.4	-15.8	-11.0	-6.7	-4.9	-3.2	-1.5	-0.7

Table 6.7 Mean b-terms over a range of blade numbers using DW_{ro} G_{z,alt} and DW_{alt} G_{z,alt} schemes.

Since PROPELLER acquisition times are directly dependent on blade numbers used, arbitrarily high blade numbers are undesirable. From the simulations in Section 6.3.2, DW_{alt} was found to be much more robust to tissue geometry and anisotropy than DW_{ro} and DW_{pe}. Hence, the simulation of DW_{alt} G_{z,alt} was repeated with blade numbers from 6 to 64 in step sizes of 1, to determine if lower blade numbers could give rise to effectively isotropic DW.

The result in Figure 6-41 shows an oscillation in the $\overline{b_{ij,max}}/\overline{b_{ii}}$ term that had a frequency of four blades, and an asymptotic trend towards zero at higher blade numbers. The gradual reduction with higher blade numbers was due to the more effective cancellation of off-diagonal terms as mentioned, while the oscillations corresponded to the periodicity of b_{xz} and

b_{yz} . Closer inspection revealed that using number of blades=6, 10, 14 and so forth up to 62 yielded a $\overline{b_{ij,max}}/\overline{b_{ii}}$ term of less than 1%.

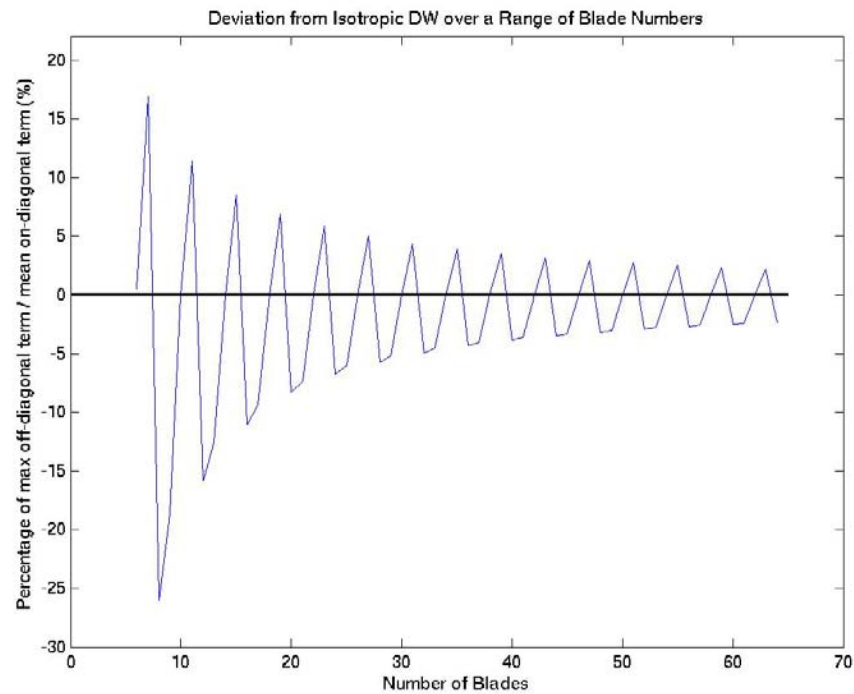


Figure 6-41 Variation of percentage error between maximum off-diagonal terms and mean of on-diagonal terms of b-tensor for blade numbers = 6 to 64, using the $DW_{alt} G_{z,alt}$ scheme.

A confirmation that the on-diagonal terms remained largely equal across these blade numbers is presented in Figure 6-42. These data expressed the ratio of the error between maximum on-diagonal terms and minimum on-diagonal terms, $(\overline{b_{ii,max}}/\overline{b_{ii,min}})-1$, as a percentage. Odd numbers of blades generated significant differences in b_{xx} and b_{yy} due to unequal diffusion weighting generated from the rotating in-plane DW that failed to average out. This diminished with larger blade numbers. Even numbers of blades however, consistently maintained $(\overline{b_{ii,max}}/\overline{b_{ii,min}})-1$ at <1%. This coincided with blade numbers that generated <1% off-diagonal terms above, confirming that $DW_{alt} G_{z,alt}$ with blade numbers of 6, 10, 14 and so on, could generate effectively isotropic DW.

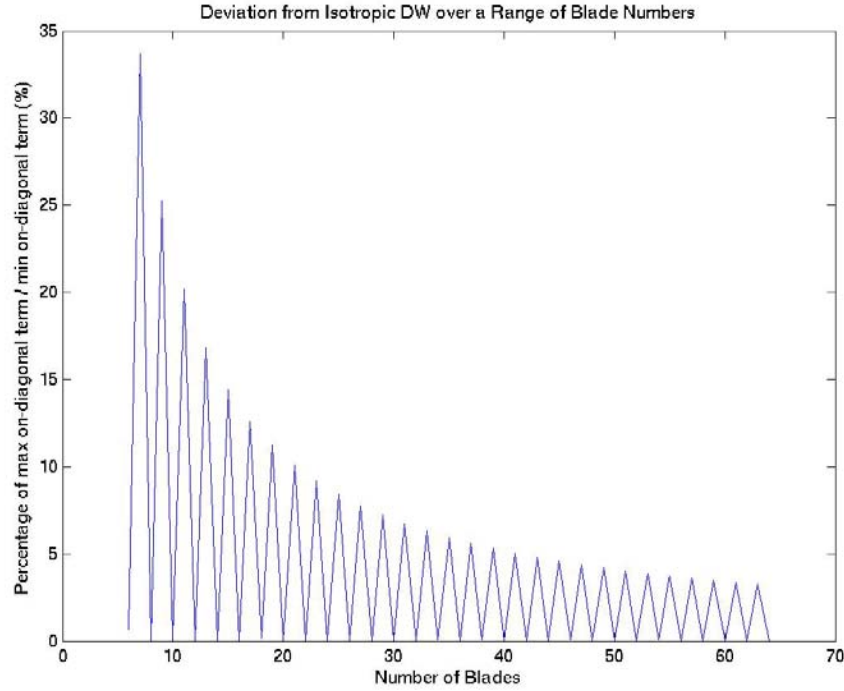


Figure 6-42 Variation of percentage error between maximum on-diagonal terms and minimum on-diagonal terms of b-tensor for blade numbers = 6 to 64, using the $DW_{alt} G_{z,alt}$ scheme.

6.4 Conclusion

DW-FSE-PROPELLER methods require significantly longer acquisition times compared to ssDW-EPI methods. In this chapter, rotating DW gradients were explored as a means to halve the acquisition time needed to obtain effectively isotropic DW within a single scan.

Simulation data showed that when the DW was aligned to either the readout or phase encoding direction that rotated with each blade, the measured ADC was highly dependent on a number of factors including the relative orientations of the tissue geometry, principal diffusivity and diffusion weighting, as well as the effect of adjacent tissues on one another. This was due to the anisotropic DW at the periphery of k-space. Tissues with more edges and smaller geometries were more susceptible to anisotropic DW. This was also enhanced with higher FA values. Alternating the direction of the DW between the two orthogonal directions with successive blades led to an effective averaging of not only the centre of k-space, but also the periphery of k-space. It was found that using DW_{alt} with a modest ETL and blade width of 8 improved the accuracy of the mean ADC measurements. Despite the

smaller central overlapping, and hence effectively isotropic, region of k-space, the increased frequency of DW direction changes in the periphery meant that the periphery had a higher degree of DW isotropy than if wider blades were used.

The in-vivo data in healthy mouse brain were consistent with the findings of the simulations. The relatively homogenous and large grey matter region in the mouse cortex displayed no significant differences using DW_{fix} and DW_{rot} methods. On the other hand, the highly anisotropic and narrow geometry of the corpus callosum led to an under- and overestimation of the mean ADC using DW_{ro} and DW_{pe} respectively, as compared with DW_{fix} data. The DW_{alt} data were more consistent with the DW_{fix} data. As an alternative method to halving acquisition times, DW_{fix} data were reconstructed with k-space undersampling by halving the number of blades used. These produced data that were slightly blurred with lower SNR, but maintained similar image quality and contrast. Due to shorter effective TE, centric phase encoding yielded higher SNR and lower AP than linear phase encoding.

The tumour data acquired in MT-ret/AAD mice were mixed. Even though the same qualitative observations were made in the GM and WM, the heterogeneity in tumour geometry and anisotropy meant that large errors were obtained in the tumour measurements. While k-space undersampling and DW_{alt} methods maintained qualitatively similar contrast to DW_{fix} methods, the data did not show any quantitative improvement over DW_{ro} and DW_{pe} methods.

Clinical data in a stroke patient demonstrated that rotating DW methods could produce data that were robust to geometric distortion and had good stroke contrast. The drawbacks were a longer acquisition time and poorer GM-WM contrast. The stroke lesions that could be identified were in general agreement with those identified using control ssDW-EPI data. However, DW_{rot} methods failed to positively identify at least one lesion in one slice of the brain. This was linked to the small size and possibly highly anisotropic nature of the lesion. It was also likely due to the suboptimal implementation of DW_{rot} at 3T that limited the number of blades acquired to 6 and extended the ETL to 32, resulting in excessive T_2 blurring.

Closer inspection of the effective b-tensor used in the DW_{ro} and DW_{alt} schemes showed that they retained significant off-diagonal terms and hence degrees of anisotropy. This was primarily due to the b_{yz} term that did not cancel out across blades. Alternating the polarity of G_z with successive blades (for DW_{ro}) and successive blade pairs (for DW_{alt}), led to alternating polarities in the b_{yz} terms, the sum of which progressively cancelled out as blade numbers increased. Simulations showed that the maximum off-diagonal terms oscillated with blade

numbers, and there existed specific blade numbers that minimized the off-diagonal terms to <1% of the mean on-diagonal terms. These blade numbers were $2+4N$ where N was any positive integer. These coincided with blade numbers whose errors between the maximum and minimum on-diagonal terms were <1%.

The feasibility of rotating DW, as a method to reduce the acquisition time of DW-FSE-PROPELLER, was demonstrated in simulations as well as in mouse brain, mouse tumours and human stroke. Simulations with well defined anisotropies and geometries showed that DW_{alt} was far more independent of tissue geometry and orientation of principal diffusivity than DW_{ro} and DW_{pe} , a crucial factor for robust imaging in pathology where these are generally unknown. It was found that effectively isotropic DW at the centre of k-space could be obtained by alternating G_z , and using specific numbers of blades that led to the effective averaging of on-diagonal b-terms and cancellation of off-diagonal b-terms. Successful implementation of DW_{alt} would entail using sufficient blades to avoid excessive T_2 , allow for DW averaging at the k-space periphery and obtain effectively isotropic DW at the central overlapping k-space. The resultant 50% reduction in acquisition time combined with PROPELLER acquisition could be useful in rapid whole body screening applications, where acquisition times and motion are significant challenges. Future work should also take into account the effect of imaging gradients and revisit methods to reduce residual non-MG magnetization.

7 Conclusions

This final chapter summarizes the main findings that have been described, together with their impact on practical imaging strategies.

7.1 Summary of findings

Imaging in small animals at high field strengths poses unique challenges in terms of small voxel size, low SNR and short T_2 and T_2^* . Geometric distortion due to off-resonance effects, susceptibility and chemical shift are likewise more pronounced at high fields. Conventional acquisition methods with Cartesian sampling led to either severe T_2 or T_2^* blurring where a single-shot was used, or to motion artifacts where multiple shots were used. EPI methods led to severe distortion and off-resonance artifacts.

FSE-PROPELLER was introduced at 9.4T as a rapid, self-navigated, motion-robust and distortion-resistant method to overcome these challenges. At 3T, the motion correction effects of PROPELLER were demonstrated and this was consistent with the work of others. In the absence of motion, the image fidelity was comparable to that using Cartesian sampling. In T_2 -weighted MRI at 9.4T, Cartesian sampling led to marked blurring in the phase encoding direction. This was compounded by motion artifacts in the imaging of mouse liver in-vivo. Here, FSE-PROPELLER was not only robust to motion, but achieved significantly better SNR, CNR and reduced AP than msFSE as a result of the multiple sampling of the centre of k-space and rotational symmetry of the acquisition. The better image fidelity was likewise reflected in the simulation data which showed a greater reduction in AP with PROPELLER at 9.4T relative to PROPELLER at 3T. Hence for specific blade configurations with blade widths of 8 and 16, it was shown that PROPELLER sampling could replace Cartesian sampling for T_2 -weighted imaging at 9.4T, irrespective of the presence of motion, at the cost of a longer minimum scan time.

Because of the averaging of multiple blades at the centre of k-space, overall signal and contrast in PROPELLER is sensitive to mixing of echoes from different blades with different values of TE. In PD-weighted imaging with centric phase encoding, this mixing of early and late echoes led to errors in the reconstructed signal. PETALS was proposed as a postprocessing method that reduced the overlap between blades post motion correction. This improved the consistency of the final data at the expense of SNR. Simulations at 9.4T showed an improvement in the contrast, PSF and AP in PETALS over PROPELLER for

ETL $\leq$ 64. At lower field strengths, the benefit was reduced as a consequence of lesser T_2 -modulation. In-vivo data at 9.4T exhibited lower SNR and better contrast as predicted, while human data at 3T showed no improvement in imaging parameters. Besides PD-weighted imaging at high field strength, PETALS was also shown to be useful in DWI, where the time required for DW preparation and short T_2 meant that centric phase encoding schemes may be preferable to linear encoding schemes. The effect was to likewise improve image contrast at the expense of SNR.

Ignoring the improvements in image fidelity, one issue in PROPELLER is the 50% increase in the minimum time required to fully sample k-space over Cartesian methods. It was proposed that k-space undersampling methods could be used to reduce the acquisition times. Various methods of undersampling, degrees of undersampling, field strengths and blade configurations were explored in an effort to optimize undersampling strategies in T_2 -weighted PROPELLER. Simulations showed that for a fixed acquisition time at 9.4T, blade widths of 16 led to better quality data than blade widths of 8, due to better k-space coverage and PSF behaviour. This improvement was directly related to field strength, once again underscoring the need for more careful consideration of blade parameters in the presence of severe T_2 dependency at 9.4T. Undersampling by reducing the number of blades fared consistently better than undersampling by increasing the spacing between successive phase encoding steps. The latter was due to aliasing arising from insufficient k-space sampling. In the former, the exclusion of k-space blades led to a loss of resolution in the directions of the missing blades. Where the remaining blades are of sufficient angular frequency, artifacts appear as noise, and overall image quality is maintained. It was found that using an undersampling factor of up to 2 preserved visual image quality and increased the mean AP by just 3.3% compared to the fully sampled case. In the presence of motion, it was further determined that undersampling by the latter method led to poorer estimation and correction of motion due to insufficiently sampled k-space within each blade.

In-vivo mouse brain data support the finding that blade widths of 16 are preferable to narrower blades and that undersampling factors of up to 2 may be applied without significant detriment to the image quality. The closeness of the Cartesian and PROPELLER data in preliminary human volunteer studies without motion reiterated that the improvements in image fidelity with PROPELLER were field dependent. In the presence of motion, PROPELLER demonstrated much better resistance to motion, as did PROPELLER with a USB factor of 2. However, undersampling reduced the redundancy of blades and our ability to exclude badly corrupted blades. Hence, while proposing that undersampling by blades by

up to a factor of 2 using a blade width of 16 would be optimal for in-vivo T_2 -weighted imaging at high field strength, the degree of undersampling should be determined based on the degree and nature of the anticipated motion.

DWI provides contrast that is useful in a range of diseases, particularly stroke. In addition to issues related to high field, DWI poses the added challenge of extreme sensitivity to motion. As a result, in-vivo DWI in adult rat and mice at high field strengths had previously been restricted to regions in the brain and spine. DW-FSE-PROPELLER was successfully introduced as a strategy for in-vivo DWI in the body of small rodents without need for respiratory gating. In-vivo data from mouse liver studies at 9.4T showed a significant improvement in SNR and reduction of AP over DW-FSE with Cartesian sampling, and a significantly lower measured ADC value due to lower signal dropout and artifacts in the DW images. Image quality was consistently better in both mouse brain and mouse liver data compared to other sequences based on single-shot, Cartesian sampling or EPI-based methods.

It was shown in simulations that the choice of phase encoding, blade configuration, and tissue anisotropy had an impact on the measured ADC, primarily due to the mixing of echoes with different TE. It was found that the magnitude of the errors in ADC estimation were directly related to the blade width and tissue anisotropy, while the sign of the errors were dependent on whether linear or centric phase encoding was used. To minimize the error, a narrow blade width of 8 should be used. While this reduces the capability for motion correction, the rotational nature of the acquisitions leads to more benign artifacts as shown in the in-vivo data.

DW-FSE with PROPELLER was also introduced in stroke patients at 3T. Pilot data showed good resistance to geometric distortion compared to standard single-shot DW-EPI methods, and were consistent with other published results at 1.5T.

Finally, the use of rotating DW gradients as a method to reduce DW-FSE-PROPELLER acquisition times was investigated. Simulations of anisotropic phantoms neglecting T_2 and motion showed that in DW_{ro} and DW_{pe} methods, the measured ADC was dependent on the relationship between the tissue geometry and anisotropy. With DW_{ro} , the mean ADC was overestimated in tissues with orthogonal geometry and principal diffusivity, and underestimated in tissues with collinear geometry and principal diffusivity. The reverse was true with DW_{pe} . The error in ADC estimation was directly related to the degree of anisotropy.

Further, the measured ADC in a given voxel was influenced by the ADC in the immediately adjacent tissues. Since tissue geometry and anisotropy is heterogeneous in-vivo and generally unknown in pathological conditions, it was necessary to find a method that could provide a measurement of ADC that was more independent of these factors. Simulations using DW_{alt} showed that it was much more robust to unknown tissue geometry and anisotropy. Testing different blade configurations in the presence of T_2 showed that ADC errors were minimized using a blade width of 8 and differed from the nominal value by -1% to -8%. This relatively narrow blade meant that although the central overlapping and hence effectively isotropically DW region was small, the periphery of k-space was sampled by DW that had a rapid orthogonal oscillation with successive blades. This resulted in effectively isotropic DW in the periphery of k-space as well. While DW_{alt} with radial acquisition would maximize the frequency of this oscillation, the PSF would be poorer and motion correction would be limited to 1D within each k-line.

In-vivo data with rotating DW gradients were acquired in healthy mouse brains, mouse models of tumour and human patients with stroke. In healthy mice, significant over and underestimations in the mean ADC of the highly anisotropic corpus callosum were observed depending on whether DW_{ro} or DW_{pe} was used. These were consistent with the simulation data. It was found that DW_{alt} yielded intermediate ADC estimates that were not significantly different from DW_{fix} methods. Similar observations with regard to GM-WM contrast were made. Results in the tumours in mice proved more difficult to assess due to the heterogeneity of tissue orientation and anisotropies. Similarly, while most stroke lesions could be detected in human studies, at least one small lesion escaped detection. This may have been due to the lesion being small and having a higher degree of anisotropy.

Careful simulations of the effective b-value at the centre of k-space were constructed to identify any discrepancies in the expected and applied b-value in an effort to improve the confidence of tumour and stroke lesion detection. These accounted for off-diagonal terms in the three rotating DW sequences. It was found that significant residual off-diagonal terms b_{xz} and b_{yz} remained. These were 4% and 30% of the nominal b-value respectively in DW_{ro} , and 19% and 15% in DW_{alt} . An effective method was presented to eliminate the off-diagonal terms. By alternating the sign of the DW gradient in the z-direction, the off-diagonal terms from the collection of blades cancel out, resulting in effectively isotropically DW data with $\leq 1\%$ deviation in any components of $\mathbf{b}$. Exploiting the rotational symmetry of PROPELLER in this way allowed pseudo-isotropic DW to be obtained without resorting to extended DW

preparation schemes as previously proposed that lead to intolerable T_2 decay at high fields. Further work remains to implement and validate DW_{alt} with alternating G_z in-vivo.

7.2 Concluding remarks

Diffusion weighted imaging provides unique contrast and structural information in a rapidly expanding range of small animal applications. High field imaging compounds the difficulties faced in conventional DWI. To this end, DW-FSE-PROPELLER was implemented and validated at 9.4T, improving the acquisition of DW data in mouse brain and liver. PROPELLER was also found to improve the image fidelity in T_2 -weighted imaging at 9.4T and could supplant Cartesian methods. In view of the lengthened minimum acquisition times associated with PROPELLER, k-space undersampling and rotating diffusion gradient methods were identified as viable methods to reduce acquisition times. These combine to make for exciting and efficient strategies for acquiring high resolution diffusion-weighted and non-diffusion-weighted data at high field strengths.

References

1. Bloch F, Hansen WW, Packard MM. The nuclear induction experiment. *Phys Rev* 1946;70:474-485.
2. Purcell EM, Torrey HC, Pound RV. Resonance absorption by nuclear magnetic moments in a solid. *Phys Rev* 1946;69:37-38.
3. Lauterbur PC. Image formation by induced local interactions: Examples employing nuclear magnetic resonance. *Nature* 1973;242:190-191.
4. Mansfield P, Grannell PK. NMR diffraction in solids? *J Phys C: Solid State Phys* 1973;6:L422-L426.
5. Bernstein MA, King KF, Zhou J. Handbook of MRI pulse sequences; 2004.
6. Haacke ME, Brown RW, Thompson MR, Venkatesan R. Magnetic resonance imaging. Physical Principles and Sequence Design; 1999.
7. Gerlach W, Stern O. Das magnetische Moment des Silberatoms. *Zeitschrift für Physik* 1922;9:353-355.
8. Hahn EL. Spin echoes. *Phys Rev* 1950;80:580-594.
9. Schmitt F, Stehling MK, Turner R. Echo planar imaging. Berlin: Springer 1998.
10. Schick F, Forster J, Machann J, Kuntz R, Claussen CD. Improved clinical echo-planar MRI using spatial-spectral excitation. *J Magn Reson Imaging* 1998;8(4):960-967.
11. Jesmanowicz A, Wong EC, Hyde JS. Phase correction for EPI using internal reference lines. In: Proceedings of the 3rd Annual Meeting of ISMRM 1995:1239.
12. Buonocore MH, Gao L. Ghost artifact reduction for echo planar imaging using image phase correction. *Magn Reson Med* 1997;38(1):89-100.
13. Hennig J, Nauerth A, Friedburg H. RARE imaging: a fast imaging method for clinical MR. *Magn Reson Med* 1986;3(6):823-833.
14. Meiboom S, Gill D. Modified spin echo method for measuring nuclear relaxation times. *Rev Sci Instrum* 1958;29:668.
15. Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. *Phys Rev* 1954;94:630-638.
16. Jiang H, Golay X, van Zijl PC, Mori S. Origin and minimization of residual motion-related artifacts in navigator-corrected segmented diffusion-weighted EPI of the human brain. *Magn Reson Med* 2002;47(4):818-822.
17. Liu C, Moseley ME, Bammer R. Simultaneous phase correction and SENSE reconstruction for navigated multi-shot DWI with non-cartesian k-space sampling. *Magn Reson Med* 2005;54(6):1412-1422.
18. Atkinson D, Counsell S, Hajnal JV, Batchelor PG, Hill DL, Larkman DJ. Nonlinear phase correction of navigated multi-coil diffusion images. *Magn Reson Med* 2006;56(5):1135-1139.
19. Roberts TP, Rowley HA. Diffusion weighted magnetic resonance imaging in stroke. *European journal of radiology* 2003;45(3):185-194.

20. Einstein A. Investigations on the theory of the Brownian movement. New York: Dover Publications, Inc.; 1926. p 119.
21. Torrey HC. Bloch equations with diffusion terms. *Phys Rev* 1956;104(3):563-565.
22. Clark CA, Le Bihan D. Water diffusion compartmentation and anisotropy at high b values in the human brain. *Magn Reson Med* 2000;44(6):852-859.
23. Niendorf T, Dijkhuizen RM, Norris DG, van Lookeren Campagne M, Nicolay K. Biexponential diffusion attenuation in various states of brain tissue: implications for diffusion-weighted imaging. *Magn Reson Med* 1996;36(6):847-857.
24. Zhong JH, Gore JC. Studies of restricted diffusion in heterogeneous media containing variations in susceptibility. *Magn Reson Med* 1991;19(2):276-284.
25. Pfeuffer J, Provencher SW, Gruetter R. Water diffusion in rat brain in vivo as detected at very large b values is multicompartamental. *MAGMA* 1999;8(2):98-108.
26. Kiselev VG, Il'yasov KA. Is the "biexponential diffusion" biexponential? *Magn Reson Med* 2007;57(3):464-469.
27. Cohen Y, Assaf Y. High b-value q-space analyzed diffusion-weighted MRS and MRI in neuronal tissues - a technical review. *NMR Biomed* 2002;15(7-8):516-542.
28. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magn Reson Med* 2005;53(6):1432-1440.
29. Heemskerk AM. Diffusion tensor imaging of mouse skeletal muscle; 2006.
30. Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. *Magn Reson Med* 1990;14(2):330-346.
31. Thomsen C, Henriksen O, Ring P. In vivo measurement of water self diffusion in the human brain by magnetic resonance imaging. *Acta Radiol* 1987;28(3):353-361.
32. Beaulieu C, Allen PS. Water diffusion in the giant axon of the squid: implications for diffusion-weighted MRI of the nervous system. *Magn Reson Med* 1994;32(5):579-583.
33. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed* 2002;15(7-8):435-455.
34. Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J Chem Phys* 1965;42:288-292.
35. Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 2006;51(5):527-539.
36. Mori S, Van Zijl P. Diffusion weighting by the trace of the diffusion tensor within a single scan. *Magn Reson Med* 1995;33:41-52.
37. Wong EC, Cox RW, Song AW. Optimized isotropic diffusion weighting. *Magn Reson Med* 1995;34(2):139-143.
38. Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* 1994;103(3):247-254.

39. Papadakis NG, Xing D, Houston GC, Smith JM, Smith MI, James MF, Parsons AA, Huang CL, Hall LD, Carpenter TA. A study of rotationally invariant and symmetric indices of diffusion anisotropy. *Magn Reson Imaging* 1999;17(6):881-892.
40. Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med* 1996;36(6):893-906.
41. Nakada T, Matsuzawa H. Three-dimensional anisotropy contrast magnetic resonance imaging of the rat nervous system: MR axonography. *Neurosci Res* 1995;22(4):389-398.
42. Pajevic S, Pierpaoli C. Color schemes to represent the orientation of anisotropic tissues from diffusion tensor data: application to white matter fiber tract mapping in the human brain. *Magn Reson Med* 1999;42(3):526-540.
43. Douek P, Turner R, Pekar J, Patronas N, Le Bihan D. MR color mapping of myelin fiber orientation. *Journal of computer assisted tomography* 1991;15(6):923-929.
44. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* 2000;44(4):625-632.
45. Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR Biomed* 2002;15(7-8):456-467.
46. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magn Reson Med* 2002;48(4):577-582.
47. Farrell JA, Landman BA, Jones CK, Smith SA, Prince JL, van Zijl PC, Mori S. Effects of signal-to-noise ratio on the accuracy and reproducibility of diffusion tensor imaging-derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5 T. *J Magn Reson Imaging* 2007;26(3):756-767.
48. Bammer R, Keeling SL, Augustin M, Pruessmann KP, Wolf R, Stollberger R, Hartung HP, Fazekas F. Improved diffusion-weighted single-shot echo-planar imaging (EPI) in stroke using sensitivity encoding (SENSE). *Magn Reson Med* 2001;46(3):548-554.
49. Alexander AL, Tsuruda JS, Parker DL. Elimination of eddy current artifacts in diffusion-weighted echo-planar images: the use of bipolar gradients. *Magn Reson Med* 1997;38(6):1016-1021.
50. Papadakis NG, Martin KM, Pickard JD, Hall LD, Carpenter TA, Huang CL. Gradient preemphasis calibration in diffusion-weighted echo-planar imaging. *Magn Reson Med* 2000;44(4):616-624.
51. Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magn Reson Med* 2003;49(1):177-182.
52. Haselgrove JC, Moore JR. Correction for distortion of echo-planar images used to calculate the apparent diffusion coefficient. *Magn Reson Med* 1996;36(6):960-964.
53. Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magn Reson Med* 1999;42(3):515-525.
54. Bastin ME, Armitage PA. On the use of water phantom images to calibrate and correct eddy current induced artefacts in MR diffusion tensor imaging. *Magn Reson Imaging* 2000;18(6):681-687.
55. Chen B, Guo H, Song AW. Correction for direction-dependent distortions in diffusion tensor imaging using matched magnetic field maps. *Neuroimage* 2006;30(1):121-129.

56. Mori S, Itoh R, Zhang J, Kaufmann WE, van Zijl PC, Solaiyappan M, Yarowsky P. Diffusion tensor imaging of the developing mouse brain. *Magn Reson Med* 2001;46(1):18-23.
57. Williams CF, Redpath TW, Norris DG. A novel fast split-echo multi-shot diffusion-weighted MRI method using navigator echoes. *Magn Reson Med* 1999;41(4):734-742.
58. Sarlls JE, Pierpaoli C. Diffusion-weighted radial fast spin-echo for high-resolution diffusion tensor imaging at 3T. *Magn Reson Med* 2008;60(2):270-276.
59. Pipe JG, Farthing VG, Forbes KP. Multishot diffusion-weighted FSE using PROPELLER MRI. *Magn Reson Med* 2002;47(1):42-52.
60. Liu C, Bammer R, Kim DH, Moseley ME. Self-navigated interleaved spiral (SNAILS): application to high-resolution diffusion tensor imaging. *Magn Reson Med* 2004;52(6):1388-1396.
61. Pipe JG. Motion correction with PROPELLER MRI: application to head motion and free-breathing cardiac imaging. *Magn Reson Med* 1999;42(5):963-969.
62. Wintersperger BD, Runge VM, Jonmenjoy B, Nelson CB, Stemmer A, Simonetta AB, Reiser MF, Naul LG, Schoenberg SO. Brain magnetic resonance imaging at 3T using BLADE compared with standard rectilinear data sampling. *Invest Radiol* 2006;41(7):586-592.
63. Welch EB, Avison RG, Gatenby GC, Anderson AW, Gore JC. PROPELLER MRI at 7T. In: *Proceedings of the 15th Annual Meeting of ISMRM, Berlin 2007*:3093.
64. Chuang TC, Huang TY, Lin FH, Wang FN, Juan CJ, Chung HW, Chen CY, Kwong KK. PROPELLER-EPI with parallel imaging using a circularly symmetric phased-array RF coil at 3.0 T: application to high-resolution diffusion tensor imaging. *Magn Reson Med* 2006;56(6):1352-1358.
65. Glover GH, Pauly JM. Projection reconstruction techniques for reduction of motion effects in MRI. *Magn Reson Med* 1992;28(2):275-289.
66. Ahn CB, Kim JH, Cho ZH. High-speed spiral-scan echo planar NMR imaging-I. *IEEE Trans Med Imaging* 1986;5(1):2-7.
67. Ordidge RJ, Helpert JA, Qing ZX, Knight RA, Nagesh V. Correction of motional artifacts in diffusion-weighted MR images using navigator echoes. *Magn Reson Imaging* 1994;12(3):455-460.
68. Anderson AW, Gore JC. Analysis and correction of motion artifacts in diffusion-weighted imaging. *Magn Reson Med* 1994;32(3):379-387.
69. Pandit P, King KF, Johnson GA. Abdominal imaging in free-breathing mice using PROPELLER. In: *Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008*:420.
70. Skare S, Li TQ, Newbould R, Clayton DB, Bammer R. Diffusion weighted EPI vs MinD SAP-EPI at 7T. In: *Proceedings of the 14th Annual Meeting of ISMRM, Seattle 2006*:1033.
71. Teh I, Larkman DJ, Golay X. Diffusion weighted fast spin echo PROPELLER at 9.4T. In: *Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008*:1804.
72. Walden J. Analysis of the direct Fourier method for computer tomography. *IEEE Trans Med Imaging* 2000;19(3):211-222.
73. Liu C, Bammer R, Moseley ME. Parallel imaging reconstruction for arbitrary trajectories using k-space sparse matrices (kSPA). *Magn Reson Med* 2007;58(6):1171-1181.

74. Weerasinghe C, Yan H. An improved algorithm for rotational motion artifact suppression in MRI. *IEEE Trans Med Imaging* 1998;17(2):310-317.
75. Seiberlich N, Breuer FA, Blaimer M, Barkauskas K, Jakob PM, Griswold MA. Non-Cartesian data reconstruction using GRAPPA operator gridding (GROG). *Magn Reson Med* 2007;58(6):1257-1265.
76. Strohmer T. Computationally attractive reconstruction of bandlimited images from irregular samples. *IEEE Trans Image Process* 1997;6(4):540-548.
77. Pruessmann KP, Weiger M, Bornert P, Boesiger P. Advances in sensitivity encoding with arbitrary k-space trajectories. *Magn Reson Med* 2001;46(4):638-651.
78. Dutt A, Rokhlin V. Fast Fourier-Transforms for Nonequispaced Data. *Siam J Sci Comput* 1993;14(6):1368-1393.
79. Sha L, Guo H, Song AW. An improved gridding method for spiral MRI using nonuniform fast Fourier transform. *J Magn Reson* 2003;162(2):250-258.
80. Fessler JA, Sutton BP. Nonuniform fast Fourier transforms using min-max interpolation. *IEEE T Signal Proces* 2003;51(2):560-574.
81. Shepp LA, Logan BF. The fourier reconstruction of a head section. *IEEE Trans Nucl Sc NS* 1974;21:21-43.
82. Van de Walle R, Barrett HH, Myers KJ, Altbach MI, Desplanques B, Gmitro AF, Cornelis J, Lemahieu I. Reconstruction of MR images from data acquired on a general nonregular grid by pseudoinverse calculation. *IEEE Trans Med Imaging* 2000;19(12):1160-1167.
83. Gach MH, Tanase C, Boada F. 2D & 3D Shepp-Logan Phantom Standards for MRI. *Systems Engineering* 2008:521-526.
84. Ouwekerk R. Matlab simulation of raw MRI data of a Shepp Logan head phantom. 2002.
85. Stanisiz GJ, Odrobina EE, Pun J, Escaravage M, Graham SJ, Bronskill MJ, Henkelman RM. T1, T2 relaxation and magnetization transfer in tissue at 3T. *Magn Reson Med* 2005;54(3):507-512.
86. Yrjana SK, Vaara T, Karttunen A, Koivukangas J. Pulse repetition time and contrast enhancement: simulation study of Gd-BOPTA and conventional contrast agent at different field strengths. *Invest Radiol* 2008;43(4):267-275.
87. Watrin A, Ruaud JP, Olivier PT, Guingamp NC, Gonord PD, Netter PA, Blum AG, Guillot GM, Gillet PM, Loeuille DH. T2 mapping of rat patellar cartilage. *Radiology* 2001;219(2):395-402.
88. Kuo YT, Herlihy AH, So PW, Bhakoo KK, Bell JD. In vivo measurements of T1 relaxation times in mouse brain associated with different modes of systemic administration of manganese chloride. *J Magn Reson Imaging* 2005;21(4):334-339.
89. Sun Y, Mulkern RV, Schmidt K, Doshi S, Albert MS, Schmidt NO, Ziu M, Black P, Carrol R, Kieran MW. Quantification of water diffusion and relaxation times of human U87 tumors in a mouse model. *NMR Biomed* 2004;17(6):399-404.
90. Huang TY, Liu YJ, Juan CJ, Chen CY, Poncelet BP, Kwong KK. Respiratory self-gating with PROPELLER encoding: Application to free-breathing cardiac imaging. In: *Proceedings of the 14th Annual Meeting of ISMRM, Seattle* 2006:147.
91. Chang S, Gaddipati A, Bayram E, Harlley MR. Corrections to accelerated PROPELLER acquisition to maintain contrast and reduce T2 decay artifacts. In: *Proceedings of the 15th Annual Meeting of ISMRM, Berlin* 2007:1733.

92. Zhang L, Kholmovski EG, Guo J, Parker DL. TSE with average-specific phase encoding ordering for motion detection and artifact suppression. *J Magn Reson Imaging* 2007;25(6):1271-1282.
93. Pipe JG. Whole blade method for robust DWI. In: *Proceedings of the 15th Annual Meeting of ISMRM, Berlin 2007*:1486.
94. Determination of signal-to-noise ratio (SNR) in diagnostic magnetic resonance imaging. NEMA Standards Publication MS 1-2001 2001:4-6.
95. Park J, Zhang Q, Jellus V, Simonetti O, Li D. Artifact and noise suppression in GRAPPA imaging using improved k-space coil calibration and variable density sampling. *Magn Reson Med* 2005;53(1):186-193.
96. Eggers H, van Yperen GH, Nehrke K. Contrast Optimization by Data Weighting in Propeller Imaging. In: *Proceedings of the 15th Annual Meeting of ISMRM, Berlin 2007*:1737.
97. Yacoub E, Shmuel A, Pfeuffer J, Van De Moortele PF, Adriany G, Andersen P, Vaughan JT, Merkle H, Ugurbil K, Hu X. Imaging brain function in humans at 7 Tesla. *Magn Reson Med* 2001;45(4):588-594.
98. Speck O, Stadler J, Zaitsev M. High resolution single-shot EPI at 7T. *Magma* 2008;21(1-2):73-86.
99. Nakada T. Clinical application of high and ultra high-field MRI. *Brain & development* 2007;29(6):325-335.
100. Tamhane AA, Pipe JG, Arfanakis K. PROPELLER and Turboprop Acquisition Parameters for Optimal Motion Correction. In: *Proceedings of the 14th Annual Meeting of ISMRM, Seattle 2006*:1037.
101. Skare S, Newbould RD, Clayton DB, Bammer R. Propeller EPI in the other direction. *Magn Reson Med* 2006;55(6):1298-1307.
102. Weigel M, Hennig J. Development and optimization of T2 weighted methods with reduced RF power deposition (Hyperecho-TSE) for magnetic resonance imaging. *Zeitschrift fur medizinische Physik* 2008;18(3):151-161.
103. van den Bos IC, Hussain SM, Krestin GP, Wielopolski PA. Extending slice coverage for breathhold fat-suppressed T2-weighted fast spin-echo of the liver at 3.0T: application of variable-rate selective-excitation (VERSE) RF pulses. *J Magn Reson Imaging* 2008;27(1):110-116.
104. Pipe JG, Zwart N. Turboprop: improved PROPELLER imaging. *Magn Reson Med* 2006;55(2):380-385.
105. Arfanakis K, Tamhane AA, Pipe JG, Anastasio MA. k-space undersampling in PROPELLER imaging. *Magn Reson Med* 2005;53(3):675-683.
106. Beatty PJ, Li Z, Slavens ZW, Brau AC. Parallel imaging PROPELLER with across-blade calibration: In vivo results. In: *Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008*:1464.
107. Huo D, Li Z, Aboussouan E, Karis JP, Pipe JG. Parallel Imaging Method for Split-Blade PROPELLER DWI. In: *Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008*:756.
108. Skare S, Newbould R, Bammer R. GRAPPA estimations using undersampled PROPELLER trajectories. In: *Proceedings of the 15th Annual Meeting of ISMRM, Berlin 2007*:1734.

109. Blaimer M, Barkauskas K, Kannengiesser S, Breuer F, Jakob PM, Duerk JL, Griswold MA. Artifact reduction in undersampled BLADE/PROPELLER MRI by k-space extrapolation using parallel imaging. In: Proceedings of the 14th Annual Meeting of ISMRM, Seattle 2006:5.
110. Chuang TC, Huang TY, Lin FH, Wang FN, Ko CW, Kwong KK, Chung HW. PROPELLER EPI with parallel imaging on high resolution DTI at 3T. In: Proceedings of the 13th Annual Meeting of ISMRM, Miami 2005:9.
111. Natsuaki Y, Buonocore MH, Nordahl TE, Salo RE. Optimization of k-space undersampled DW-PROPELLER using fast RIGR algorithm. In: Proceedings of the 14th Annual Meeting of ISMRM, Seattle 2006:1039.
112. Karis JP, Pipe JG. ASSET enabled Turboprop: an improved PROPELLER sequence for motion corrected T2 imaging. In: Proceedings of the 13th Annual Meeting of ISMRM, Miami 2005:2235.
113. Tamhane AA, Anastasio MA, Arfanakis K. PROPELLER Image reconstruction using the non-uniform Fast Fourier Transform. In: Proceedings of the 15th Annual Meeting of ISMRM, Berlin 2007:7.
114. Tamhane AA, Anastasio MA, Arfanakis K. Accelerating PROPELLER MRI by means of undersampling and iterative image reconstruction using the non-uniform fast fourier transform. In: Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008:1356.
115. Beaulieu CF, Zhou X, Cofer GP, Johnson GA. Diffusion-weighted MR microscopy with fast spin-echo. *Magn Reson Med* 1993;30(2):201-206.
116. Deng J, Omary RA, Larson AC. Multishot diffusion-weighted SPLICE PROPELLER MRI of the abdomen. *Magn Reson Med* 2008;59(5):947-953.
117. Schick F. SPLICE: sub-second diffusion-sensitive MR imaging using a modified fast spin-echo acquisition mode. *Magn Reson Med* 1997;38(4):638-644.
118. Alsop DC. Phase insensitive preparation of single-shot RARE: application to diffusion imaging in humans. *Magn Reson Med* 1997;38(4):527-533.
119. Strik C, Klose U, Erb M, Strik H, Grodd W. Intracranial oscillations of cerebrospinal fluid and blood flows: analysis with magnetic resonance imaging. *J Magn Reson Imaging* 2002;15(3):251-258.
120. Mori S, van Zijl PC. A motion correction scheme by twin-echo navigation for diffusion-weighted magnetic resonance imaging with multiple RF echo acquisition. *Magn Reson Med* 1998;40(4):511-516.
121. von Mengershausen M, Norris DG, Driesel W. 3D diffusion tensor imaging with 2D navigated turbo spin echo. *MAGMA* 2005;18(4):206-216.
122. Seifert MH, Jakob PM, Jellus V, Haase A, Hillenbrand C. High-resolution diffusion imaging using a radial turbo-spin-echo sequence: implementation, eddy current compensation, and self-navigation. *J Magn Reson* 2000;144(2):243-254.
123. Trouard TP, Theilmann RJ, Altbach MI, Gmitro AF. High-resolution diffusion imaging with DIFRAD-FSE (diffusion-weighted radial acquisition of data with fast spin-echo) MRI. *Magn Reson Med* 1999;42(1):11-18.
124. Deng J, Virmani S, Young J, Harris K, Yang GY, Rademaker A, Woloschak G, Omary RA, Larson AC. Diffusion-weighted PROPELLER MRI for quantitative assessment of liver tumor necrotic fraction and viable tumor volume in VX2 rabbits. *J Magn Reson Imaging* 2008;27(5):1069-1076.

125. Forbes KP, Pipe JG, Karis JP, Heiserman JE. Improved image quality and detection of acute cerebral infarction with PROPELLER diffusion-weighted MR imaging. *Radiology* 2002;225(2):551-555.
126. Abe O, Mori H, Aoki S, Kunimatsu A, Hayashi N, Masumoto T, Yamada H, Masutani Y, Kabasawa H, Ohtomo K. Periodically rotated overlapping parallel lines with enhanced reconstruction-based diffusion tensor imaging. Comparison with echo planar imaging-based diffusion tensor imaging. *Journal of computer assisted tomography* 2004;28(5):654-660.
127. Kiryu S, Watanabe M, Kabasawa H, Akahane M, Aoki S, Ohtomo K. Evaluation of super paramagnetic iron oxide-enhanced diffusion-weighted PROPELLER T2-fast spin echo magnetic resonance imaging: Preliminary experience. *Journal of computer assisted tomography* 2006;30(2):197-200.
128. Vonarbourg A, Sapin A, Lemaire L, Franconi F, Menei P, Jallet P, Le Jeune JJ. Characterization and detection of experimental rat gliomas using magnetic resonance imaging. *Magma* 2004;17(3-6):133-139.
129. Nair G, Tanahashi Y, Low HP, Billings-Gagliardi S, Schwartz WJ, Duong TQ. Myelination and long diffusion times alter diffusion-tensor-imaging contrast in myelin-deficient shiverer mice. *Neuroimage* 2005;28(1):165-174.
130. Boretius S, Wurfel J, Zipp F, Frahm J, Michaelis T. High-field diffusion tensor imaging of mouse brain in vivo using single-shot STEAM MRI. *Journal of neuroscience methods* 2007;161(1):112-117.
131. Norris DG, Bornert P, Reese T, Leibfritz D. On the application of ultra-fast RARE experiments. *Magn Reson Med* 1992;27(1):142-164.
132. Hogers B, Gross D, Lehmann V, Zick K, De Groot HJ, Gittenberger-De Groot AC, Poelmann RE. Magnetic resonance microscopy of mouse embryos in utero. *The Anatomical record* 2000;260(4):373-377.
133. Lee SP, Silva AC, Ugurbil K, Kim SG. Diffusion-weighted spin-echo fMRI at 9.4 T: microvascular/tissue contribution to BOLD signal changes. *Magn Reson Med* 1999;42(5):919-928.
134. Lee SP, Silva AC, Kim SG. Comparison of diffusion-weighted high-resolution CBF and spin-echo BOLD fMRI at 9.4 T. *Magn Reson Med* 2002;47(4):736-741.
135. Bockhorst KH, Narayana PA, Liu R, Ahobila-Vijjula P, Ramu J, Kamel M, Wosik J, Bockhorst T, Hahn K, Hasan KM, Perez-Polo JR. Early postnatal development of rat brain: in vivo diffusion tensor imaging. *Journal of neuroscience research* 2008;86(7):1520-1528.
136. Chahboune H, Ment LR, Stewart WB, Ma X, Rothman DL, Hyder F. Neurodevelopment of C57B/L6 mouse brain assessed by in vivo diffusion tensor imaging. *NMR Biomed* 2007;20(3):375-382.
137. Larvaron P, Boespflug-Tanguy O, Renou JP, Bonny JM. In vivo analysis of the post-natal development of normal mouse brain by DTI. *NMR Biomed* 2007;20(4):413-421.
138. Deo AA, Grill RJ, Hasan KM, Narayana PA. In vivo serial diffusion tensor imaging of experimental spinal cord injury. *Journal of neuroscience research* 2006;83(5):801-810.
139. Bilgen M, Al-Hafez B, Berman NE, Festoff BW. Magnetic resonance imaging of mouse spinal cord. *Magn Reson Med* 2005;54(5):1226-1231.
140. Madi S, Hasan KM, Narayana PA. Diffusion tensor imaging of in vivo and excised rat spinal cord at 7 T with an icosahedral encoding scheme. *Magn Reson Med* 2005;53(1):118-125.

141. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, Tomanek A, Frayne R, Buchan AM. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *Journal of neurology, neurosurgery, and psychiatry* 2005;76(11):1528-1533.
142. Moffat BA, Hall DE, Stojanovska J, McConville PJ, Moody JB, Chenevert TL, Rehemtulla A, Ross BD. Diffusion imaging for evaluation of tumor therapies in preclinical animal models. *Magma* 2004;17(3-6):249-259.
143. Guilfoyle DN, Helpert JA, Lim KO. Diffusion tensor imaging in fixed brain tissue at 7.0 T. *NMR Biomed* 2003;16(2):77-81.
144. Wang Y, Zhang J, Mori S, Nathans J. Axonal growth and guidance defects in Frizzled3 knock-out mice: a comparison of diffusion tensor magnetic resonance imaging, neurofilament staining, and genetically directed cell labeling. *J Neurosci* 2006;26(2):355-364.
145. Shepherd TM, Ozarslan E, King MA, Mareci TH, Blackband SJ. Structural insights from high-resolution diffusion tensor imaging and tractography of the isolated rat hippocampus. *Neuroimage* 2006;32(4):1499-1509.
146. Zhang J, Miller MI, Plachez C, Richards LJ, Yarowsky P, van Zijl P, Mori S. Mapping postnatal mouse brain development with diffusion tensor microimaging. *Neuroimage* 2005;26(4):1042-1051.
147. Zhang J, Richards LJ, Yarowsky P, Huang H, van Zijl PC, Mori S. Three-dimensional anatomical characterization of the developing mouse brain by diffusion tensor microimaging. *Neuroimage* 2003;20(3):1639-1648.
148. Zhang J, van Zijl PC, Mori S. Three-dimensional diffusion tensor magnetic resonance microimaging of adult mouse brain and hippocampus. *Neuroimage* 2002;15(4):892-901.
149. Chenevert TL, Pipe JG. Effect of bulk tissue motion on quantitative perfusion and diffusion magnetic resonance imaging. *Magn Reson Med* 1991;19(2):261-265.
150. Yongbi MN, Ding S, Dunn JF. A modified sub-second fast-STEAM sequence incorporating bipolar gradients for in vivo diffusion imaging. *Magn Reson Med* 1996;35(6):911-916.
151. Leroux P, Hinks RS. Stabilization of Echo Amplitudes in Fse Sequences. *Magnet Reson Med* 1993;30(2):183-190.
152. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Annals of neurology* 1995;37(2):231-241.
153. Rowley HA. Noninvasive imaging of the ischemic penumbra. *Annals of neurology* 1997;42(4):539-541.
154. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Annals of neurology* 1999;46(4):568-578.
155. Landman BA, Farrell JA, Jones CK, Smith SA, Prince JL, Mori S. Effects of diffusion weighting schemes on the reproducibility of DTI-derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5T. *Neuroimage* 2007;36(4):1123-1138.
156. Correia MM, Carpenter TA, Williams GB. Looking for the optimal DTI acquisition scheme given a maximum scan time: are more b-values a waste of time? *Magn Reson Imaging* 2008.
157. Tamhane AA, Anastasio MA, Arfanakis K. Image noise considerations for PROPELLER k-space sampling. In: *Proceedings of the 14th Annual Meeting of ISMRM, Seattle 2006*:1025.

158. Zhang J, van Zijl PC, Larterra J, Salhotra A, Lal B, Mori S, Zhou J. Unique patterns of diffusion directionality in rat brain tumors revealed by high-resolution diffusion tensor MRI. *Magn Reson Med* 2007;58(3):454-462.
159. Chepuri NB, Yen YF, Burdette JH, Li H, Moody DM, Maldjian JA. Diffusion anisotropy in the corpus callosum. *Ajnr* 2002;23(5):803-808.
160. Hasan KM, Narayana PA. Retrospective measurement of the diffusion tensor eigenvalues from diffusion anisotropy and mean diffusivity in DTI. *Magn Reson Med* 2006;56(1):130-137.
161. Walker-Samuel S, McPhail LD, Ryan AJ, Robinson SP. Using BOLD MRI with carbogen to evaluate tumour response to antiangiogenic therapy. In: *Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008*:664.
162. Whalen M, Shapiro JI. Controlled ventilation during NMR spectroscopic studies: hemodynamic and biochemical consequences. *Magn Reson Imaging* 1991;9(2):229-234.
163. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology* 1992;42(9):1717-1723.
164. Marks MP, Tong DC, Beaulieu C, Albers GW, de Crespigny A, Moseley ME. Evaluation of early reperfusion and i.v. tPA therapy using diffusion- and perfusion-weighted MRI. *Neurology* 1999;52(9):1792-1798.
165. Van Lookeren Campagne M, Thomas GR, Thibodeaux H, Palmer JT, Williams SP, Lowe DG, van Bruggen N. Secondary reduction in the apparent diffusion coefficient of water, increase in cerebral blood volume, and delayed neuronal death after middle cerebral artery occlusion and early reperfusion in the rat. *J Cereb Blood Flow Metab* 1999;19(12):1354-1364.
166. Xue R, Sawada M, Goto S, Hurn PD, Traystman RJ, van Zijl PC, Mori S. Rapid three-dimensional diffusion MRI facilitates the study of acute stroke in mice. *Magn Reson Med* 2001;46(1):183-188.
167. Busza AL, Allen KL, King MD, van Bruggen N, Williams SR, Gadian DG. Diffusion-weighted imaging studies of cerebral ischemia in gerbils. Potential relevance to energy failure. *Stroke; a journal of cerebral circulation* 1992;23(11):1602-1612.
168. Chenevert TL, McKeever PE, Ross BD. Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging. *Clin Cancer Res* 1997;3(9):1457-1466.
169. Herneth AM, Guccione S, Bednarski M. Apparent diffusion coefficient: a quantitative parameter for in vivo tumor characterization. *European journal of radiology* 2003;45(3):208-213.
170. Chun T, Ulug AM, van Zijl PC. Single-shot diffusion-weighted trace imaging on a clinical scanner. *Magn Reson Med* 1998;40(4):622-628.
171. Cercignani M, Horsfield MA. An optimized pulse sequence for isotropically weighted diffusion imaging. *J Magn Reson* 1999;140(1):58-68.
172. Dietrich O, Filidoro L, Reiser M. Measuring anisotropic diffusion with rotating diffusion gradients. In: *Proceedings of the 19th Annual Meeting of ESMRMB, Cannes, France 2002*.
173. Cheryauka AB, Lee JN, Samsonov AA, Defrise M, Gullberg GT. MRI diffusion tensor reconstruction with PROPELLER data acquisition. *Magn Reson Imaging* 2004;22(2):139-148.

174. Sarlls JE, Newbould RD, Altbach MI, Gmitro AF, Seeger J, Trouard TP. Isotropic diffusion weighting in radial fast spin-echo magnetic resonance imaging. *Magn Reson Med* 2005;53(6):1347-1354.
175. Conturo TE, McKinstry RC, Akbudak E, Robinson BH. Encoding of anisotropic diffusion with tetrahedral gradients: a general mathematical diffusion formalism and experimental results. *Magn Reson Med* 1996;35(3):399-412.
176. Lauzon ML, Rutt BK. Polar sampling in k-space: reconstruction effects. *Magn Reson Med* 1998;40(5):769-782.
177. Engstrom M, Nordell A, Nordell B, Skare S. Fast diffusion imaging using undersampled PROPELLER EPI. In: *Proceedings of the 16th Annual Meeting of ISMRM, Toronto 2008*:415.
178. Sotak CH. The role of diffusion tensor imaging in the evaluation of ischemic brain injury - a review. *NMR Biomed* 2002;15(7-8):561-569.
179. Lengagne R, Graff-Dubois S, Garcette M, Renia L, Kato M, Guillet JG, Engelhard VH, Avril MF, Abastado JP, Prevost-Blondel A. Distinct role for CD8 T cells toward cutaneous tumors and visceral metastases. *J Immunol* 2008;180(1):130-137.